Chapter 6
Other Effects

Introduction

This chapter addresses evidence on smoking and health effects over a range of specific diseases and nonspecific but adverse consequences. The associations reviewed appear to reflect both specific and nonspecific pathways of injury by tobacco smoke. The evidence indicates that smoking should be considered not only a cause of specific diseases and conditions, but a contributing factor to nonspecific morbidity and a diminished quality of life.

Diminished Health Status

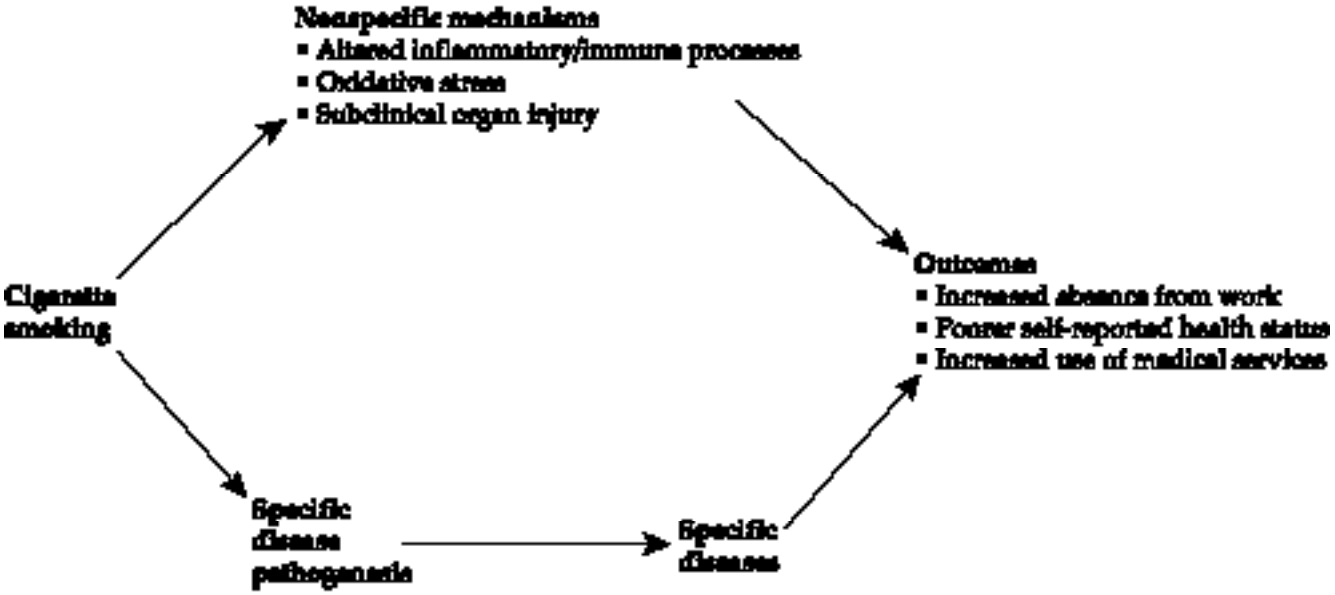
This section focuses on the question of whether cigarette smokers have poorer health in comparison with nonsmokers, beyond the already well-characterized burden of morbidity and mortality from the specific diseases caused by smoking. The hypothesis that smoking might impair health in general draws plausibility from the toxicologic richness of tobacco smoke, the well-documented systemic distribution of tobacco smoke components and metabolites, and the effects on host defenses, including the immune system. Additionally, impairment of organ function short of the level at which clinical disease is diagnosed may leave the smoker vulnerable to otherwise well-tolerated threats to health. For example, the reduction of lung function found in many smokers who do not have overt chronic obstructive pulmonary disease (COPD) may increase the risk for developing a more severe illness with a respiratory infection, or having a respiratory complication following surgery.

This section reviews studies that have addressed a number of health status indicators (Figure 6.1) including direct reports of health status or responses to an instrument that provides a health status index, and indirect indicators such as medical services utilization data. When interpreting the findings of these studies, consideration needs to be given to the potential causal pathways linking smoking to a poor health status, the assessment and measurement of health status, and the potential for biases, such as from confounding, to affect associations of smoking with these outcome measures.

For the diseases caused by smoking, direct causal pathways are implicit. For example, substantial evidence supports the hypothesis that smoking causes lung cancer through the direct deposition of tobacco smoke carcinogens in the respiratory tract. For some of the outcome measures considered in this section, pathways are far less certain and may be both direct and indirect. Increased absenteeism might reflect, for example, the tendency of smokers to have more severe respiratory illnesses than nonsmokers, possibly attributable to the effects of smoking on respiratory defenses or because smokers tend to have a lower level of lung function.

The outcomes considered in this section have multiple determinants. Health status itself is an integrative measure reflecting the net consequences of the many varied factors that determine health and well-being. To the extent that smokers differ from nonsmokers in these factors, there is a potential for confounding to distort associations of smoking with the outcome measures. Studies show, for example, that smokers and nonsmokers differ in aspects of lifestyle and in their approaches to health care (e.g., the use of preventive services such as multiphasic testing [Oakes et al. 1974] and screening [Beaulieu et al. 1996; Edwards and Boulet 1997]). Additionally, the suite of relevant confounding factors may differ from outcome to outcome, and for some outcomes there is uncertainty as to the relevant confounding factors. Some of the individual characteristics that affect the decision to start smoking and to continue to smoke also may be determinants of risk for the outcomes considered here.

Figure 6.1 A conceptual model for the relationship between cigarette smoking and diminished health status



Conclusions of Previous Surgeon General's Reports

Extensive research over time has identified cigarette smoking as a cause of specific diseases, and many reports from the Surgeon General have focused on smoking and these diseases. These reports have also addressed more general and nonspecific adverse consequences of smoking, such as increased rates of absenteeism from work or the utilization of medical services among smokers in comparison with nonsmokers. Conclusions from the reports that relate to these outcomes are listed in Table 6.1, including findings on general respiratory morbidity. Reports of increased morbidity from common and frequent viral and bacterial respiratory infections among smokers have been reviewed (U.S. Department of Health and Human Services [USDHHS] 1990) and are among the topics covered in Chapter 4 of this report. However, the overall health status of smokers compared with nonsmokers has not been comprehensively addressed in prior Surgeon General's reports.

Biologic Basis

Cigarette smoke, inhaled through the mouth into the lungs, reaches lung airways and alveoli, where the tobacco smoke components pass into the systemic circulation (Murray 1986). The airways and alveoli themselves are exposed to the gaseous and particulate components of tobacco smoke as many of these components readily pass through the alveolar-capillary membrane into the alveolar capillaries and then circulate throughout the body. Nicotine, for example, which is among these components, reaches the brain within 10 seconds after smoke is inhaled (USDHHS 1988). It is distributed throughout the body and has been found in breast milk (Schwartz-Bickenbach et al. 1987; Schulte-Hobein et al. 1992; Golding 1997) and in cervical mucus (Prokopczyk et al. 1997). Carbon monoxide, a diffusible gas, moves from the alveoli into the capillaries where it binds tightly to the hemoglobin of the red blood cells. Benzo[*a*]pyrene, a well-characterized carcinogen in tobacco smoke, can be found bound to the blood cells in the epithelial cells of the airways of smokers and in their major organs. The effects of smoking on host defenses and aspects of immune function have been covered in prior reports (USDHHS 1990, 1994) and again in this report. These effects may have the consequence of increasing risks for infections, whether of the respiratory tract or other organs. However, there has been less research to date on infections beyond those of the respiratory tract. This systemic distribution of tobacco smoke components underlies the associations between smoking and disease that are well documented for many organs including cardiovascular disease, stroke,

Table 6.1 Conclusions from previous Surgeon General's reports concerning smoking as a cause of diminished health status and respiratory morbidity

Statement	Surgeon General's report
"Cough, sputum production, or the two combined are consistently more frequent among cigarette smokers than among non-smokers." (p. 302)	1964
"Even relatively young cigarette smokers show increased respiratory symptoms and decreased ventilatory function." (p. 31)	1967
"Cigarette smokers have higher rates of disability than nonsmokers, whether measured by days lost from work among the employed population, by days spent ill in bed, or by the most general measure — days of 'restricted activity' due to illness or injury." (p. 24)	1967
"Cigarette smokers show an increased prevalence of respiratory symptoms, including cough, sputum production, and breathlessness, when compared with nonsmokers." (pp. 9–10)	1971
"Respiratory infections are more prevalent and severe among cigarette smokers, particularly heavy smokers, than among nonsmokers." (p. 10)	1971
"Investigations of high school students have demonstrated that abnormal pulmonary function and pulmonary symptoms are more common in smokers than nonsmokers." (p. 48)	1972
"Cigarette smokers have also been shown to have a significantly longer duration of respiratory symptoms following mild viral illness than nonsmokers." (p. 78)	1975
"In addition to an increased risk of COPD, cigarette smokers are more frequently subject to and require longer convalescence from other respiratory infections than nonsmokers. Also, if they require surgery, they are more likely to develop postoperative respiratory complications." (p. 61)	1975
"The age-adjusted incidence of acute conditions (e.g., influenza) for males who had ever smoked was 14 percent higher, and for females 21 percent higher, than for those who had never smoked cigarettes." (p. 1-12)	1979
"A wide variety of alterations in the immune system have been observed due to cigarette smoking." (p. 1-18)	1979
"Cessation of smoking definitely improves pulmonary function and decreases the prevalence of respiratory symptoms." (p. 1-18)	1979
"Cigarette smokers have an increased frequency of respiratory symptoms, and at least two of them, cough and sputum production, are dose-related." (p. 1-18)	1979

Table 6.1 Continued

Statement	Surgeon General's report
"The relationship between smoking and an increased prevalence of respiratory symptoms in the adult has been well established in studies of hospital and clinic patients, working groups, total communities, and representative samples of the community." (p. 6-20)	1979
"In summary, many recent studies demonstrate a higher frequency of respiratory symptoms in women who smoke as compared to women who do not smoke. This is true in surveys including children, adolescents, young adults, working age, and elderly women. The effect of cigarette smoking is related in terms of both the number of cigarettes and years smoked." (p. 156)	1980
"Relationships between smoking and cough or phlegm are strong and consistent; they have been amply documented and are judged to be causal." (p. 47)	1984
"Consideration of evidence from many different studies has led to the conclusion that cigarette smoking is the overwhelmingly most important cause of cough, sputum, chronic bronchitis, and mucus hypersecretion." (p. 48)	1984
"Smoking cessation reduces rates of respiratory symptoms such as cough, sputum production, and wheezing, and respiratory infections such as bronchitis and pneumonia, compared with continued smoking." (p. 349)	1990
"Former smokers have better health status than current smokers as measured in a variety of ways, including days of illness, number of health complaints, and self-reported health status." (p. 92)	1990

Sources: U.S. Department of Health, Education, and Welfare 1964, 1967, 1971, 1972, 1975, 1979; U.S. Department of Health and Human Services 1980, 1984, 1990.

and cancers of the kidney and urinary bladder. The widespread distribution may also lead to more general effects on health.

This same systemic distribution may have nonspecific effects as well, contributing to a reduction in health status. Exposure to tobacco smoke components causes smoke-specific diseases such as bladder cancer (carcinogens in urine come in contact with the bladder) and atherosclerosis, probably reflecting multiple underlying mechanisms with inflammation having a central role (Cross et al. 1999). Underlying mechanisms might include heightened oxidative stress and reduced antioxidant defenses, increased inflammatory activity, reduced host defenses against infection, and lowered reparative capacities of tissues. The evidence on these mechanisms is at varying levels of development. This section focuses on oxidative stress as an example, selected because the available literature is extensive.

Oxidative Stress

Oxidative stress refers to an increased exposure to oxidants and/or a decreased antioxidant capacity, caused by oxygen radicals that mutate DNA, promote atherosclerosis, and lead to chronic lung injury. Oxidative stress is now hypothesized to be a general mechanism underlying aging and many of the chronic diseases associated with aging, contributing to the development of cancer, cardiovascular disease, and COPD (Ames et al. 1995). Mounting evidence points to chronic oxidative stress as one mechanism whereby smoking affects health. Smoking is associated with

evidence of chronic systemic inflammation, perhaps a consequence of the chronic oxidative stress experienced by the smoker (Cross et al. 1999; Hecht 1999). The oxidant load posed by cigarette smoke is substantial; the tar component is estimated to contain 10^{18} oxygen radicals per gram of tar and the gas component to have as many as 10^{15} other organic radicals per puff (Repine et al. 1997).

A number of comparisons between smokers and nonsmokers have been made with respect to measures of biomolecular oxidative damage, including oxidative injury to DNA, proteins, and lipids. A widely used assay for quantifying oxidative damage to DNA is 8-hydroxydeoxyguanosine (8-OH-dG). The assay measures hydroxyl radical-induced DNA damage at C8 of guanine (Lagorio et al. 1994), which has been linked experimentally to cigarette smoke condensate (Leanderson and Tagesson 1990). Cultured human lung cells exposed to cigarette smoke had 70 percent higher 8-OH-dG levels than unexposed cells (Leanderson and Tagesson 1992). DNA from the lung tissue of smokers had 42 percent higher 8-OH-dG levels than the DNA from nonsmokers, and 8-OH-dG concentrations increased according to the number of cigarettes smoked per day (Asami et al. 1997).

Studies comparing 8-OH-dG levels in DNA from smokers and nonsmokers are summarized in Table 6.2. In general, regardless of the biologic material, smokers tend to have greater damage. A strong dose-response association with the number of cigarettes smoked was observed in one study (Lodovici et al. 2000), but an inverse dose-response trend was observed in another (van Zeeland et al. 1999). When levels of 8-OH-dG in circulating lymphocytes were compared before and after cigarettes were smoked, Kiyosawa and colleagues (1990) observed that 8-OH-dG levels increased 54 percent after smoking. A similar but less frequently used approach to determine biomolecular oxidative damage is to assay 8-hydroxyguanine, which has been found in leukocyte DNA (Asami et al. 1997) and in urine (Suzuki et al. 1995) of smokers at concentrations at least 90 percent higher than in nonsmokers.

Oxidative damage to proteins can occur in both amino acid residues and the peptide backbone in protein, and can be assessed by assaying protein carbonyls (Reznick et al. 1992; Eiserich et al. 1995). Studies document that exposing human plasma (Reznick et al. 1992; Eiserich et al. 1995; Panda et al. 1999) or saliva (Nagler et al. 2000) to cigarette smoke increased protein carbonyl concentrations by more than 300 percent. Compared with unexposed guinea pigs, guinea pigs exposed to cigarette smoke had plasma protein carbonyl concentrations more than 30 times greater (Panda et al. 2000). In humans, protein carbonyl concentrations in 15 smokers were 61 percent higher than in 5 comparison nonsmokers (Lee et al. 1998).

Isoprostanes constitute a specific measure of lipid peroxidation and serve as good general markers of oxidative injury (Morrow and Roberts 1996). Free radicals catalyze the peroxidation of arachidonic acid to F2-isoprostanes (Morrow and Roberts 1996). Circulating (Morrow et al. 1995) and urinary (Morrow et al. 1995; Reilly et al. 1996) isoprostane levels have been shown to be markedly higher in smokers than in nonsmokers (Table 6.2). Circulating (Morrow et al. 1995; Pilz et al. 2000) and urinary (Reilly et al. 1996; Pilz et al. 2000) isoprostane concentrations decreased at least 20 percent within two weeks of smoking cessation. Babies of smoking mothers had concentrations of isoprostane levels in their umbilical arteries and veins more than 110 percent higher than babies of nonsmoking mothers (Obwegeser et al. 1999).

Another widely used measure of free radical catalyzed lipid peroxidation is thiobarbituric acid reactive substances (TBARS) (Bonithon-Kopp et al. 1997). Comparisons of TBARS between smokers and nonsmokers have shown that (1) current smokers have higher TBARS levels—sometimes strikingly higher, (2) levels of TBARS rise after smoking, and (3) the influence of smoking on increased lipid peroxidation can be offset somewhat by administering the antioxidant micronutrients vitamins C and E (Table 6.2).

Antioxidant Depletion

Even as smokers are exposed to the oxidative stress of regularly inhaling cigarette smoke, substantial evidence shows that blood levels of individual antioxidant micronutrients are lower in current smokers than in nonsmokers. This association has been clearly demonstrated for vitamin C (McClean et al. 1976; Bolton-Smith et al. 1991; Ross et al. 1995; Lykkesfeldt et al. 1997) and for total and selected carotenoids including α-carotene, β-carotene, and cryptoxanthin (Aoki et al. 1987; Stryker et al. 1988; Bolton-Smith et al. 1991; Pamuk et al. 1994; Ross et al. 1995; Brady et al. 1996; Alberg et al. 2000). For vitamin C (Brook and Grimshaw 1968; Buiatti et al. 1996; Marangon et al. 1998) and several of the specific carotenoids (Comstock et al. 1988; Nierenberg et al. 1989; Buiatti et al. 1996; Marangon et al. 1998), circulating concentrations tend to decline with increasing number of cigarettes smoked.

Table 6.2 Studies on the association between smoking and oxidative injury

Study	Population	Group
	8-OH-dG* in DNA from peripheral leukocytes	
Kiyosawa et al. 1990	10 healthy male volunteers, aged 20–22 years, blood drawn before and 10 minutes after smoking 2 cigarettes in 10 minutes	Total
Takeuchi et al. 1994	79 healthy male factory workers, aged 25–59 years	Current and never Former and never
Degan et al. 1995	180 smokers and 73 nonsmokers	Total
Lee et al. 1998	20 healthy volunteers, 15 smokers, aged 19–31 years	Total
van Zeeland et al. 1999	102 healthy adults, aged 25–45 years	Current and never Former and never
Lodovici et al. 2000	56 healthy male and female volunteers, aged 18–64 years	Current and never Former and never
	8-OH-dG in DNA from urine	
Loft et al. 1992	83 randomly selected persons, aged 40–64 years	Total
Tagesson et al. 1993	129 persons (30 asbestos-exposed workers, 28 rubber workers, 30 azo dye factory workers, 41 controls)	Total Controls Asbestos-exposed Rubber Azo dye
Lagorio et al. 1994	65 randomly sampled gas station attendants, Italy	Current and never Former and never
Tagesson et al. 1996	343 workers from the Swedish art glass industry	Total Men Women
	Protein carbonyls in plasma	
Lee et al. 1998	20 healthy volunteers, 15 smokers, aged 19–31 years	Total

*8-OH-dG = 8-hydroxydeoxyguanosine.

Results			
Precessation	**Postcessation**	**Percentage difference**	**Comments**
3.3 (before smoking)	5.1 (after smoking)	54.5	8-OH-dG / 10^6 dG
1.10 (never) 1.10 (never)	1.075 (current) 1.00 (former)	-2.3 -9.1	8-OH-dG / 10^5 dG; numbers were abstracted from figure
5.94	7.14	20.2	8-OH-dG mol / 10^5 mol dG
2.21	3.61	63.3	8-OH-dG / 10^5 dG
34.0 (never) 34.0 (never)	29.3 (current) 35.2 (former)	-13.8 3.5	8-OH-dG / 10^6 dG
15.3 (never) 15.3 (never)	33.1 (current) 17.8 (former)	116.3 16.3	8-OH-dG / 10^6 dG
2.13	3.20	50.2	8-OH-dG pmol / 24 hours
1.367 1.01 1.38 1.60 2.10	1.478 1.13 1.41 1.34 1.88	8.1 11.9 2.2 -16.3 -10.5	Weighted average; 8-OH-dG µmol / mol creatinine
1.32 (never) 1.32 (never)	1.41 (current) 1.29 (former)	6.8 -2.3	8-OH-dG µmol / mol creatinine
11.5 12.6 9.3	13.4 14.1 12.1	16.5 11.9 30.1	Weighted average; 8-OH-dG nmol / L
1.59	2.56	61.0	Protein carbonyl / nmol / mg of protein

Table 6.2 Continued

Study	Population	Group
	Isoprostanes in plasma	
Morrow et al. 1995	Pilot: 16 smokers, 8 nonsmokers Main study: 10 smokers, 10 age- and gender-matched nonsmokers	Pilot: free Pilot: esterified Main: free Main: esterified Main: cessation / free Main: cessation / esterified
Pilz et al. 2000	47 smokers ready to quit smoking, aged 30–66 years	Total: cessation
	Isoprostanes in urine	
Morrow et al. 1995	10 smokers, 10 age- and gender-matched nonsmokers	Total
Reilly et al. 1996	24 chronic smokers, 24 age- and gender-matched controls, aged 20–47 years	Total Moderate Heavy Cessation
Practicò et al. 1998	6 smokers, 6 nonsmokers, aged 31–45 years	Total IPF_{2a} pg / ng creatinine Total 8-iso PGF_{2a} pg creatinine
Pilz et al. 2000	47 smokers ready to quit smoking, aged 30–66 years	Total: cessation
	Thiobarbituric acid reactive substances (TBARS) in malondialdehyde (MDA)	
Harats et al. 1989	16 smokers, 12 age-matched nonsmokers, aged 23–56 years	Total (stored) Total (fresh)

[†]LDL = Low-density lipoprotein.

Results			
Precessation	**Postcessation**	**Percentage difference**	**Comments**
90	166	84.4	
290	496	71.0	
103	242	135.0	
345	574	66.4	
250	156	60.3	2 weeks after cessation
624	469	33.0	
490	300	63.3	pmol/L (serum in plasma) 3 weeks after cessation
415	870	109.6	pmol/nmol creatinine
63.7	122.5	92.3	pmol/mmol creatinine
54.1	92.7	71.3	
54.1	176.5	226.2	dose-response relationship
145.5	114.6	27.0	
1,525	740	106.1	Cox-dependent and independent
270	95	184.2	excretion in human urine
580	330	75.8	3 weeks after cessation; pg 8-epi-PGF_{2a}/mg creatine
0.287	0.198	44.9	Smokers had not smoked for
0.180	0.154	16.9	24–40 hours Plasma: nmol/mL LDL[†]: nmol/mg protein

Table 6.2 Continued

Study	Population	Group
Thiobarbituric acid reactive substances (TBARS) in malondialdehyde (MDA)		
Harats et al. 1990	17 smokers before and 2 weeks after vitamin C supplementation; 10 smokers before and 90 minutes after smoking	Study I No treatment Vitamin C treatment Study II: TBARS in LDL No treatment Vitamin C treatment Vitamin E treatment Study II: Plasma TBARS No treatment Vitamin C treatment Vitamin E treatment
Scheffler et al. 1990	17 male smokers, 21 male nonsmokers, mean age 30–32 years	Time course of TBARS in LDL during incubation 0 hours 1 hour 2 hours 3 hours 4 hours 5 hours 6 hours
Scheffler et al. 1992	17 smokers, 21 nonsmokers	Incubation for 3 hours 1 week storage
Duthie et al. 1993	242 adults, aged 45–69 years	Total
Miller et al. 1997	107 nonsmokers, 14 smokers, mean age 48–49 years	Total
Mosca et al. 1997	90 adults, aged 39–80 years	Total: former vs. never
Motoyama et al. 1997	40 healthy males, 20 smokers, 20 nonsmokers, aged 26–35 years	Total Smokers: pre/postsmoking
Berr 1998	74 men and 815 women, aged 59–71 years	Men Women
Durak et al. 1999	61 adults, aged 25–81 years	Total

Results			
Precessation	**Postcessation**	**Percentage difference**	**Comments**
Before smoking	After smoking		Plasma: nmol/mL
0.106	0.187	76.4	LDL: nmol/mg protein
0.138	0.145	5.1	
0.584	1.275	118.3	
0.683	1.333	95.2	
0.627	0.663	5.7	
0.106	0.197	85.4	
0.107	0.118	10.3	
0.119	0.123	3.4	
			LDL: nmol/mL
1	1	0	
1	1	0	
9	4	125	
14	7	100	
14	7	100	
14	7	100	
14	7	100	
14.2	7.3	94.5	
12.0	9.8	22.4	
1.87	1.76	6.3	nmol/mL
24	21	14.3	µmol/mL
0.05 (former)	0.07 (never)	-28.6	LDL: µmol/nmol
1.8	1.3	38.5	nmol/mL
2.7 (after smoking)	1.7 (before smoking)	35.3	After: 10 minutes Before: at least 8 hours of abstaining from smoking
2.97	2.90	2.41	µmol/L in plasma
3.06	2.96	3.4	
0.55	0.31	77.4	nmol/g tissue

Whether the differences in antioxidant levels across smoking categories reflect direct depletion or differing dietary intake has been controversial. If smoking directly depletes antioxidant micronutrients, the effect would presumably be acute. In fact, levels of vitamin C and selected carotenoids increased when measured in persons after 84 hours without smoking a cigarette (Brown 1996), and an experimental exposure of plasma equivalent to six puffs of cigarette smoke completely depleted the ascorbic acid present in the serum (Handelman et al. 1991; Eiserich et al. 1995). When measurements were taken at baseline and 20 minutes after smoking a cigarette, decreases in circulating micronutrient concentrations were observed (Yeung 1976).

Smoking and the Leukocyte Count

Studies show that smokers when compared with nonsmokers have generally heightened inflammation, increased white blood cell counts that remain elevated after cessation, and increased levels of other markers of inflammation such as C-reactive protein (Allen et al. 1985; Das 1985; de Maat et al. 1996; Tracy et al. 1997; Danesh et al. 1999).

The association between smoking and the leukocyte count has been extensively investigated, with numerous studies showing that current smokers have higher leukocyte counts than nonsmokers (Table 6.3). In most studies, the increase was 20 percent or more in smokers compared with nonsmokers and was present across strata of age, gender, and race. The leukocyte count increases with the number of cigarettes smoked per day and with the depth of inhalation. Similar dose-response trends were evident in other studies that did not lend themselves to inclusion in the summary tables (Petitti and Kipp 1986; Schwartz and Weiss 1991). Dose-response trends tend to be weaker when examined in relation to either pack-years[1] or duration of smoking, suggesting that smoking has an immediate effect on the leukocyte count.

The findings from former smokers are consistent with both an immediate and a persistent effect of smoking. In comparisons with lifetime nonsmokers (Table 6.4), former smokers consistently have higher white blood cell counts, but the difference is smaller than that between current smokers and lifetime nonsmokers. In most of the studies, the leukocyte counts for former smokers were only about 5 percent greater than those for lifetime nonsmokers. The excess is persistent (Petitti and Kipp 1986; Schwartz and Weiss 1991; Sunyer et al. 1996), although it decreases with increasing duration of cessation, becoming closer to the average counts found in lifetime nonsmokers (Yarnell et al. 1987; Hansen et al. 1990b). A short-term (overnight) abstention from cigarettes did not strongly influence the counts (Noble and Penny 1975).

Prospective cohort studies have tracked changes in leukocyte counts in relation to changes in smoking. In a study of Kaiser Permanente enrollees in the San Francisco Bay area, the leukocyte counts increased 12 percent among those who started smoking during the follow-up, but it decreased 7 percent among smokers who had quit during the follow-up (Friedman et al. 1973). In a subsequent study that compared leukocyte counts of 9,392 persistent smokers with those of 3,825 smokers who had quit, the quitters experienced significantly higher declines (Friedman and Siegelaub 1980). In a cohort of homosexual men seronegative for human immunodeficiency virus (HIV), Sunyer and colleagues (1996) observed that decreases in smoking were followed by decreased white blood cell counts, and increases in smoking were followed by increased white blood cell counts. Furthermore, changes in white blood cell counts were proportional to changes in smoking patterns (Table 6.5).

These observations of inflammatory markers, particularly the leukocyte counts, are consistent with the induction of systemic chronic inflammation in smokers, perhaps reflecting the substantial oxidant load from habitual cigarette smoking. Studies of former smokers suggest that this state of inflammation does not simply reflect an acute effect. These observations support one of the mechanisms, oxidative stress, proposed as contributing to the general effects of smoking on health.

Epidemiologic Evidence

Absenteeism

Absenteeism from work is frequent and costly (Steers and Rhodes 1978); its multiple causes include individual and organizational factors (Steers and Rhodes 1978). Researchers investigating the effect of smoking on absenteeism face the challenges of controlling for potential confounding by individual-level factors such as alcoholism, and specifying how smoking could act in combination with other factors at both

[1]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

individual and group levels. While the literature is extensive (Table 6.6), the studies vary in the success with which these challenges have been met, partially reflecting the extent and quality of available data.

Current Smokers

In studies with varying designs conducted in diverse locations, cigarette smokers consistently have had higher rates of absenteeism than nonsmokers (Table 6.6). The evidence also indicates that the duration of sickness absences tends to be longer for smokers and smokers miss more cumulative worktime than nonsmokers. The association between smoking and absenteeism has been observed in both men and women of all ages. Sickness absences have been measured in a variety of ways, including lost worktime per unit of time, episodes of absenteeism, and the duration of absences. The finding that smoking is associated with absenteeism, regardless of the index used, documents consistency of the observed association. Although most studies were cross-sectional or retrospective in design, two were prospective cohort studies (North et al. 1993; Niedhammer et al. 1998) and another studied smoking histories in relation to workplace attendance records during the preceding nine years (Holcomb and Meigs 1972). The findings of these prospective studies confirm that smoking preceded the absenteeism. In a few studies, the association with smoking was observed primarily in men but not in women (Green et al. 1992; North et al. 1993), but in general the findings have been consistent across all of the subgroups studied. Of the 30 studies that were the sources for the data abstracted into Table 6.6, 17 studies found that absenteeism among smokers was at least 20 percent greater than among nonsmokers in all subgroups.

Two additional reports not included in the table also provide evidence of an association between smoking and absence frequency (Ferguson 1973; Donaldson et al. 1999). In a study of 516 men employed in four occupational groups in Australia, Ferguson noted that ". . .the employee with repeated absence also tended ($p < 0.10$), more often than the resister" (employee without repeated absences) ". . .to smoke more than 15 cigarettes daily" (Ferguson 1973, p. 336). In a study of 146 lumber company employees, a tobacco use scale was not correlated ($r = 0.01$) with absenteeism (Donaldson et al. 1999).

In several studies summarized in Table 6.6 that assessed the relationship between current smoking and absenteeism (Athanasou 1979; Andersson and Malmgren 1986; Hawker and Holtby 1988; Bertera 1991), current smokers were compared with all nonsmokers, including former smokers. As discussed in the following section, absenteeism rates among former smokers are persistently elevated compared with those of lifetime nonsmokers. Thus, using an "unexposed" comparison category that includes former smokers along with lifetime nonsmokers will dilute associations that would be estimated when using a "pure" unexposed category consisting solely of persons who have never smoked.

In the two studies that assessed the dose-response relationship with the number of cigarettes smoked, the likelihood of being absent increased strongly with the number of cigarettes smoked per day (Lowe 1960; Holcomb and Meigs 1972). In a retrospective cohort study of 226 male factory employees in Connecticut that included eight years of follow-up, the rate of long-term absences increased 43 percent, 57 percent, and 100 percent compared with nonsmokers for those who smoked less than one pack, one pack, and more than one pack of cigarettes per day, respectively (Holcomb and Meigs 1972). In a study of more than 3,300 male General Electric employees in England, the number of days absent for medical reasons increased 11 percent, 13 percent, 26 percent, and 57 percent compared with nonsmokers for those who smoked 1 to 9, 10 to 19, 20 to 29, and 30 or more cigarettes per day, respectively (Lowe 1960).

This body of evidence shows increased absenteeism among smokers, while providing only limited information on the reasons for the absences. A significant proportion of sickness absences in smokers would be expected to be due to smoking-associated illnesses. Athanasou and colleagues (1981) hypothesized that smoking acts as a susceptibility factor, increasing the risks for other harmful occupational exposures. In one study, smoking was associated with a significantly increased likelihood of absences resulting from problems as diverse as back symptoms, digestive tract symptoms, and neck and upper limb symptoms (Dimberg et al. 1989). A recent review summarizing 38 studies showed an increased risk for back pain in smokers compared with nonsmokers in the majority of studies (Goldberg et al. 2000). In another study, absences were elevated not only for "medical reasons" but also for "other" reasons (Lowe 1960). Substantial evidence also documents that smokers are more likely than nonsmokers to have on-the-job injuries (Lowe 1960; Naus et al. 1966; Reynolds et al. 1994; Forrester et al. 1996). Because smoking increases absences for a broad set of health problems, and not just specific smoking-associated illnesses, the underlying causal pathways are likely to be multiple and general, reflecting the systemic nature of the effects of smoking.

Table 6.3 Studies on the association between current smoking and white blood cell counts

Study	Population	Group
Howell 1970	2,483 men, aged 40–54 years	Total
Corre et al. 1971	4,264 men, aged 46–52 years	Total
Friedman et al. 1973	86,488 Kaiser Permanente enrollees	Men Women
Okuno 1973	106 men, aged 20–39 years	Total
Parulkar et al. 1973	130 Indian men, aged 16–60 years	Total
Billimoria et al. 1975	121 men and women	Men Women
Fisch and Freedman 1975	14,961 women, aged 18–60 years	Total
Helman and Rubenstein 1975	800 healthy patients, aged 20–69 years	Men Women
Noble and Penny 1975	40 male medical students, aged 20–30 years	Total
Parulkar et al. 1975	379 Indian men, aged 20–60 years	Total
Silverman et al. 1975	263 persons, aged 20–78 years	Total
Tibblin et al. 1979	1,462 women, aged 38–60 years	Total
Dodsworth et al. 1981	737 men and women, aged 18–64 years	Men Women
Zalokar et al. 1981	7,206 men, aged 43–53 years, France	Total
Heinemann et al. 1982	30 male students	Total
Mellstrom et al. 1982	449 men, aged 70 years, Goteberg, Sweden	Total
Nancy et al. 1982	100 male smokers, 100 male nonsmokers	Total
Chan-Yeung et al. 1984	2 cohorts of men (652 cedar mill workers, 440 office workers), British Columbia	Powell River Kitimat
Sparrow et al. 1984	1,510 men, aged 23–80 years	Total

Results (white blood cell counts)			
Smokers	**Nonsmokers**	**Percentage difference**	**Comments**
7,257	5,818	24.7	Per mm^3 of blood
6,549	5,705	14.8	Per mm^3 of blood
8.2 8.3	7.1 7.3	15.5 13.7	10^{-3} per mm^3 of blood; weighted averages
6,719	5,440	23.5	Per mm^3 of blood; weighted average for smokers
8,868	6,369	39.2	Per mm^3 of blood
8.0 7.0	5.5 5.8	45.5 20.7	10^{-3} per mm^3 of blood
7.59	6.26	21.2	10^{-3} per mm^3 of blood; weighted averages
8.7 8.8	7.1 7.1	22.5 23.9	10^{-3} per mm^3 of blood; weighted average
7,625	5,934	28.5	Per mm^3 of blood
9,782	7,299	34.0	Per mm^3 of blood
6,803	6,023	13.0	Per mm^3 of blood
6.1	4.9	24.5	10^{-3} per mm^3 of blood; weighted average for smokers
7.2 7.2	6.1 6.5	14.8 10.8	10^{-3} per mm^3 of blood
5,740	7,280	26.8	10^{-3} per mm^3 of blood
7.85	6.95	12.9	10^{-3} per mm^3 of blood
6.3	5.3	18.9	10^{-3} per mm^3 of blood
9,156	7,310	25.3	Per mm^3 of blood
8.4 7.6	6.7 6.2	25.4 22.6	10^{-3} per mm^3 of blood; weighted averages
8,400	6,830	23.0	Per mm^3 of blood; weighted average for smokers

Table 6.3 Continued

Study	Population	Group
Vanuxem et al. 1984	43 persons, France	Total
Carel and Eviatar 1985	35,000 Israelis, aged 20–80 years	Men Women
Nielsen 1985	82 healthy persons, aged 21–74 years	Total
Husgafvel-Pursiainen 1987	70 persons, mean age 38 years	Total
Yarnell et al. 1987	4,445 men, aged 45–59 years, from 2 communities in the United Kingdom	Caerphilly Speedwell
Chan-Yeung et al. 1988	750 male aluminum smelter workers	Total
Hansen et al. 1990b	12,866 men, aged 35–37 years	Total
Olsen et al. 1991	1,900 Dow Chemical Company employees	Men Women
Casasnovas et al. 1992	572 military academy cadets, mean age 19 years	Total
Mühlhauser et al. 1993	288 patients with diabetes	Men Women
Mercelina-Roumans et al. 1994	712 pregnant women	Total
Hogarty et al. 1995	6,837 men and women, mean age 58 years	Men Women
Bovill et al. 1996	5,201 persons, aged >64 years	Men Women
Calori et al. 1996	27 monozygotic twin pairs discordant for smoking	Total
Jensen et al. 1998	434 persons	Total

Results (white blood cell counts)			
Smokers	**Nonsmokers**	**Percentage difference**	**Comments**
8.0	5.8	37.9	10^{-3} per mm^3 of blood
8.2 7.9	7.2 7.1	13.9 11.3	10^{-3} per mm^3 of blood
7.6	5.9	28.8	10^{-3} per mm^3 of blood
9.3	6.8	36.8	10^{-3} per mm^3 of blood; weighted average for smokers
8.0 8.2	5.9 6.0	35.6 36.7	10^{-3} per mm^3 of blood; weighted average for smokers
7,560	6,113	2.37	Per mm^3 of blood; weighted average for smokers
7,553	6,094	28.9	Per mm^3 of blood
8,290 7,790	6,340 6,460	30.8 20.6	Per mm^3 of blood
8,194	7,332	11.8	Per mm^3 of blood
8.1 7.6	6.4 6.8	26.6 11.8	10^{-3} per mm^3 of blood
10.7	9.1	17.6	10^{-3} per mm^3 of blood
7.0 6.8	6.2 6.4	11.4 6.3	10^{-3} per mm^3 of blood; smokers included all ever smokers
7.6 7.3	6.3 6.1	20.6 19.7	10^9 per liter of blood
6.2	5.2	8.4	10^3 per µL of blood
7.6	5.8	31.0	10^{-3} per mm^3 of blood

Table 6.4 Studies on the association between former smoking and white blood cell counts

Study	Population	Group
Friedman et al. 1973	86,488 Kaiser Permanente enrollees	Men: 38,279 Women: 48,207
Tibblin et al. 1979	1,462 women, aged 38–60 years	Total
Zalokar et al. 1981	7,206 men, aged 43–53 years, France	Total
Mellstrom et al. 1982	449 men, aged 70 years, Goteberg, Sweden	Total
Chan-Yeung et al. 1984	2 male cohorts, British Columbia	652 cedar mill workers 440 office workers
Sparrow et al. 1984	1,510 men, aged 23–80 years	Total
Knoke et al. 1987	2,225 white men with high cholesterol	Total
Yarnell et al. 1987	4,445 men, aged 45–59 years, in 2 communities	Quit <1 year Quit 1–4 years Quit 5–9 years Quit ≥10 years
Chan-Yeung et al. 1988	750 male aluminum smelter employees	Total
Hansen et al. 1990b	12,866 men, aged 35–37 years	Quit 1–2 years Quit 2–3 years Quit 3–5 years Quit 5–10 years Quit ≥10 years
Olsen et al. 1991	1,900 Dow Chemical Company employees	Men Women
Sunyer et al. 1996	2,435 patients, aged >18 years	Total

Results (white blood cell counts)			
Former smokers	**Never smokers**	**Percentage difference**	**Comments**
7.3 7.7	7.1 7.3	2.8 5.5	10^{-3} per mm^3 of blood; weighted averages
5.1	4.9	4.1	10^{-3} per mm^3 of blood
5,840	7,280	1.7	Per mm^3 of blood
5.8	5.3	9.3	10^{-3} per mm^3 of blood
6.8 6.3	6.7 6.2	1.5 1.6	10^{-3} per mm^3 of blood; weighted averages
6,900	6,830	1.0	Per mm^3 of blood
5,558	5,355	3.8	Per mm^3 of blood
6.96 6.64 6.38 6.15	5.95 5.95 5.95 5.95	17.0 11.6 7.2 3.4	10^{-3} per mm^3 of blood; weighted averages
6,302	6,113	3.1	Per mm^3 of blood
6,371 6,343 6,297 6,285 6,212	6,094 6,094 6,094 6,094 6,094	4.5 4.1 3.3 3.1 1.9	Per mm^3 of blood
6,650 7,110	6,340 6,460	4.9 10.1	Per mm^3 of blood
6,501	6,265	3.8	Per mm^3 of blood

Table 6.5 Studies on the percentage difference in white blood cell counts stratified by smoking patterns

Study	Population	Measure of dose	Group
Howell 1970	2,483 men, aged 40–54 years	Number of cigarettes / day	Total
Corre et al. 1971	4,264 men, aged 46–52 years	Inhalation[†] Number of cigarettes / day Number of cigarettes / day	Total Noninhalers[‡] Inhalers
Okuno 1973	106 men, aged 20–39 years	Number of cigarettes / day	Total
Fisch and Freedman 1975	14,961 women, aged 18–60 years	Number of cigarettes / day	Total
Parulkar et al. 1975	379 Indian men, aged 20–60 years	Inhalation Duration of smoking Number of cigarettes / day	Total
Silverman et al. 1975	268 persons, aged 20–78 years	Pack-years[§]	Total
Tibblin et al. 1979	1,462 women, aged 38–60 years	Number of cigarettes / day	Total
Dodsworth et al. 1981	737 men and women, aged 18–64 years	Number of cigarettes / day	Men Women
Zalokar et al. 1981	7,206 French men, aged 43–53 years	Inhalation Number of cigarettes / day	Total
Sparrow et al. 1984	1,510 men, aged 23–80 years	Number of cigarettes / day	Total
Tell et al. 1985	439 Norwegians, aged 14–16 years	Number of cigarettes / day	Males Females
Petitti and Kipp 1986	63,041 enrollees in Kaiser Permanente	Number of cigarettes / day	White men White women Black men Black women
Husgafvel-Pursiainen 1987	70 persons, mean age 38 years	Number of cigarettes / day	Total
Knoke et al. 1987	2,225 white men with high cholesterol	Number of cigarettes / day	Total

*NR = Data were not reported.
[†]Inhalation = Inhaling cigarette smoke.
[‡]Noninhalers = Not inhaling cigarette smoke.
[§]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Nonsmokers (referent)	Percentage difference: Smokers, by category of dose (1 = low) 1	2	3	4	5	6	Comments
0	22.0	30.1	NR*	NR	NR	NR	None
0	6.3	23.5	NR	NR	NR	NR	None
0	1.7	7.4	9.8	10.0	NR	NR	
0	10.8	21.5	27.7	29.7	NR	NR	
0	18.9	37.9	NR	NR	NR	NR	
0	10.9	28.1	NR	NR	NR	NR	Weighted averages
0	31.5	36.8	NR	NR	NR	NR	None
0	31.5	34.9	35.5	38.4	NR	NR	
0	28.1	28.1	40.1	38.9	NR	NR	
0	6.5	12.9	16.9	14.2	11.2	27.2	None
0	8.2	24.5	24.5	34.7	38.8	NR	None
0	12.9	1.6	17.7	14.5	29.0	NR	None
0	4.9	3.3	13.1	16.4	31.1	NR	
0	6.5	26.8	NR	NR	NR	NR	None
NR	12.5	24.6	29.3	33.6	NR	NR	
0	19.4	29.2	NR	NR	NR	NR	None
0	5.8	13.5	NR	NR	NR	NR	None
0	-3.8	16.4	NR	NR	NR	NR	
0	10.4	17.9	25.4	23.9	31.3	NR	None
0	8.5	15.5	21.1	22.5	19.7	NR	
0	10.0	13.3	21.7	18.3	18.3	NR	
0	4.5	10.4	13.4	16.4	10.4	NR	
0	47.1	33.8	NR	NR	NR	NR	None
0	21.9	36.8	46.6	49.0	54.9	NR	None

Table 6.5 Continued

Study	Population	Measure of dose	Group
Yarnell et al. 1987	4,445 men, aged 45–59 years, in 2 communities	Number of cigarettes / day	Caerphilly Speedwell
Chang-Yeung et al. 1988	750 male aluminum smelter workers	Number of cigarettes / day	Total
Hansen et al. 1990b	12,866 men, aged 35–37 years	Number of cigarettes / day Inhalation[†]	Total Total
Olsen et al. 1991	1,900 Dow Chemical Company employees	Number of cigarettes / day Pack-years[§]	Men Women Men Women
Sunyer et al. 1996	2,435 patients, aged >18 years	Number of cigarettes / day	Total
Jensen et al. 1998	434 (298 smokers, 136 nonsmokers)	Number of cigarettes / day	Total

[‡]Inhalation = Inhaling cigarette smoke.
[§]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Former Smokers

The evidence is consistent that former smokers are less likely to be absent from work compared with persistent smokers. Former smokers tend to have somewhat higher absenteeism rates than persons who have never smoked (Table 6.7), but the increases are much smaller than those for current smokers. The analyses performed by Wooden and Bush (1995) with former smokers (n = 4,812) in the 1989–1990 Australian National Health Survey illustrate the seemingly paradoxic relationship between quitting smoking and absenteeism. In a multiple regression model that included both the duration of active smoking and time since quitting, the number of years that a former smoker had smoked remained a strong predictor of absenteeism, and the likelihood of absences declined gradually over time since cessation (Wooden and Bush 1995). Similarly, Manning and colleagues (1989) found differences between recent and sustained quitters, and observed considerably higher absenteeism rates for recent quitters compared with long-term quitters. These results indicate that both prior smoking history and time since quitting are factors strongly associated with absenteeism, but in opposite directions. This pattern may arise because some smokers may quit when diagnosed with an illness caused by smoking, and the recent quitters may thus already have a smoking-induced illness that predisposes them to lost worktime.

In interpreting evidence linking smoking to a diminished health status, including absenteeism, untangling the direct effects of smoking from the indirect effects is challenging, as smokers and nonsmokers may differ in potential confounding factors. Nonetheless, given the scope of the evidence available and the diversity of the populations studied, the literature does provide insights into the role of smoking as a cause of absenteeism.

With regard to confounding, alcohol use is a major factor of concern. Alcohol use has been linked to absenteeism in some studies, and smokers drink more than nonsmokers (Smith 1970; Turner 1988; Ault

Percentage difference							
	Smokers, by category of dose (1 = low)						
Nonsmokers (referent)	**1**	**2**	**3**	**4**	**5**	**6**	**Comments**
0	30.4	37.2	40.1	NR	NR	NR	None
0	33.4	36.4	41.8	NR	NR	NR	
0	17.7	24.7	28.7	NR	NR	NR	None
0	11.2	22.1	25.5	28.2	30.7	NR	None
0	12.5	18.6	19.7	23.9	27.0	NR	
0	11.8	32.0	45.6	NR	NR	NR	None
0	2.2	23.8	34.4	NR	NR	NR	
0	13.9	26.3	32.3	42.4	NR	NR	
0	3.1	29.4	24.1	34.5	NR	NR	
0	2.4	13.5	26.4	32.1	NR	NR	None
0	31.0	46.6	NR	NR	NR	NR	None

et al. 1991; Marmot et al. 1993; Vasse et al. 1998). Smokers are also more likely to be heavy alcohol drinkers and to use illicit substances (Merrill et al. 1999; Best et al. 2000; Brain et al. 2000; Dawson 2000), and heavy alcohol and illicit substance use, rather than cigarette smoking, could increase the likelihood of workplace absences. Studies that adjusted for alcohol consumption have generally (Hendrix and Taylor 1987; Bush and Wooden 1995; Wooden and Bush 1995), but not universally (Ault et al. 1991), found smoking to be associated with frequent absences, implying that the association of smoking with alcoholism is not due to confounding. Studies were not found that accounted for illicit substance use in assessing the association between smoking and workplace absences. Less likely is the possibility that the association between smoking and absences reflects confounding by characteristics that are linked both to smoking (see the section on "Health Status" later in this section) and to an increased risk for frequent absences. For example, women are consistently absent from work more often than men (Leigh 1983; Pines et al. 1985; Steinhardt et al. 1991). But women assume a disproportionate share of family responsibilities such as staying home with sick children, and the relative importance of smoking may therefore be less. Observations of persons with "psychosocial problems" (Leijon and Mikaelsson 1984) and anxiety / neuroses (Taylor 1968; Ferguson 1973) document increased risks for absenteeism, and if such persons are more likely to smoke, confounding is possible. Given the range of populations studied, confounding by psychosocial factors seems unlikely.

Of the relevant pathway factors leading to health-related absences, age is the primary demographic characteristic that is a potential modifying or confounding factor. Socioeconomic status, another potential confounding or modifying factor, is inherently restricted in studies within occupational groups. Age is associated with both absenteeism (Pines et al. 1985) and health status. The association between smoking and absenteeism has been observed consistently across a broad spectrum of age strata in the summarized

Table 6.6 Studies on the association between current smoking and absenteeism

Study	Population	Group
Lowe 1960	3,341 male General Electric Company employees, England	Total Medical reasons Other reasons
Holcomb and Meigs 1972	226 male factory employees	Total
Wilson 1973	1970 National Health Interview Survey, persons aged ≥17 years	Total Men Women 17–44 years 45–64 years ≥65 years
Athanasou 1979	424 persons, aged 15–67 years	Men Women
U.S. Department of Health and Human Services 1980	Representative sample of U.S. population aged ≥17 years	1965 Men Women 1977 Men Women
Janzon et al. 1981	1,037 Swedish men, aged 47–48 years	Total
Smith et al. 1981	826 staff members from 12 Australian organizations	Men Women

Results			
Smokers	**Nonsmokers**	**Percentage difference**	**Comments**
Number of days absent during the year			None
11.19	9.81	4.1	
6.59	5.49	20.0	
4.61	4.32	6.7	
Total days lost per person-year			Short-term: <7 days (unverified medical absences)
6.37	4.42	44.1	
Absence rate: short-term			Long-term: ≥10 days (verified medical absences) during 1956–1964
0.96	0.38	152.6	
Days lost: short-term			
1.89	0.95	98.9	
Absence rate: long-term			
0.10	0.07	42.9	
Days lost: long-term			
4.48	3.47	29.1	
Mean workdays lost per year			None
6.3	4.4	43.2	
5.8	3.7	56.8	
7.4	5.1	45.1	
5.8	3.8	52.6	
7.2	5.7	26.3	
7.7	4.3	79.1	
Duration of sickness absence (days)			Nonsmokers included never smokers plus former smokers
1.15	0.68	69.1	
1.05	1.03	1.9	
Workdays lost per year due to illness and injury per currently employed persons			None
5.9	4.6	28.3	
6.6	4.8	37.5	
5.9	4.2	40.5	
6.6	5.7	15.8	
Percent who used sick leave >3 times during the past year			None
13	4	225.0	
Mean number of days off work			Ratio of days off work for smokers compared with nonsmokers
1.59	1.0	59.0	
1.36	1.0	36.0	

Table 6.6 Continued

Study	Population	Group
Leigh 1983	1,200 participants in the 1973 Quality of Employment survey, based on a nation-wide probability sample	Men White collar Blue collar Women White collar Blue collar
Parkes 1983	221 nursing students, aged 18–25 years	Total
Andersson and Malmgren 1986	1,313 Saab employees, aged 50–59 years, Sweden	Wage earners Salaried
Van Tuinen and Land 1986	406 Missouri Department of Health employees	Total Men Women
Hendrix and Taylor 1987	463 U.S. Department of Defense employees	Total
Blake et al. 1988	1,230 army recruits in basic training	Total
Hawker 1988	252 female student nurses	Total
Dimberg et al. 1989	2,814 Volvo employees, Sweden	Total
Gallop 1989	169 pulp and paper industrial company employees	Self-reported records (n = 82) Payroll records
Manning et al. 1989	324 employees of 2 companies, aged 20–75 years	Baseline Short-term Long-term 1-year follow-up Short-term Long-term

*OR = Odds ratio.

Results			
Smokers	**Nonsmokers**	**Percentage difference**	**Comments**
Mean number of absences during the past 2 weeks			OR*
1.07	1.0	7.0	
0.72	1.0	-28.0	
1.50	1.0	50.0	
1.89	1.0	89.0	
1.23	1.0	23.0	
2.19	1.0	119.0	
Mean number of absences during 6 months			None
3.46	1.95	77.4	
Mean number of days absent			Nonsmokers included never smokers plus former smokers
26	24	8.3	
20	16	25.0	
Mean hours of sick leave per month			None
5.0	4.3	16.3	
4.5	3.7	21.6	
5.4	4.7	14.9	
Average number of sick days in the past 6 months			None
3.2	2.9	10.3	
Mean time spent in the clinic for visits related to upper respiratory infections (hours)			Not absenteeism per se; military conditions controlled confounding
30.6	17.3	76.9	
Percent absent >7 days (yes / no)			Nonsmokers included never smokers plus former smokers
37.5	15.0	150.0	
Average days lost in 1 year			None
21	14	50.0	
Mean illness absences last year			Payroll records were used to verify self-reported records
5.1	4.1	24.4	
10.3	7.9	30.4	
Mean hours absent per month			Short-term: ≤2 days Long-term: >2 days
2.15	1.69	27.2	
1.44	0.78	84.6	
1.73	1.17	47.9	
1.85	1.67	10.8	

Table 6.6 Continued

Study	Population	Group
Batenburg and Reinken 1990	907 employees from 4 worksites, employed at least 12 months	Men by age Total <20 years 20–29 years 30–39 years 40–49 years ≥50 years Women by age Total <30 years 30–39 years ≥40 years
Jones et al. 1990	1,893 Johnson & Johnson Company employees, aged 17–45 years	1979 1980 1981
Ault et al. 1991	2,406 (subset of 5,000) randomly sampled U.S. families; data were collected in 1967	Total
Bertera 1991	45,976 DuPont employees	Total Total
Low and Mitchell 1991	30 steel foundry workers, mean age 33.5 years	Total Total Total
Green et al. 1992	5,826 employees of 21 Israeli factories, aged 20–64 years	Men 20–44 years 45–64 years Women 20–44 years 45–64 years Men 20–44 years 45–64 years Women 20–44 years 45–64 years

Results			
Smokers	**Nonsmokers**	**Percentage difference**	**Comments**
Sickness absence hours			Authors noted that male nonsmokers aged ≥50 years had medical conditions predisposing them to absenteeism
3.9	3.5	11.4	
3.7	3.4	8.8	
4.0	3.6	11.1	
4.0	3.3	21.2	
3.6	2.9	24.1	
3.9	4.5	-13.3	
3.6	3.1	16.1	
3.0	3.1	-3.2	
3.8	2.7	40.7	
4.1	3.6	13.9	
Mean sick hours per year			None
49.5	31.4	45.2	
52.8	37.7	40.1	
54.2	38.5	40.8	
Days absent from work			The association disappeared when the effects of other job characteristics were properly assessed
8.37	6.49	29.0	
Mean annual illness days			Nonsmokers included never smokers plus former smokers
3.69	2.79	32.3	
Mean annual illness costs			
$3,971.27	$3,011.23	31.9	
Mean number of absence episodes during the year			It is unclear how the total percentage difference could occur, given the results for the number and duration of absence episodes
6.0	5.0	20.0	
Mean duration of episodes in days			
2.0	1.0	100.0	
Total days absent during the year			
6.0	9.0	-33.3	
Mean days lost over 2 years			The percentages noted in italics were adjusted for age and occupation (and also present cause-specific data)
9.99	7.40	*35.0*	
8.57	6.44	33.1	
14.45	11.15	29.6	
15.19	16.13	*-5.8*	
13.91	13.69	1.6	
17.49	24.93	-29.8	
Mean days per absence episodes			
5.17	4.65	11.2	
9.09	7.51	21.0	
3.86	4.04	-4.5	
7.07	7.66	-7.7	

Table 6.6 Continued

Study	Population	Group
Ryan et al. 1992, 1996	2,537 U.S. Postal Service employees	Total 1-year follow-up 2-year follow-up
North et al. 1993	10,314 London civil servants, aged 35–55 years, prospective cohort	 Men Women Men Women
Halpern and Warner 1994	1990 U.S. National Health Interview Survey (nationally representative sample)	Total
Post et al. 1994	405 workers at an animal feed mill, mean ages 38 years (clerks) and 42 years (blue collar), Netherlands	 Clerks Blue collar
Bush and Wooden 1995	1989 Australian National Health Survey; n = 21,984 employed persons from randomly selected households	 Men Women
Tsai et al. 1997	2,287 Shell Oil Company employees, mean age 36 years	 Men Women Men Women
Niedhammer et al. 1998	12,555 men (aged 40–50 years) and women (aged 35–50 years), prospective cohort	 Men Women Men Women

Results			
Smokers	**Nonsmokers**	**Percentage difference**	**Comments**
Mean absence rate			None
5.4	4.1	31.7	
7.9	5.8	36.2	
Periods of absence: short			Adjusted rate ratios; short-term: unverified medical absences; long-term: verified medical absences
1.46	1.0	46.0	
1.09	1.0	9.0	
Periods of absence: long			
1.81	1.0	81.0	
1.37	1.0	37.0	
Work-loss days past 2 weeks			
1.48	1.0	48.0	OR
Limitations of ability to work			
1.27	1.0	27.0	OR
Absence prevalence rate			
2.36	1.0	136.0	OR
1.64	1.0	64.0	OR
Any absence 2 weeks before the interview			Adjusted OR; also adjusted for health status and health indicators
1.43	1.0	43.0	
1.32	1.0	32.0	
Average duration of absence (days)			None
6.1	3.5	74.3	
6.8	3.6	88.9	
Morbidity frequency rate			
28.5	13.3	114.3	
20.4	13.2	54.5	
Periods of absence			Adjusted rate ratios
1.24	1.0	24.0	
1.26	1.0	26.0	
Absence days			
1.45	1.0	45.0	
1.26	1.0	26.0	

results, implying that the association does not reflect confounding by age.

Only a few studies provide prospective data concerning absenteeism following smoking cessation; the findings suggest that smoking cessation is associated with better attendance at work. A particularly informative study conducted with employees of a North Carolina pharmaceutical company compared the attendance patterns of former smokers before and after quitting with attendance patterns of a matched group of persistent smokers (Jackson et al. 1989). In the time preceding smoking cessation by the cessation group, the persistent smokers tended to have fewer absences than the smokers who went on to stop smoking. However, during the three years following cessation, the mean number of annual sick days declined among those who quit. Absences continued to increase for persistent smokers, leading to a widening gap in absences between the two groups. The study was small, with only 70 persons participating. In a randomized trial of nine worksite smoking cessation programs, employees who were smokers at baseline had a significant reduction ($p = 0.002$) in self-reported sick days after stopping smoking (Jeffrey et al. 1993). In another study evaluating a workplace health promotion program that reduced smoking prevalence, the authors reported significant reductions in absenteeism for program participants but not for nonparticipants (Wood et al. 1989).

The evidence that reduced absenteeism follows cessation complements findings based on comparisons of current smokers with nonsmokers. The reduced rate after cessation supports a causal interpretation, rather than attributing the association to an indirect pathway or to confounding factors.

In summary, there is consistent evidence demonstrating that employees who are current smokers have a greater likelihood of absences from work compared with employees who have never smoked. Additional evidence is needed on dose-response trends and, more importantly, on changes in absence rates before and after smoking cessation. Other reviewers have concluded that reduced absenteeism could lead to potential savings that can be accrued from smoking cessation programs in the workplace (Kristein 1983; Warner et al. 1996).

Medical Services Utilization

Medical services utilization provides another measure of the global effects of smoking on health. The most important utilization indicators in studies on smoking can be grouped into three general categories: (1) costs, (2) outpatient visit rates, and (3) hospitalization rates. Interpreting these findings requires consideration of the many factors influencing medical services utilization. Smokers, for example, are less likely than nonsmokers to use preventive services such as screening (Beaulieu et al. 1996; Edwards and Boulet 1997). However, the high incidence of smoking-induced diseases among smokers will tend to drive their medical care needs. The socioeconomic and educational differences between smokers and nonsmokers also complicate data interpretation because of potential confounding. Comparisons of smokers within well-defined groups, such as particular workforces or health care plans, should provide unbiased comparisons.

Costs

In evaluating the relationship between smoking and medical care costs, only those studies directly addressing expenditures were considered (Table 6.8). The literature on comparative lifetime costs of medical care for smokers and nonsmokers based on assumed models and projections was not considered relevant to this chapter. Of the seven studies reviewed, six showed the medical costs of smokers to be greater by at least 15 percent in at least one subgroup. In one study of enrollees in a health maintenance organization, smokers had costs 25 percent higher than nonsmokers among those younger than 65 years of age, but few differences were observed in those age 65 years or older (Terry et al. 1998). Only the study by Vogt and Schweitzer (1985) on enrollees in Kaiser Permanente found no differences between smokers and nonsmokers.

Two studies not included in Table 6.8 are also relevant. In a population of retirees followed for one year, smoking was associated with added health care costs of more than $1,900 per year per pack of cigarettes smoked per day, after adjusting for age, gender, education, seat belt use, and alcohol consumption (Leigh and Fries 1992). In a study conducted as part of a worksite health promotion program in Birmingham, Alabama, smokers were found to have incurred more costs than nonsmokers, but the data were not presented (Weaver et al. 1998).

Outpatient Services

In several studies (Table 6.8), smokers were at least 15 percent more likely than nonsmokers to use outpatient services (Peters and Ferris 1967; Palmore 1970; Chetwynd and Rayner 1986; Freeborn et al. 1990);

one study found an increased likelihood of 6 percent (Rice et al. 1986). In studies that stratified age and gender, strong associations with smoking were observed in particular groups. Male smokers were more frequent users of outpatient services than were male nonsmokers, but this difference was not found among females in one study (Oakes et al. 1974). In another study, this gender difference occurred in young but not old persons (Ashford 1973). Three studies showed only small differences in the use of outpatient services between smokers and nonsmokers (Vogt and Schweitzer 1985; Halpern and Warner 1994; Miller et al. 1999).

The frequency of outpatient visits does not appear to increase with the number of cigarettes smoked (Peters and Ferris 1967; Balarajan et al. 1985; Marsden et al. 1988). However, regardless of the number of cigarettes smoked, some studies documented a large difference in the number of visits by smokers compared with nonsmokers.

Hospitalization

In all but one of the studies considered (Terry et al. 1998), smokers had higher hospitalization rates than nonsmokers; the differences were at least 10 percent. In two other studies that stratified age and gender, one study found an association in males but not in females (Oakes et al. 1974), and the other study found an association only among younger females (Ashford 1973).

Additional studies corroborate the results summarized in Table 6.8. In a study of a cohort of retirees followed for one year, the number of packs of cigarettes smoked per day was significantly associated with the number of days hospitalized (Leigh and Fries 1992). In a study of 1,000 veterans accessing the Veterans Administration system in Connecticut, tobacco users were significantly more likely ($p < 0.01$) than nonusers to be hospitalized, and tobacco users were significantly more likely ($p<0.01$) than nonusers to be hospitalized and to spend more days in the hospital (Benedetto et al. 1998). In a study of Kaiser Permanente enrollees in Oregon, Pope (1982) observed a weak, nonsignificant correlation between a smoking index and hospitalization rates in the youngest age group for men and women (aged <35 years), but this association was not present in the other age groups studied.

Dose-response data are available from two prospective cohort studies (Table 6.9). In the Coronary Drug Project, the five-year hospitalization rates for smokers compared with nonsmokers plateaued at the lowest smoking category, and were more compatible with a threshold relationship than with a nonthreshold dose-response relationship. However, it was unclear whether these analyses accounted for the higher mortality rates experienced by smokers relative to nonsmokers during the follow-up period (Coronary Drug Project Research Group 1976). In a two-year follow-up of smokers in the American Cancer Society Cancer Prevention Study I (CPS-I) a strong dose-response relationship was present: compared with those who smoked 1 to 9 cigarettes per day, those who smoked 10 to 19, 20 to 39, and 40 or more cigarettes per day had an increased likelihood of hospitalization during the follow-up period of 8.5 percent, 14.6 percent, and 28.0 percent, respectively (Hammond 1965). In a cross-sectional survey of U.S. military personnel that compared smokers with nonsmokers, those who smoked one-half of a pack or less, one pack, and one and one-half packs or more per day had increases in self-reported days hospitalized of 28.1 percent, 6.3 percent, and 54.7 percent, respectively (Marsden et al. 1988).

Former Smokers

Studies comparing the use of medical services by former smokers with lifetime nonsmokers are summarized in Table 6.10. Costs were 26 percent higher for former smokers in one study (Pronk et al. 1999), and higher for some services but not higher overall in another study (Vogt and Schweitzer 1985). In every study, former smokers were more likely than lifetime nonsmokers to use outpatient services. In a study conducted in the United Kingdom that was stratified by age and gender, smokers were more likely than nonsmokers to have general practice health care providers visit their homes for an illness (Ashford 1973). The use of outpatient services by smokers remained elevated compared with that of nonsmokers long after smoking cessation (Halpern and Warner 1994). For hospitalizations the findings were mixed, with three studies showing higher rates in former smokers (Van Peenen et al. 1986; Kaplan et al. 1992; Halpern and Warner 1994). In one of these studies, however, the difference was eliminated after adjusting for age, and in two other studies there were only small differences between former smokers and lifetime nonsmokers. In another study that stratified age and gender, former smokers were more likely than lifetime nonsmokers to be hospitalized in some strata, but less likely in others, without a consistent pattern (Ashford 1973).

These studies generally have not taken into account prior smoking history and time since quitting, nor have they considered whether development of a

Table 6.7 Studies on the association between former smoking and absenteeism

Study	Population	Group
Holcomb and Meigs 1972	226 male factory employees	Total
Wilson 1973	1970 National Health Interview Survey, persons aged ≥17 years	Total Men Women 17–44 years 45–64 years ≥65 years
U.S. Department of Health and Human Services 1980	Nationally representative population sample, aged ≥17 years, United States	1965 Men Women 1977 Men Women
Janzon et al. 1981	1,037 Swedish men, aged 47–48 years	Total
Gallop 1989	169 pulp and paper industrial company employees	Total self-reported records (n = 82) Payroll records
Jackson et al. 1989	70 persons (started with 100—50 matched former and persistent smokers), North Carolina pharmaceutical company	Persistent smokers 3 years precessation 2 years precessation 1 year precessation Former smokers 1 year postcessation 2 years postcessation 3 years postcessation

Results			
Former smokers	**Nonsmokers**	**Percentage difference**	**Comments**
Total days lost per person per year			Short-term: <7 days unverified medical absences Long-term: ≥10 days verified medical absences
6.37	4.42	44.1	
Absence rate: short-term			
0.75	0.38	97.4	
Absence rate: long-term			
0.10	0.07	42.9	
Mean workdays lost per year			None
5.2	4.4	18.2	
5.1	3.7	37.8	
5.3	5.1	3.9	
4.3	3.8	13.2	
5.7	5.7	0	
8.6	4.3	100.0	
Workdays lost per year due to illness and injury per currently employed persons			None
6.8	4.6	47.8	
6.7	4.8	39.6	
6.1	4.2	45.2	
5.4	5.7	-5.3	
Percent using sick leave >3 times during the past year			None
7	4	75.0	
Mean illness absences last year			Payroll records were used to verify self-reported records
4.7	4.1	14.6	
9.1	7.9	15.2	
Annual mean ranked sick days			Ranked using absent days minus days due to personal leave, death in family, jury duty
Persistent	Former		
32.9	38.1	-13.6	
30.7	40.3	-23.8	
36.5	34.5	5.8	
38.3	32.7	17.1	
41.0	30.0	36.7	
42.1	28.9	45.7	
44.7	26.3	70.0	

Table 6.7 Continued

Study	Population	Group
Manning et al. 1989	324 employees of 2 companies, aged 20–75 years	Baseline Short-term absences Recent quitters Sustained quitters Long-term absences Recent quitters Sustained quitters 1-year follow-up Short-term absences Recent quitters Sustained quitters Long-term absences Recent quitters Sustained quitters
Low and Mitchell 1991	30 steel foundry workers, mean age 33.5 years	Total
Halpern and Warner 1994	1990 U.S. National Health Interview Survey (nationally representative sample)	Time since cessation 0–2 months 3 months–1 year 2–4 years 5–10 years 11–19 years ≥20 years
Post et al. 1994	405 workers at an animal feed mill, mean ages 38 years (clerks) and 42 years (blue collar), Netherlands	Clerks Blue collar
Bush and Wooden 1995	1989 Australian National Health Survey, n = 21,984 employed persons from randomly selected households	Men: 12,839 Women: 9,145

*OR = Odds ratio.

Results			
Former smokers	**Nonsmokers**	**Percentage difference**	**Comments**
Mean hours absent per month			Short-term: ≤2 days Long-term: >2 days
2.21	1.69	30.8	Sustained: >1 year
1.47	1.69	-13.0	Recent: ≤1 year
1.38	0.78	76.9	
0.68	0.78	-12.8	
2.21	1.17	88.9	
1.15	1.17	-1.7	
1.90	1.67	13.8	
1.95	1.67	16.8	
Mean number of absence episodes during the year			None
4.5	5.0	-10.0	
Mean duration of episodes			
1.0	1.0	0	
Total days absent			
6.0	9.0	-33.3	
Work-loss days during the past 2 weeks			OR*
2.69	1.0	169.0	
1.47	1.0	47.0	
1.45	1.0	45.0	
1.31	1.0	31.0	
1.41	1.0	41.0	
1.26	1.0	26.0	
Absence prevalence			
0.74	1.0	-26.0	OR
1.22	1.0	22.0	OR
Any absence 2 weeks before the interview			OR was adjusted for demographics (age, gender, ethnicity, marital status, education, location of residence); job characteristics (employment status, hours worked, income, occupation, industry); and health risk factors (alcohol use, physical exercise, body weight); additional factors measured overall health and happiness (more specific information was not provided)
1.33	1.0	33.0	
1.19	1.0	19.0	

Table 6.7 Continued

Study	Population	Group
Wooden and Bush 1995	4,812 randomly sampled former smokers, Australian National Health Survey	
		Total
		Time since cessation
		1–4 years
		5–9 years
		10–19 years
		≥20 years
Niedhammer et al. 1998	9,065 men (aged 40–50 years) and 3,490 women (aged 35–50 years), prospective cohort	Men
		Women
		Men
		Women

disease led to quitting. The extent of smoking before quitting is a determinant of risk, and risks fall for many diseases as the duration of quitting lengthens. The somewhat inconsistent findings may reflect (1) the heterogeneity of former smokers in these studies and (2) analysis strategies that did not fully account for risk determinants in the former smokers. In an analysis of the 1990 National Health Interview Survey data that accounted for time since quitting, former smokers had significantly more hospital admissions until 10 years following cessation, at which point former smokers and lifetime nonsmokers had similar numbers of hospital admissions (Halpern and Warner 1994).

The clinical trials of Wagner and colleagues (1995) provide additional evidence. Two cessation trials followed participants and collected medical care utilization data. After six years of follow-up, quitters experienced reductions in outpatient visits, hospital admissions, and hospital days in both trials compared with persistent smokers. In contrast, medical care utilization continued to increase among persistent smokers: 7 to 15 percent for outpatient visits, 30 to 45 percent for hospital admissions, and 75 to 100 percent for days spent in the hospital. These divergent patterns in the use of medical care services resulted in substantially greater rates of hospitalization, hospital days, and outpatient visits for persistent smokers.

Age

Several studies suggest that smoking may have a greater impact on the youngest age groups compared with older age groups. More frequent use of outpatient (Peters and Ferris 1967; Newcomb and Bentler 1987) and inpatient (Newcomb and Bentler 1987) services among smokers than among nonsmokers has been observed even in adolescents and young adults, suggesting that the differences observed in smoking and nonsmoking older adults are not solely a result of smoking-induced diseases. In fact, in a few studies higher levels of service utilization were observed among smokers than among nonsmokers in the younger age groups, but such differences were either not present or were reversed in the oldest age groups. This pattern is evident in the cross-sectional analyses of the 1970 U.S. National Health Interview Survey data, a random sample of U.S. households in which both smoking men and smoking women had a markedly higher number of days hospitalized per year than their nonsmoking counterparts until they reached their mid-40s, at which point the differences between smokers and nonsmokers became more subtle (Weinkam et al. 1987).

In general, compared with nonsmokers, smokers tend to incur more medical costs, to see physicians more often in the outpatient setting, and to be

Results			
Former smokers	**Nonsmokers**	**Percentage difference**	**Comments**
ORs for incidence of absence during past 2 weeks (modeled)			Adjusted for several potential confounders
1.04	1.0	4.0	
0.53			
0.50			
0.32			
0.22			
Periods of absence			Adjusted rate ratios
1.10	1.0	10.0	
1.03	1.0	3.0	
Days absent			
1.06	1.0	6.0	
1.05	1.0	5.0	

admitted to the hospital more often. Among patients admitted to the hospital, smokers have longer lengths of stay and incur greater expenses per admission than nonsmokers. Less information is available concerning the use of medical services such as prescription drugs and emergency department visits, but increases for smokers compared with nonsmokers have also been observed with respect to these outcomes (Chetwynd and Rayner 1986; Miller et al. 1999). Although smokers use more palliative care services, as demonstrated by this review, smokers have been less likely than nonsmokers to use preventive services such as multiphasic testing (Oakes et al. 1974) and screening (Beaulieu et al. 1996; Edwards and Boulet 1997).

Postoperative Complications

In comparison with nonsmokers, smokers have been hypothesized to be at a higher risk for postoperative complications because of a greater frequency of chronic diseases, impaired pulmonary reserve, altered immune responses, and impaired wound healing. Higher rates of postoperative complications in smokers could contribute to the greater costs that they incur for health care services.

Substantial clinical and experimental research has been conducted on the relevant effects of smoking on host defenses, immune responses, and wound healing. As reviewed elsewhere in this report and in a previous Surgeon General's report (USDHHS 1990), smoking produces a range of effects on respiratory defense mechanisms that may increase the risk for postoperative pneumonia. Compromised lung function and the presence of COPD increase the risks for respiratory complications, including respiratory failure. The increased likelihood of coronary heart disease (CHD) in smokers increases the risk for cardiac events during and after surgery. In animal and clinical models, exposure to tobacco smoke and nicotine specifically impaired aspects of wound healing (Brown et al. 1986; Silcox et al. 1995; Haverstock and Mandracchia 1998; Jorgensen et al. 1998; Hollinger et al. 1999).

The literature on postoperative complications is extensive and diverse in the scope of complications associated with smoking. Table 6.11 provides evidence for lower survival rates after surgery for smokers compared with nonsmokers and suggests that this increased mortality may reflect a range of specific and nonspecific consequences of smoking, including a greater risk for postoperative complications related to the surgery. A number of reports address specific surgical complications such as flap failures, wound infections, and poor orthopedic outcomes. A similarly diverse set of reports consistently shows that smoking also increases the risk of respiratory complications.

Table 6.8 Studies on the association between current smoking and medical service costs

Study	Population	Group
	Costs	
Vogt and Schweitzer 1985	2,582 adult HMO* enrollees	Laboratory X-ray Surgery Total
Freeborn et al. 1990	515 HMO enrollees, aged >17 years	Group I (1970–1974) Group II (1970–1979)
Penner and Penner 1990	20,831 employees enrolled in a fee-for-service plan	Total Average cost per admission Average inpatient cost per day
Hodgson 1992	U.S. National Health Interview Survey, persons aged >17 years	Men Women
Callahan et al. 1998	12,581 patients who had at least 2 ambulatory visits plus 1 hospitalization, 1993–1996, aged >60 years	Total
Terry et al. 1998	5,780 HMO enrollees, aged >18 years	Aged <65 years Aged ≥65 years
Pronk et al. 1999	6,589 adult HMO enrollees, Minnesota	Total
	Outpatient services	
Peters and Ferris 1967	Harvard / Radcliffe students	Total
Palmore 1970	268 community volunteers, aged 60–94 years at baseline	Total

*HMO = Health maintenance organization.
†NR = Data were not reported.

Results			
Smokers	**Nonsmokers**	**Percentage difference**	**Comments**
$18,515	$19,772	-6.4	None
12,412	11,958	3.8	
6,819	6,923	-1.5	
93,234	93,326	-0.1	
$ 238	$ 206	15.5	Average ambulatory care costs
231	225	2.7	
			None
$ 3,716.28	$ 3,188.19	16.6	
459.56	241.74	90.1	
$35,914	$27,276	31.7	None
52,902	42,783	23.7	
$17,362	$ 8,560	102.8	Average costs over 4 years
$ 119	$ 95	25.3	Charges per month
255	258	-1.2	
NR[†]	NR	18.0	Absolute values were not reported; adjusted for age, gender, race, body mass index, physical activity, and comorbidity conditions
9.25	7.52	23.0	Clinic visits, Harvard 1964–1965
33.0	26.0	26.9	Percentage with ≥3 doctor visits per year; nonsmokers / slight present use of tobacco vs. moderate present use / heavy present use of tobacco; nonsmokers had never used tobacco; slight present use of tobacco was defined as 1–4 cigarettes per day, 1–2 cigars and / or pipes per day, occasional use of snuff, or occasional tobacco chewing; moderate present use was defined as 5–10 cigarettes per day, 3–4 cigars and / or pipes per day, frequent use of snuff, or frequent tobacco chewing; heavy present use was defined as ≥11 cigarettes per day, ≥5 cigars and / or pipes per day, constant use of snuff, or constant use of chewing tobacco

Table 6.8 Continued

Study	Population	Group
	Outpatient services	
Ashford 1973	32,319 residents of Exeter, United Kingdom, aged ≥15 years	Home visits Men: 15–29 years 30–44 years 45–59 years ≥60 years Women: 15–29 years 30–44 years 45–59 years ≥60 years Hospital outpatient Men: 15–29 years 30–44 years 45–59 years ≥60 years Women: 15–29 years 30–44 years 45–59 years ≥60 years
Oakes et al. 1974	2,557 HMO enrollees, aged ≥20 years	Men: Total 20–39 years 40–59 years ≥60 years Women: Total 20–39 years 40–59 years ≥60 years
Vogt and Schweitzer 1985	2,582 adult HMO enrollees	Total
Chetwynd and Rayner 1986	978 women, aged 18–60 years	Illness episodes General practitioner visits Specialist visits Outpatient visits Chiropractor visits
Rice et al. 1986	1979 National Health Interview Survey participants	Total Aged 17–44 years Aged 45–64 years Aged ≥65 years
Freeborn et al. 1990	515 HMO enrollees, aged >65 years	Group I (1970–1974) Group II (1970–1979)

Results			
Smokers	**Nonsmokers**	**Percentage difference**	**Comments**
			Number of visits during the survey year
0.21	0.17	23.5	
0.28	0.18	55.6	
0.43	0.33	30.3	
1.4	2.3	-39.1	
1.3	1.1	18.2	
0.67	0.64	4.7	
0.44	0.49	-10.2	
2.1	2.2	-4.5	
0.62	0.45	37.8	
0.47	0.38	23.7	
0.52	0.46	13.0	
0.46	0.57	-19.3	
0.56	0.46	21.7	
0.51	0.45	13.3	
0.48	0.52	-7.7	
0.47	0.59	20.3	
3.4	2.8	21.4	Mean number of office visits during the past year
3.1	2.4	29.2	
3.2	2.4	33.3	
5.4	3.9	38.5	
4.2	4.8	-12.5	
5.0	5.4	-7.4	
3.5	4.0	-12.5	
3.3	5.0	-34.0	
3,690	3,667	0.6	Total office visits
3.31	2.56	29.3	Smokers = ever smokers
5.71	4.90	16.5	
0.83	0.45	84.4	
0.81	0.64	26.6	
0.16	0.12	33.3	
5.2	4.9	6.1	Physician visits per person per year
4.7	4.4	6.8	
5.3	4.9	8.2	
7.0	6.6	6.1	
6.12	5.33	19.8	Office visits per year
6.18	5.30	16.6	

Table 6.8 Continued

Study	Population	Group
	Outpatient services	
Halpern and Warner 1994	1990 U.S. National Health Interview Survey	Total
Miller et al. 1999	1987 National Medical Expenditure Survey, n = 38,446	Total
	Hospitalizations/inpatient services	
Palmore 1970	268 community volunteers, aged 60–94 years at baseline	Total
Ashford 1973	32,219 residents of Exeter, United Kingdom, aged ≥15 years	Men: 15–29 years 30–44 years 45–59 years ≥60 years Women: 15–29 years 30–44 years 45–59 years ≥60 years
Oakes et al. 1974	2,557 HMO enrollees, aged >20 years	Men: 20–39 years 40–59 years ≥60 years Women: 20–39 years 40–59 years ≥60 years
Coronary Drug Project Research Group 1976	2,789 men with a history of myocardial infarction, aged 30–64 years at baseline	Total

‡OR = Odds ratio.

Results			
Smokers	**Nonsmokers**	**Percentage difference**	**Comments**
1.01	1.00	1.0	Physician visits in the past year; OR‡
0.7417	0.7379	0.5	Probability of ambulatory expense
38.0	33.0	15.2	Percentage with ≥1 operation; nonsmokers / slight present use of tobacco vs. moderate present use / heavy present use of tobacco; nonsmokers had never used tobacco; slight present use of tobacco was defined as 1–4 cigarettes per day, 1–2 cigars and / or pipes per day, occasional use of snuff, or occasional tobacco chewing; moderate present use was defined as 5–10 cigarettes per day, 3–4 cigars and / or pipes per day, frequent use of snuff, or frequent tobacco chewing; heavy present use was defined as ≥11 cigarettes per day, ≥5 cigars and / or pipes per day, constant use of snuff, or constant use of chewing tobacco
1.0	0.4	150.0	Average number of days hospitalized during the survey year
0.9	0.8	12.5	
0.8	0.6	25.0	
1.0	0.7	42.9	
1.8	1.2	50.0	
1.2	1.1	9.1	
0.9	0.8	12.5	
1.2	1.5	-20.0	
9	6	50.0	Percentage hospitalized during the past year
7	8	-12.5	
26	11	136.4	
14	17	-17.6	
6	10	-40.0	
13	15	-13.3	
55.2	49.7	11.1	5-year hospitalization rates

Table 6.8 Continued

Study	Population	Group
	Hospitalizations/inpatient services	
Vogt and Schweitzer 1985	2,582 adult HMO enrollees	Total
Chetwynd and Rayner 1986	978 women, aged 18–60 years	Hospitalized Emergency admissions
Rice et al. 1986	1979 National Health Interview Survey participants	Total
Van Peenen et al. 1986	AMOCO Corporation white male employees	Total
Freeborn et al. 1990	515 HMO enrollees, aged >65 years	Group I (1970–1974) Group II (1970–1979)
Penner and Penner 1990	20,831 employees enrolled in a fee-for-service plan	Total Admissions per 1,000 employees Days per 1,000 employees Average length of stay (days)
Kaplan et al. 1992	630 residents of a southern California community, aged >65 years	Total
Halpern and Warner 1994	1990 U.S. National Health Interview Survey participants	Total
Terry et al. 1998	5,780 HMO enrollees (n = 3,825, aged 18–64 years; n = 1,955, aged ≥65 years)	Aged <65 years Aged ≥65 years Aged <65 years Aged ≥65 years
Miller et al. 1999	1987 National Medical Expenditure Survey, n = 38,446	Total

Results			
Smokers	**Nonsmokers**	**Percentage difference**	**Comments**
801.5	668.6	19.9	Nonobstetric hospital days
0.22 0.09	0.15 0.06	46.7 50.0	Smokers = ever smokers
1.3	0.8	62.5	Smokers = ever smokers
2.7	2.4	12.5	Average number of insurance claims during the second quarter of 1984, the number submitted divided by the number eligible (for whom smoking habits were known) multiplied by 100, then adjusted for age; the difference is smaller after adjusting for age
0.17 0.17	0.15 0.15	13.3 13.3	Hospital admissions per year
126.66 800.39 6.47	75.82 381.21 5.03	63.1 110.0 38.6	None
42.3	31.9	32.6	Age-adjusted hospitalization rates Prospective study
1.30	1.00	30.0	ORs for hospital admissions
6 6	8 15	-25.0 -60.0	Percentage with any inpatient service
$113 324	$ 95 258	18.9 25.6	Charges per month
0.1236	0.1113	11.1	Probability of having a hospital expense

Table 6.9 Studies on the association between the amount smoked and medical service utilization rates

Study	Population	Group
	5-year hospitalization rates	
Hammond 1965	69,069 male smokers, U.S. men aged 50–69 years	Total
Coronary Drug Project Research Group 1976	2,789 men with a history of myocardial infarction, aged 30–64 years at baseline	Total
Marsden et al. 1988	17,328 active U.S. military personnel, aged >17 years	Total
	Medical encounters during the past 30 days	
Peters and Ferris 1967	Harvard / Radcliffe students	Total
Balarajan et al. 1985	United Kingdom General Household Survey, 1980, participants	Outpatient visits Consultations with a physician
Marsden et al. 1988	17,328 active U.S. military personnel, aged >17 years	Total

Health Status

Comparisons of self-rated health statuses in smokers and nonsmokers provide further evidence of the global effects of smoking on health. Although self-ratings are inherently subjective, they provide direct evidence of the relationship of smoking to a diminished health status. Consonant with the complex concept of "health," health status is itself a multidimensional construct, challenging to measure and approached with varied measurement methods, including direct questions on perceived health status and standardized scales. For example, the Short Form 36 (SF-36) is a standardized, 36-item scale that measures eight dimensions of health (Lyons et al. 1994), three of which have a direct relevance to this review: general health perceptions (five items), physical health (four items), and mental health (five items). Table 6.12 (smokers versus nonsmokers), Table 6.13 (dose-responses), and Table 6.14 (former smokers versus nonsmokers) summarize the evidence. Studies were grouped according to the aspect of health status measured: symptoms / illnesses / health complaints, perceived health status (poor / good), physical function, physical status, general health status, life satisfaction / dissatisfaction, well-being, quality of life, tiredness, and mental health. In some studies "poor" health was measured whereas in others "good" health was measured, so the anticipated directions of the effects of smoking vary with the specified outcome.

Studies with varying designs, as well as studies measuring physical health status (Table 6.12), have shown uniformly that smokers tend to rate their general health status lower than do nonsmokers. Studies that do not include sufficient data to summarize in the tables obtained similar results. A study of 558 Bank of America retirees in California comparing smokers with nonsmokers showed that smoking was strongly associated with a higher number of sick days confined to home (Leigh and Fries 1992). In an analysis of 1990 National Health Interview Survey data, the perception

Nonsmokers (referent)	Percentage difference: Smokers, by category of dose (1 = low) 1	2	3	Comments
Not applicable	Referent	8.5	14.6	None
0	13.9	8.7	11.5	None
0	28.1	6.3	54.7	Days hospitalized in the past year
0	33.9	21.1	30.3	Years smoked
0	46.0	46.0	43.0	None
0	12.0	8.0	9.0	
0	-1.7	6.2	31.1	Number of cigarettes per day in the past year

of health status held by current smokers was significantly lower than that held by nonsmokers (Erickson 1998). In a multiple regression analysis of data collected from approximately 18,000 men and women in Finland, which included variables for sociodemographic characteristics, family life, morbid conditions, pain, psychosocial problems, and relative weight, smoking was associated with a significantly lower perceived health status in men but not in women (Fylkesnes and Førde 1991). In a random sample of 1,200 adults in South Wales, United Kingdom, the mean score on the SF-36 general health perception scale among participants who had ever smoked was 7.8 points lower than for those who had never smoked (Lyons et al. 1994). A study using the same scale with 921 U.S. male military veterans showed that current smoking was significantly inversely correlated with good general health perceptions (Schnurr and Spiro 1999). In a telephone survey of Newfoundland residents, the likelihood of rating one's health as good declined in proportion to the number of cigarettes smoked per day; those who had never smoked were more than four times more likely than smokers of more than 30 cigarettes per day to rate their health as good (Segovia et al. 1989). In a survey of 1,623 patients from nine medical practices in Scotland who had a history of smoking, persistent smokers rated their general health 8.0 percent lower than former smokers rated theirs on the SF-36 scale (Tillmann and Silcock 1997). Among 2,502 enrollees in an Oregon health maintenance organization, smoking was negatively correlated with general health status for both men and women, an observation that extended to measures of mental and physical health status (Pope 1982).

Smokers in at least one subgroup were at least 10 percent more likely than nonsmokers to rate their health as poor, including studies that compared self-reported chronic conditions (Balarajan et al. 1985;

Table 6.10 Studies on the association between former smoking and medical services utilization costs and rates

Study	Population	Group
	Costs	
Vogt and Schweitzer 1985	2,582 adult HMO* enrollees	Laboratory X-ray Surgery Total
Pronk et al. 1999	6,589 adult HMO enrollees, Minnesota	Total
	Outpatient services	
Peters and Ferris 1967	Harvard / Radcliffe college students	Total
Ashford 1973	32,219 residents of Exeter, United Kingdom, aged >15 years	Home visits Men: 15–29 years 30–44 years 45–59 years ≥60 years Women: 15–29 years 30–44 years 45–59 years ≥60 years Hospital outpatient Men: 15–29 years 30–44 years 45–59 years ≥60 years Women: 15–29 years 30–44 years 45–59 years ≥60 years
Oakes et al. 1974	2,557 HMO enrollees, aged >20 years	Men: Total 20–39 years 40–59 years ≥60 years Women: Total 20–39 years 40–59 years ≥60 years

*HMO = Health maintenance organization.
†NR = Data were not reported.

Results			
Former smokers	**Nonsmokers**	**Percentage difference**	**Comments**
$21,150	$19,772	7.0	None
13,419	11,958	12.2	
8,639	6,923	24.8	
94,254	93,326	1.0	
NR[†]	NR	25.8	Absolute values were not reported; adjusted for age, gender, race, body mass index, physical activity, and comorbidity conditions
10.09	7.52	34.2	Clinic visits, Harvard, 1964–1965
			Number of visits during the survey year
0.28	0.17	64.7	
0.28	0.18	55.6	
0.46	0.33	39.4	
2.1	2.3	-8.7	
2.7	1.1	145.5	
0.78	0.64	21.9	
0.58	0.49	18.4	
3.3	2.2	50.0	
0.69	0.45	53.3	
0.37	0.38	-2.6	
0.39	0.46	-15.2	
0.69	0.57	21.1	
0.56	0.46	21.7	
0.44	0.45	-2.2	
0.73	0.52	40.4	
0.57	0.59	-3.4	
3.3	2.8	17.9	Mean number of office visits during the past year
2.7	2.4	12.5	
2.9	2.4	20.8	
4.3	3.9	10.3	
5.9	4.8	22.9	
5.1	5.4	-5.6	
7.4	4.0	-85.0	
5.0	5.0	0.0	

Table 6.10 Continued

Study	Population	Group
	Outpatient services	
Balarajan et al. 1985	1980 General Household Survey, United Kingdom	Outpatient visits Stopped >1 year Stopped <1 year Consultations with a physician Stopped >1 year Stopped <1 year
Vogt and Schweitzer 1985	2,482 adult HMO enrollees	Total
Halpern and Warner 1994	1990 U.S. National Health Interview Survey participants	Quit 0–2 months Quit 3 months–1 year Quit 2–4 years Quit 5–10 years Quit 11–19 years Quit ≥20 years
	Hospitalizations/inpatient services	
Ashford 1973	32,219 residents of Exeter, United Kingdom, aged >15 years	Men: 15–29 years 30–44 years 45–59 years ≥60 years Women: 15–29 years 30–44 years 45–59 years ≥60 years
Vogt and Schweitzer 1985	2,582 adult HMO enrollees	Total
Van Peenen et al. 1986	AMOCO Corporation white male employees	Total
Kaplan et al. 1992	630 residents of a southern California community, aged >65 years	Total

[†]OR = Odds ratio.

Results			
Former smokers	**Nonsmokers**	**Percentage difference**	**Comments**
1.40	1.0	40.0	OR† for prevalence of chronic illness after adjustment for age, gender, and socioeconomic group
1.25	1.0	25.0	
1.19	1.0	19.0	
1.47	1.0	47.0	
4,115	3,667	12.2	Total office visits
1.20	1.0	20.0	OR for the number of physician visits during the past year
1.47	1.0	47.0	
1.32	1.0	32.0	
1.24	1.0	24.0	
1.25	1.0	25.0	
1.18	1.0	18.0	
1.0	0.4	150.0	Average number of days hospitalized during the year
0.2	0.8	-75.0	
0.4	0.6	-33.3	
1.4	0.7	100.0	
1.7	1.2	41.7	
1.0	1.1	-9.1	
1.9	0.8	137.5	
1.55	1.5	0.0	
704.3	668.6	5.3	Nonobstetric hospital days
3.0	2.4	25.0	There was no difference after adjusting for age
41.0	31.9	28.5	Age-adjusted rates of hospitalization; prospective study

Table 6.10 Continued

Study	Population	Group
	Hospitalizations/inpatient services	
Halpern and Warner 1994	1990 U.S. National Health Interview Survey participants	Quit 0–2 months Quit 3 months–1 year Quit 2–4 years Quit 5–10 years Quit 11–19 years Quit ≥20 years
Terry et al. 1998	5,780 HMO enrollees, aged >18 years	Age <65 years Age ≥65 years

Halpern and Warner 1994), acute conditions (Balarajan et al. 1985), and physical symptoms (Macnee 1991; York and Hirsh 1995). An increasing number of cigarettes smoked per day was consistently associated with increased risks for symptoms or illnesses (Balarajan et al. 1985; Marsden et al. 1988; Joung et al. 1995), and with a greater likelihood of rating one's health as poor (Joung et al. 1995; Poikolainen et al. 1996; Manderbacka et al. 1999) (Table 6.13), with differences between the highest and lowest exposure categories of about 30 percent or greater in every study that assessed dose-response trends (Table 6.13). For several measures of poor health, the differences between former smokers and lifetime nonsmokers (Table 6.14) tended to be even more striking than for comparisons between current smokers and lifetime nonsmokers, probably because of the increased likelihood of quitting among those experiencing symptoms or diagnosed with illnesses.

A few studies examined reports of fatigue or tiredness. In a survey of New Zealand women who worked at home, smokers were 71 percent more likely than nonsmokers to report frequently feeling tired for no reason (Chetwynd and Rayner 1986). In a study of retired persons in the United States, after adjusting for age, current smokers were 60 percent more likely than lifetime nonsmokers to report becoming very tired easily (Rimer et al. 1990); former smokers were 25 percent more likely than lifetime nonsmokers to report getting very tired easily (Rimer et al. 1990).

Smokers tend to rate their general level of well-being lower than do nonsmokers whether well-being is measured directly (Dennerstein et al. 1994), assessed overall as quality of life (Sippel et al. 1999), or rated by degrees of general satisfaction with life (Blair et al. 1980) (Table 6.12). Similar findings have been observed when former smokers were compared with lifetime nonsmokers (Table 6.14) (Blair et al. 1980; Sippel et al. 1999). Conversely, compared with lifetime nonsmokers, current smokers tend to rate themselves as more dissatisfied with life (Table 6.12) (Kaprio and Koskenvuo 1988), but few differences in the prevalence rates of life dissatisfaction were observed between former smokers and nonsmokers (Table 6.14) (Kaprio and Koskenvuo 1988).

With respect to mental health and well-being, smokers tend to rate themselves slightly lower on measures of mental health or mental well-being (Wakefield et al. 1995; Wooden and Bush 1995; Sippel et al. 1999). In addition, smokers are more likely than nonsmokers to have psychological symptoms such as depressed mood and phobic anxiety (Matarazzo and Saslow 1960; Macnee 1991; Schoenborn and Horm 1993). In the South Wales study, not included in the summary tables, current smokers had a mean SF-36 mental health score that was slightly but not significantly lower than that of people who had never smoked (Lyons et al. 1994). Former smokers also tend to rate themselves less favorably than do nonsmokers

Results			
Former smokers	Nonsmokers	Percentage difference	Comments
1.79	1.0	79.0	ORs for hospital admissions
2.59	1.0	159.0	
1.25	1.0	25.0	
1.32	1.0	32.0	
1.04	1.0	4.0	
1.0	1.0	-3.0	
7	8	-12.5	Percentage with any inpatient use
16	15	6.7	

(Table 6.14). The differences between former smokers and lifetime nonsmokers were small with respect to mental health and well-being (Wetzler and Ursano 1988; Wooden and Bush 1995; Sippel et al. 1999), but were more marked on measures of symptoms or morbidity (Table 6.14) (Lilienfeld 1959; Lindenthal et al. 1972; Macnee 1991). A strong dose-response trend was observed between smoking frequency and depressed moods in nationally representative U.S. data from the National Health Interview Survey (Schoenborn and Horm 1993). However, dose-response trends generally did not occur for mental health measures (Table 6.13) (Lindenthal et al. 1972; Wetzler and Ursano 1988; Stansfeld et al. 1993).

Studies of physical functioning, or functional status, among elderly populations also provide relevant evidence. Although they are not a focus of this review, such studies have provided prospective evidence that cigarette smoking is associated with accelerated declines in physical function (Pinsky et al. 1987; Guralnik and Kaplan 1989; Berkman et al. 1993; Strawbridge 1993). An analysis of data from the Honolulu Heart Study showed that smoking was inversely associated with freedom from clinical illnesses, physical impairment, and cognitive impairment (Reed et al. 1998).

The evidence provides a clear indication that smokers perceive their health as poorer than nonsmokers perceive theirs. Smokers report more symptoms (including mental health symptoms) and illness episodes, feel more tired, and have lower ratings for physical health status. Compared with nonsmokers, smokers even report lower overall levels of well-being for reasons that may at least partially reflect their diminished health status. The consistent indications of a poorer health status among smokers compared with nonsmokers across numerous health status dimensions provide direct evidence that smoking is associated with a diminished health status.

Evidence Synthesis

This section reviewed evidence on smoking and a diverse but interrelated set of measures of health status. Although the measures are nonspecific and likely to be affected by factors other than smoking, there is abundant and consistent evidence that smokers generally have a poorer health status than nonsmokers. This section reviewed findings on self-reported health statuses, absenteeism, and medical services utilization rates, as well as complications of surgical care. For each of these outcomes, the weight of the evidence indicates an adverse effect from smoking. There are many studies with differing designs and a variety of populations. The strength of the association with smoking is variable across the outcome measures and across study

Table 6.11 Studies on the association between smoking and complications of surgery

Study	Population	Outcome studied
	Postoperative and wound-healing complications	
Abidi et al. 1998	Retrospective study, 63 consecutive patients with fractures of the calcaneus who underwent open reduction and internal fixation during a 3-year period	Postoperative and wound complications
Golosow et al. 1999	Retrospective study, 91 patients with sternal wound-healing complications between January 1990 and December 1996, seen at the Indiana University Medical Center and affiliated hospitals	Operative procedure and outcome
Goodman et al. 1999	Retrospective study, 48 spinal cord-injured patients with pressure ulcers, seen at a tertiary referral Veterans hospital between 1992 and 1997	Wound healing and postoperative complications
Spelman et al. 2000	693 patients undergoing CABG* between December 1, 1996, and November 30, 1997	Surgical wound infections (SWIs) and postoperative bacteremia
	Postoperative complications	
Ashraf et al. 1995	48 consecutive patients who underwent cardiovascular surgery	Mortality
Watterson et al. 1995	556 women who had transverse rectus abdominis musculocutaneous (TRAM) flap breast reconstruction	Postoperative complications
D'Agostino et al. 1996	Prospective study, 1,835 consecutive patients undergoing first-time isolated CABG between March 1990 and July 1995 in Massachusetts	Postoperative risk of stroke
Kroll et al. 1996	854 consecutive free flaps	Successful outcome
Samuels et al. 1996	All patients aged <40 years who had a CABG at the Allegheny University Hospital in Pennsylvania, between July 1990 and June 1995	Postoperative cardiac-related events
Utley et al. 1996	Prospective study, 2,916 patients with a history of 1 CABG	Preoperative and postoperative characteristics

*CABG = Coronary artery bypass graft.

Results
A history of active smoking was correlated with an increase in time to heal the wound in the outpatient group; risk factors for wound complications: high body mass index, extended time between injury and surgery, smoking, and single layered closure
Smoking history, chronic obstructive pulmonary disease, steroid use, previous sternotomy, age, diabetes, operation time, emergency operation, elevated white blood cell count, fever, and positive wound or blood cultures all correlated with one another
Chronic smokers had longer courses of antibiotic therapy, but smoking did not correlate with other variables, including wound-healing complications
Diabetes, obesity, and previous cardiovascular procedures were independent predictors of SWIs, and obesity was a risk factor for bacteremia
Smoking was related to later mortality ($p = 0.04$) in a univariate model
Risk of hernia formation was higher among those smoking at the time of surgery ($p = 0.0001$); risk factors for any complication were associated with smoking ($p < 0.002$)
Smoking was a significant predictor of carotid stenosis ($p < 0.0001$)
Smoking, age, and previous irradiation had no significant effects on flap failure rates
A history of smoking was a risk factor (83%); most patients resumed smoking, did not return to work, and did not take lipid-lowering drugs after surgery
Smoking was not predictive of mortality or morbidity; 7.5% of nonsmokers and 4.7% of smokers needed an intra-aortic pump; a recent myocardial infarction was more common in smokers

Table 6.11 Continued

Study	Population	Outcome studied
	Postoperative complications	
Arend et al. 1997	All renal transplants from the Leiden Renal Transplant Database performed between 1966 and 1994 in the Netherlands	Patient survival
Boucher et al. 1997	329 consecutive patients aged ≥70 years, who had undergone cardiac surgery between January 1990 and December 1993 in a university-affiliated tertiary care hospital in Montreal, Canada	Long-term survival and functional status
Brooks-Brunn 1997	Prospective model-building study, convenience sample of 400 patients who underwent abdominal surgical procedures between January 1993 and August 1995	Postoperative pulmonary complications
Espehaug et al. 1997	Register-based matched case-control study with 674 cases who had total hip replacements, and 1,343 controls with primary hip operations only, reported to the Norwegian Arthroplasty Register from 1987–1993	Poor total hip replacement prognosis
Gentile et al. 1997	93 patients with at least 6 months of postoperative surveillance, identified through a vascular registry	Intrinsic vein graft stenosis (postoperative) in lower extremities
Lindquist et al. 1997	Prospective study, 45 edentulous patients (21 smokers and 24 nonsmokers), followed for 10 years after treatment with a fixed implant-supported prosthesis in the mandible	Bone loss around mandibular implants
Nettleman et al. 1997	Retrospective study, 266 patients	Mortality from postoperative myocardial infarction
Rockman et al. 1997	606 patients (183 patients with preoperative strokes compared with 423 who only experienced transient ischemic attacks [TIAs]), who underwent consecutive carotid endarterectomies from 1988–1993 in New York	Perioperative stroke rates after endarterectomy
Sasajima et al. 1997	Retrospective study, 71 patients (97% smokers) who had autogenous vein bypasses in Japan	Patency rates (blood flow in veins remaining open)

[†]RR = Relative risk.
[‡]CI = Confidence interval.
[§]OR = Odds ratio.

Results
A slightly increased mortality risk in the first year after a transplant for smokers, patients aged >40 years, men, and persons with hypertension or diabetes
Current smoking on admission was associated with postoperative mortality; RR[†] = 3.6 (95% CI[‡], 1.4–10.0)
Smoking within the past 8 weeks was an independent risk factor (adjusted OR[§] = 2.27)
Smoking had no overall effect, but former smokers had a 2.8 increased risk compared with nonsmokers
Smoking was associated with the development of a vein graft flow disturbance (p = 0.03)
Mean bone loss around mandible was approximately 1 mm greater in smokers than in nonsmokers and related to the amount of cigarette smoking; smokers with poor oral hygiene were at a greater risk, especially for peri-implant bone loss
Current smoking was an independent risk factor (RR = 2.3 [95% CI, 1.2–4.7])
Patients with preoperative strokes who smoked had a greater risk for a perioperative stroke compared with those with asymptomatic TIAs or who experienced only TIAs (52 vs. 40.6%, p = 0.01)
The nonsmoking group had higher rates than the smoking group (66.8 vs. 34.7%, p <0.05)

Table 6.11 Continued

Study	Population	Outcome studied
	Postoperative complications	
Bluman et al. 1998	Prospective cohort study, 410 patients scheduled for noncardiac elective surgery at the Veterans Administration Medical Center in Syracuse, New York	Postoperative pulmonary complications
Medina et al. 1998	Retrospective study, 62 patients (40 with Crohn's disease [CD] and 22 with ulcerative colitis [UC]) with previous surgery for inflammatory bowel disease, compared with 202 patients (69 with CD and 133 with UC) in a control group with inflammatory bowel disease but without previous surgery	Development of inflammatory bowel disease in patients with CD and UC
Fujisawa et al. 1999	369 patients with stage I non-small-cell lung carcinoma	10-year survival rate
Kinsella et al. 1999	Retrospective study, 91 patients (38 current smokers, 12 former smokers, and 41 nonsmokers) with facial skin defects reconstructed with local flaps	Postoperative complications
Lavernia et al. 1999	202 patients (25 smokers and 177 nonsmokers) undergoing arthroplasty of the hip and knee	Short-term complications, resource consumption, length of hospital stay
Pereira et al. 1999	408 patients in a tertiary university hospital, analyzed prospectively for preoperative and postoperative pulmonary complications in Brazil	Pulmonary function and complication rate
Sinclair et al. 1999	17,638 consecutive outpatients who had surgery	Postoperative nausea and vomiting
Sorensen et al. 1999	333 unselected consecutive patients between January 1993 and October 1996 in 1 surgical department, who underwent colon or rectal resection with anastomosis in Denmark	Anastomotic leakage
Warner et al. 1999	135 patients undergoing abdominal surgery with a history of smoking or reduced pulmonary function	Pulmonary function and complications

[Δ]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Results
Complications occurred in 22% of current smokers, 12.8% of former smokers, and 4.9% of nonsmokers; adjusted OR = 5.5 (95% CI, 1.9–16.2) for current smokers vs. nonsmokers, 4.2 (95% CI, 1.2–14.8) for former smokers; OR for current smokers who reduced their smoking 1 month before surgery = 6.7 (95% CI, 2.6–17.1)
The number and type of complications after surgery were not related to smoking habits; inflammatory bowel disease recurred earlier in smokers among the CD patients ($p > 0.05$)
Increased mortality risk with increasing age and >30 pack-years$^{\Delta}$ of smoking
23 patients (25%) had complications (smokers = 37%, former smokers = 17%, and nonsmokers = 17%; $p < 0.03$); all full-thickness skin losses and cellulitis occurred in active smokers; former smokers had a complication rate similar to that of nonsmokers
Smokers, compared with nonsmokers, were younger and had fewer comorbidities, significantly longer surgical times, higher charges, and required more anesthesia (maybe for a more severe illness); former smokers had better short-term outcomes than did current smokers
Postoperative complication rate = 14%; predictors in univariate analyses: age >50 years, smoking, presence of chronic pulmonary disease, surgery duration >210 minutes, and comorbidity ($p < 0.04$)
Smoking was an independent risk factor; age, gender, duration and type of anesthesia, previous postoperative nausea and vomiting, and surgery type also were independent risk factors
Smokers had increased risks compared with nonsmokers (RR = 3.18 [95% CI, 1.44–7.00])
Pack-years of smoking, age, site of incision, and current smoking status were predictors of airway obstruction bronchospasm (OR = 6.9 [95% CI, 1.2–38.4]); pack-years of smoking were not associated with the need for endotracheal intubation (OR = 1.1 [95% CI, 0.4–3.2]) or with prolonged intensive care or readmission

Table 6.11 Continued

Study	Population	Outcome studied
	Postoperative complications	
Chan et al. 2000	67 consecutive patients (84% smokers) who underwent surgical resection of esophageal carcinoma from January 1989 to December 1996	5-year survival rate
Chimbira and Sweeney 2000	327 consecutive patients (85 smokers and 242 nonsmokers) undergoing arthroscopic knee surgery, who had standard anesthetic pre- and postoperative drugs	Postoperative nausea and vomiting
Kotani et al. 2000	30 smoking and 30 nonsmoking patients who had propofol-fentanyl general anesthesia in Japan	Types of alveolar immune cell and macrophage aggregation
Wetterslev et al. 2000	Healthy cardiopulmonary patients who had combined general and thoracic epidural anesthesia for abdominal surgery	Postoperative hypoxemia and complications
	Wound-healing complications	
Camilleri et al. 1996	111 consecutive recipients of Becker breast expanders	Wound infection
Erdmann et al. 1997	66 patients with flaps raised from the posteromedial border of the leg	Wound healing
Takeishi et al. 1997	114 patients who had transverse rectus abdominis musculocutaneous (TRAM) flap breast reconstruction in Japan	Wound healing complications

populations, probably reflecting the nonspecificity of these measures and the differing mixes of potential confounding and modifying factors across studies. In general, there is evidence for an increasing severity of outcome measures with an increasing number of cigarettes smoked, and current smokers tend to have worse outcomes than former smokers. Studies have addressed potential confounding factors to a limited extent, depending on the availability of data on relevant factors. Given the diversity of populations, study designs, and consistency of findings, confounding alone does not seem to be a satisfactory explanation for the overall pattern of findings. A single, unifying biologic basis for the association of smoking with the outcome measures cannot be postulated, but there are many well-supported direct and indirect mechanisms that may link smoking to the adverse effects documented in this section.

Conclusions

1. The evidence is sufficient to infer a causal relationship between smoking and diminished health status that may manifest as increased absenteeism from work and increased use of medical care services.

Results
Poor outcomes (18% survival rate) mainly because most tumors were in advanced stages when resected
6% of smokers compared with 15% of nonsmokers were affected ($p < 0.05$)
Smoking was associated with macrophage aggregation, but with markedly reduced phagocytic and microbicidal activity
Smoking ≥20 pack-years was associated with a 47% higher incidence compared with smoking <20 pack-years ($p < 0.006$)
Heavy smoking was a risk factor ($p < 0.05$)
Peripheral vascular disease and heavy smoking were contributory factors to suboptimal healing
Smoking was associated with a greater risk ($p = 0.03$)

2. The evidence is sufficient to infer a causal relationship between smoking and increased risks for adverse surgical outcomes related to wound healing and respiratory complications.

Implications

Although preventing the specific diseases caused by smoking has been a public health priority for a long time, cigarette smoking also causes a substantial and costly burden of nonspecific morbidity. Smokers have a poorer health status, lose more time from work, and use medical care services at a higher rate than their nonsmoking peers. These adverse effects occur among younger smokers even before the burden of smoking-induced diseases becomes apparent at middle age and older.

Table 6.12 Studies comparing the health status of smokers and nonsmokers

Study	Population	Group
	Mean number of illness episodes during the past year	
Chetwynd and Rayner 1986	Survey of 978 women who worked at home, Christchurch, New Zealand, aged 18–60 years	Total Aged 18–29 years Aged 30–44 years Aged 45–60 years
	Self-reported chronic conditions	
Halpern and Warner 1994	1990 U.S. National Health Interview Survey, random sample (n = 119,631), aged >17 years	Total
	Physical symptoms (% reporting)	
Macnee 1991	240 men and women, mean age 33 years	Total
	Physical symptoms (mean number)	
York and Hirsch 1995	425 alcohol drinkers, alcoholics and social drinkers, aged 20–59 years	Alcoholics Men Women Social drinkers Men Women
	Self-reported poor health	
Palmore 1970	268 male volunteers, aged 60–94 years	Total
Wilson and Elinson 1981	3,092 adults, aged 20–64 years, National Survey of Personal Health Practices and Consequences	Men Women
Seidell et al. 1986	455 men and 790 women, aged 26–66 years	Men Women
Pearson et al. 1987	864 HMO† enrollees, mean age 52 years	Total
Orleans et al. 1989	1,163 African American life insurance policyholders, mean age 39 years	Total
Halpern and Warner 1994	1990 U.S. National Health Interview Survey, random sample (n = 119,631), aged >17 years	Total
Poikolainen et al. 1996	6,040 men and women, Finland, aged 25–64 years	Total

*OR = Odds ratio.
†HMO = Health maintenance organization.

Results			
Smokers	**Nonsmokers**	**Percentage difference**	**Comments**
3.31	2.56	29.3	None
3.58	2.58	38.8	
3.14	2.57	22.2	
2.62	2.42	8.3	
1.27	1.0	27.0	OR*
25.2	21.5	17.2	None
5.11	4.75	7.6	Alcoholics were recruited from local alcoholism treatment centers; social drinkers were nominated for participation by alcoholics; teetotalers were excluded
7.11	6.14	15.8	
1.02	0.98	4.1	
1.83	1.43	28.0	
28.6	22.9	24.9	Percentage that rated their health was worse than the self-perceived average
24.8	21.3	16.4	Percentage with a physical health status score of 1–3 (poor)
37.0	33.9	9.1	
6.8	7.3	-6.8	Number of health complaints
10.2	9.0	13.8	
14.0	7.4	89.2	Percentage reporting fair / poor health
22.5	11.3	99.1	Percentage reporting fair / poor health
1.62	1.0	62.0	OR
48.8	40.7	19.9	Percentage reporting suboptimal health

Table 6.12 Continued

Study	Population	Group
	Self-reported poor health	
Bobak et al. 1998	Sample of 1,599 Russians, aged >18 years	Total
Pampalon et al. 1999	1992–1993 Quebec Health and Social Survey (n = 20,739), mean age 41 years	Total
	Self-perceived good/excellent health (% reporting)	
Colsher et al. 1990	4 population-based cohorts, aged >65 years	Men: Iowa East Boston New Haven Piedmont Women: Iowa East Boston New Haven Piedmont
York and Hirsch 1995	425 alcohol drinkers, alcoholics and social drinkers, aged 20–59 years	Alcoholics Men Women Social drinkers Men Women
	Self-perceived good physical function (% reporting)	
Colsher et al. 1990	4 population-based cohorts, aged >65 years	Men: Iowa East Boston New Haven Piedmont Women: Iowa East Boston New Haven Piedmont
	Physical health status	
Belloc and Breslow 1972	Random sample of Alameda County, California, residents, aged >20 years	Men Women
Reed 1983	542 HMO enrollees	Total

Results			
Smokers	**Nonsmokers**	**Percentage difference**	**Comments**
1.29	1.0	29.0	OR was adjusted for age, gender, education, alcohol, and marital status
1.34	1.0	34.0	OR for reporting fair / poor health status
64.4	74.6	-13.8	None
58.0	69.1	-16.1	
54.8	68.8	-20.9	
42.8	60.1	-28.8	
58.3	72.6	-19.7	
59.1	54.3	8.8	
55.2	60.8	-9.2	
53.6	54.5	-1.7	
			Health score
0.43	0.65	-33.8	
0.76	1.29	-41.1	
0.18	0.12	50.0	
0.26	0.30	-13.3	
59.1	70.5	-16.2	None
53.3	64.2	-17.0	
64.8	71.0	-8.7	
56.3	71.5	-21.2	
42.5	61.5	-30.9	
49.4	45.8	7.9	
48.9	57.1	-14.4	
49.4	50.9	-2.9	
0.51	0.47	8.5	Higher scores reflect poorer physical health status measured by ridits (mean rank sums)
0.52	0.48	8.3	
0.50	0.49	2.0	Higher scores reflect poorer physical health status, measured by ridits (mean rank sums); age and gender adjusted

Table 6.12 Continued

Study	Population	Group
	Physical health status	
Pearson et al. 1987	864 HMO enrollees, mean age 52 years	Total
Wooden and Bush 1995	23,813 Australians	Total
	General health status (health status questionnaire Short Form 36 [SF-36])	
Wakefield et al. 1995	3,010 Australians, aged >15 years	Aged 15–29 years Aged ≥30 years
Sippel et al. 1999	619 HMO members with asthma	Total
	Life dissatisfaction	
Kaprio and Koskenvuo 1988	7,094 Finns, twin cohort, men aged 20–54 years, women aged 20–39 years	Men: 20–34 years 35–54 years Women: 20–39 years
	General life satisfaction	
Blair et al. 1980	504 employees, mean age 34 years	Men Women
	Overall well-being	
Dennerstein et al. 1994	Random sample of 1,503 women, Melbourne, Australia, aged 45–55 years	Total
	Overall quality of life	
Sippel et al. 1999	619 HMO members with asthma	Total
	Tiredness for no reason (% reporting)	
Chetwynd and Rayner 1986	Survey of 978 women who worked at home, Christchurch, New Zealand, aged 18–60 years	Total
	Getting very tired easily (% reporting)	
Rimer et al. 1990	3,147 American Association of Retired Persons members, aged 50–102 years	Total

Results			
Smokers	**Nonsmokers**	**Percentage difference**	**Comments**
42.4	39.9	6.6	Percent reporting low physical health
2.090	2.316	-9.8	Higher scores reflect better physical health status (4-point scale, 4 = best)
71.0 69.1	77.4 74.6	-8.3 -7.4	Smokers = ever smokers
53	66	-19.7	Higher scores reflect better health status (100 = best, 0 = worst)
8.8 9.1 8.7	8.4 8.3 8.2	4.8 9.6 6.1	Based on a psychological scale; details were not specified
28.4 15.4	32.9 35.4	-13.7 -56.5	Age-adjusted proportion with a high level of general life satisfaction
1.43	1.57	-8.9	Higher scores reflect a greater sense of well-being
2.1	1.8	16.7	Higher scores reflect a poorer quality of life (10-point scale, 1 = best, 10 = worst)
36	21	71.4	None
32	20	60.0	Age-adjusted

Table 6.12 Continued

Study	Population	Group
Mental health (health status questionnaire Short Form 36 [SF-36])		
Wakefield et al. 1995	3,010 Australians, aged >15 years	Aged 15–29 years Aged ≥30 years
Sippel et al. 1999	619 HMO members with asthma	Total
Mental well-being		
Wooden and Bush 1995	23,813 Australians	Total
Psychosomatic symptoms		
Matarazzo and Saslow 1960	294 persons from 3 populations: psychiatric patients, student nurses, and university undergraduates	Psychiatric patients Student nurses Undergraduates Men Women
Psychological symptoms		
Macnee 1991	240 men and women, mean age 33 years	Total
Depressed mood (%)		
Schoenborn and Horm 1993	1991 National Health Interview Survey, random sample, U.S. adults (n = 43,732)	Men Women
Health behavior efficacy expectations, health status		
Grembowski et al. 1993	2,523 Medicare beneficiaries	Total Total

Results			
Smokers	**Nonsmokers**	**Percentage difference**	**Comments**
73.6 78.6	75.2 80.6	-2.1 -2.5	Smokers = ever smokers
69	76	-9.2	Higher scores reflect better mental health (100 = best, 0 = worst)
2.223	2.300	-3.3	Higher scores reflect better mental health (4-point scale, 4 = best)
13.9 8.2 3.9 6.1	12.1 6.3 3.3 3.7	14.9 30.2 18.2 64.9	Mean score on Saslow Psychosomatic Screening Inventory (higher = more symptoms)
8.8	7.9	11.4	Symptom checklist: range from 0–40; higher scores equal more symptoms based on a 10-item measure
10.3 15.8	5.8 10.0	77.6 58.0	None
2.96 7.66	9.78 9.69	-69.7 -21.0	Scales of 0 to 10 (0 = low and 10 = high); efficacy expectations of health behaviors (exercise, dietary fat, weight control, smoking, and alcohol consumption) and resulting health status expectations

Table 6.13 Studies evaluating the dose-response relationship between the number of cigarettes smoked per day and health status

Study	Population	Group
	Mean number of illnesses in the past 30 days	
Marsden et al. 1988	17,328 active U.S. military personnel	Total
	Self-reported poor health status (number of health complaints)	
Seidell et al. 1986	455 Dutch men and 790 Dutch women, aged 26–66 years	Men Women
	Subjective health complaints	
Joung et al. 1995	16,311 Dutch men and women, aged 25–74 years	Total
	Chronic conditions	
Joung et al. 1995	16,311 Dutch men and women, aged 25–74 years	Total
	Self-reported chronic conditions	
Balarajan et al. 1985	23,956 participants in the United Kingdom General Household Survey, aged >16 years	Total
	Perceived poor health	
Joung et al. 1995	16,311 Dutch men and women, aged 25–74 years	Total
Manderbacka et al. 1999	1991 Swedish Level of Living Survey (n = 5,306, aged 18–75 years)	Total
	Physical health status	
Belloc and Breslow 1972	Random sample of Alameda County, California, residents, aged >20 years	Current smokers Men Women Former smokers Men Women
	Physical health score	
Wiley and Camacho 1980	3,982 Alameda County residents, aged 20–70 years	Men Women

Percentage difference				
Nonsmokers (referent)	**Smokers, by category of dose (1 = low)**			**Comments**
	1	**2**	**3**	
0	0.4	12.3	36.4	None
0	23.3	31.5		None
0	6.8	28.4		
0	71.0	137.0		None
0	29.0	43.0		None
0	7.0	31.0	76.0	None
0	75.0	101.0		None
0	33.0	37.0		Adjusted for age, gender, and risk
0	4.3	17.0		Ridits (higher score = poorer health); whether one inhales cigarette smoke, and the extent of such inhalation, appear highly correlated with physicial health status
0	6.3	16.7		
0	6.4	14.9		
0	8.3	10.4		
0	-75.9	-265.5	-286.2	High scores = better physical health
0	50.0	-500.0	-375.0	

Table 6.13 Continued

Study	Population	Group
	Self-reported health status	
Segovia et al. 1989	Sample of 3,300 residents of St. John's, Canada, aged >20 years	Total
Poikolainen et al. 1996, Poikolainen and Vartiainen 1997	6,040 men and women, Finland, aged 25–64 years	Total
	Impaired psychological status	
Lindenthal et al. 1972	938 New Haven adults (aged >18 years), sample	Total
	Psychological well-being	
Wetzler and Ursano 1988	6,675 U.S. Air Force personnel	Total

*NR = Data were not reported.

Percentage difference				
Nonsmokers (referent)	**Smokers, by category of dose (1 = low)**			**Comments**
	1	**2**	**3**	
0	-16.3	19.1	-31.9	Percentage reporting good health; additional smoking categories, by increasing dose: -40.9, -67.4, -48.0, -76.2
0	0.2	45.7	NR*	Percentage reporting suboptimal health
0	35.8	-23.8	50.3	Based on a percentage with very impaired status; smoking frequency categories
0	1.7	3.3	NR	None

Table 6.14 Studies comparing the health status of former smokers and nonsmokers

Study	Population	Group
	Perceived poor health	
Joung et al. 1995	16,311 Dutch men and women, aged 25–74 years	Total
	Self-reported poor health (number of health complaints)	
Seidell et al. 1986	455 Dutch men and 790 Dutch women, aged 26–66 years	Men Women
	Subjective health complaints	
Lilienfeld 1959	903 residents, Buffalo, New York	Total
Joung et al. 1995	16,311 Dutch men and women, aged 25–74 years	Total
	Self-reported chronic conditions	
Balarajan et al. 1985	23,956 participants in the United Kingdom General Household Survey, aged >16 years	Quit >1 year Quit ≤1 year
	Chronic conditions	
Joung et al. 1995	16,311 Dutch men and women, aged 25–74 years	Total
	Physical symptoms	
Macnee 1991	240 men and women, mean age 33 years	Total
	Concern about physical health (% reporting)	
Thomas 1960	657 medical students	Total
	Getting very tired easily (% reporting)	
Rimer et al. 1990	3,147 American Association of Retired Persons members, aged 50–102 years	Total

*OR = Odds ratio.

Results			
Former smokers	**Nonsmokers**	**Percentage difference**	**Comments**
1.35	1.0	35.0	OR*
6.8 10.2	7.3 9.0	-6.8 13.8	None
18.9	18.3	3.3	Physical or health problem
1.32	1.0	32.0	OR
1.43 1.23	1.0 1.0	43.0 26.0	OR
1.49	1.0	49.0	ORs
36.6	21.5	32.8	Based on a scale from 0–120 (higher = more symptoms)
4.4	3.3	33.3	None
25	20	25.0	Age-adjusted

Table 6.14 Continued

Study	Population	Group
	Self-reported poor health	
Halpern and Warner 1994	1990 U.S. National Health Interview Survey, random sample (n = 119,631), aged >17 years	Time since cessation 0–2 months 3 months–1 year 2–4 years 5–10 years 11–19 years ≥20 years
Manderbacka et al. 1999	1991 Swedish Level of Living Survey (n = 5,306), persons aged 18–75 years	Total
	Self-reported health status	
Orleans et al. 1989	1,163 African American life insurance policyholders, mean age 39 years	Total
Poikolainen and Vartiainen 1997	6,040 men and women, Finland, aged 25–64 years	Total
	General health status (health status questionnaire Short Form 36 [SF-36])	
Sippel et al. 1999	619 HMO[†] members with asthma	Total
	Self-perceived good/excellent health (% reporting)	
Colsher et al. 1990	4 population-based cohorts, aged >65 years	Men: Iowa East Boston New Haven Piedmont Women: Iowa East Boston New Haven Piedmont

[†]HMO = Health maintenance organization.

Results			
Former smokers	**Nonsmokers**	**Percentage difference**	**Comments**
			OR
3.03	1.0	203.0	
2.83	1.0	183.0	
2.03	1.0	103.0	
1.35	1.0	35.0	
1.42	1.0	42.0	
1.00	1.0	0.0	
1.45	1.0	45.0	OR; adjusted for age, gender, risk factors, health behaviors, and health
22.5	11.3	99.1	Percentage fair / poor
46.7	40.7	14.7	Percentage suboptimal
61	66	-7.6	Higher scores reflect a better health status (100 = best, 0 = worst)
63.8	74.6	-14.5	None
61.7	69.1	-10.7	
61.0	68.8	-11.3	
57.0	60.1	-5.2	
67.4	72.6	-7.2	
57.1	54.3	5.2	
63.6	60.8	4.6	
57.4	54.5	5.3	

Table 6.14 Continued

Study	Population	Group
	Good physical function (% reporting)	
Colsher et al. 1990	4 population-based cohorts, aged >65 years	Men: Iowa East Boston New Haven Piedmont Women: Iowa East Boston New Haven Piedmont
	Physical health status	
Belloc and Breslow 1972	Random sample of Alameda County, California, residents aged >20 years	Men Women
Reed 1983	542 HMO enrollees	Total
Wooden and Bush 1995	23,813 Australians	Total
	Overall quality of life	
Sippel et al. 1999	619 HMO members with asthma	Total
	Mental health (health status questionnaire Short Form 36 [SF-36])	
Sippel et al. 1999	619 HMO members with asthma	Total
	Psychological symptoms	
Macnee 1991	240 men and women, mean age 33 years	Total
	Impaired psychological status	
Lindenthal et al. 1972	938 New Haven adults aged >18 years (sample)	Total
	Mental health: prevalence of psychiatric morbidity	
Stansfeld et al. 1993	9,962 men and women, Whitehall Study, aged 35–55 years	Men Women

Results			
Former smokers	**Nonsmokers**	**Percentage difference**	**Comments**
60.4	70.5	-14.3	None
58.6	64.2	-8.7	
65.7	71.0	-7.5	
64.2	71.5	-10.2	
49.0	61.5	-20.3	
44.9	45.8	-2.0	
47.9	57.1	-16.1	
49.8	50.9	-2.2	
0.51	0.47	8.5	Higher scores reflect a poorer health status, measured by ridits (mean rank sums)
0.51	0.48	6.3	
0.52	0.49	6.1	Higher scores reflect a poorer health status, measured by ridits (mean rank sums); age and gender adjusted
2.231	2.316	-3.7	Higher scores reflect a better health status (4-point scale, 4 = best)
2.4	1.8	33.3	Higher scores reflect a poorer quality of life (10-point scale, 10 = worst)
73	76	-3.9	Higher scores reflect a better mental health (100 = best, 0 = worst)
11.8	7.9	49.4	None
20.3	15.1	34.4	Percentage of very impaired
29.1	23.7	22.8	Smoking was also associated with a risk of physical symptoms in both genders
30.6	30.0	0.3	

Table 6.14 Continued

Study	Population	Group
	Feeling discouraged/blue (depression)	
Lilienfeld 1959	903 residents, Buffalo, New York	Total
	Psychological well-being	
Wetzler and Ursano 1988	6,675 U.S. Air Force personnel	Total
	Mental well-being	
Wooden and Bush 1995	23,813 Australians	Total
	Life dissatisfaction	
Kaprio and Koskenvuo 1988	7,094 Finns, twin cohort, men aged 20–54 years, women aged 20–39 years	Men: 20–34 years 35–54 years Women: 20–39 years
	General life satisfaction	
Blair et al. 1980	504 employees, mean age 34 years	Men Women

Results			
Former smokers	**Nonsmokers**	**Percentage difference**	**Comments**
32.9	24.8	32.7	Percentage sometimes / very often
4.17	4.24	-1.7	None
2.285	2.300	-0.6	Higher scores reflect better well-being (4-point scale, 4 = best)
8.3 8.5 8.4	8.4 8.3 8.2	-1.2 2.4 2.4	Based on a psychological scale
27.5 20.5	32.9 35.4	-16.4 -42.1	None

Loss of Bone Mass and the Risk of Fractures

In the United States, of the estimated 850,000 fractures per year in persons 65 years of age and older, nearly 300,000 are hip fractures (Apple and Hayes 1994; Centers for Disease Control and Prevention [CDC] 1996; Ray et al. 1997). Approximately 33 percent of women and 17 percent of men experience a hip fracture if they live to be 90 years old (Mazess 1982; Melton and Riggs 1987). Mortality in persons with a hip fracture is 12 to 20 percent higher than in persons without a hip fracture of similar age, race, and gender (Miller 1978; Jensen and Tondevold 1979; Weiss et al. 1983; Jensen 1984; Kenzora et al. 1984; Kreutzfeldt et al. 1984). The estimated annual costs for medical and nursing services related to hip fractures range from $7 billion to $10 billion (Ray et al. 1997). From July 1991 through June 1992, costs to Medicare for 10 types of fractures were estimated at $4.2 billion (Baron et al. 1996). Moreover, continued growth of the elderly population can be expected to dramatically increase the number of hip fractures, because hip fracture incidence rates increase exponentially with age (Melton and Riggs 1987; Melton et al. 1987). If these demographic and incidence trends continue, the number of hip fractures may well double or triple by the middle of the century (Kelsey and Hoffman 1987). With their frequency, adverse quality of life impacts, and economic costs, hip fractures are an urgent and major public health problem.

Bone mineral density (BMD) is one of the strongest indicators of the risk for a fracture. Several cohort studies have confirmed that even a single low BMD measurement is associated with the risk of a later fracture (Gärdsell et al. 1989; Hui et al. 1989; Cummings et al. 1993). For each standard deviation decrease in BMD, the estimated relative risk (RR) of fractures ranged from 1.5 to 2.6, depending on the site that was measured (Marshall et al. 1996). Therefore, discussions of the possible adverse effects from smoking on bone health should consider both BMD and fractures as outcome measures. An estimated 60 to 80 percent of the bone density variation is explained by genetic factors (Eisman 1999), leaving 20 to 40 percent of the variation attributable to nongenetic factors. Smoking is an important modifiable risk factor in both women and men.

Conclusions of Previous Surgeon General's Reports

Harmful effects of smoking on the skeleton have been recognized for several decades but the data were not sufficient to conclude that smoking adversely affects bone mass (USDHHS 1990); however, the most recent Surgeon General's report on women and smoking (USDHHS 2001) identified smoking as adversely affecting bone health and increasing the risks for fractures. The report concluded that smoking adversely affects bone density and increases the risks for hip fractures in postmenopausal women. Specifically, the conclusions were that (1) postmenopausal women who currently smoke have lower bone density than women who do not smoke; (2) women who currently smoke have an increased risk for hip fracture compared with women who do not smoke; and (3) the relationship among women between smoking and the risk for bone fracture at sites other than the hip is not clear (USDHHS 2001). However, because male osteoporosis also has been recognized as a considerable disease burden, the role of smoking in male bone health also deserves consideration.

Biologic Basis

Smoking has the potential for direct and indirect effects on skeletal health and the risk of fractures. Direct toxic effects of smoking on bone cells may be related to the physiologic effects of nicotine (Fang et al. 1991; Riebel et al. 1995) or possibly cadmium in tobacco smoke (Bhattacharyya et al. 1988). Indirect effects of smoking on bone cells may result from decreased intestinal calcium absorption (Krall and Dawson-Hughes 1999), reduced intake and lower levels of vitamin D (Brot et al. 1999), or alterations in the metabolism of adrenal cortical and gonadal hormones (Michnovicz et al. 1986; Khaw et al. 1988; Baron et al. 1995). These direct and indirect effects may account for the generally observed decrease in markers of bone formation such as osteocalcin in smokers compared with nonsmokers (Brot et al. 1999; Bjarnason and

Christiansen 2000). Smoking might also indirectly influence bone density through reduction in body weight, since body weight tends to be lower for smokers than for nonsmokers. This weight difference may itself lead to lower bone density and an increased risk for a fracture (Kiel et al. 1987; Cummings et al. 1995). Smokers also tend to have an earlier menopause than nonsmokers, thus extending the postmenopausal period of accelerated bone mineral loss (USDHHS 2001). Finally, smokers tend to be less physically active than nonsmokers and activity level is associated with bone density and hence risk for a fracture (Gregg et al. 1998).

In several analyses involving women, the lower weight of smokers compared with nonsmokers explains part of the increased risk for low BMD associated with smoking (Bauer et al. 1993). However, there are differences in BMD and in fracture rates between smokers and nonsmokers even after adjusting for weight differences, suggesting that the weight difference alone does not explain the effects of smoking (Kiel et al. 1992, 1996; Bjarnason and Christiansen 2000). The lower weight in smokers may increase the risk of fractures, such as hip fractures, through several mechanisms: reduced soft tissue mass overlaying the trochanter, resulting in less energy absorption from a fall on the hip; reduced weight loads on the skeleton; or reduced conversion of adrenal steroids into sex steroids in adipose tissue. The antiestrogenic effect of smoking also may contribute to osteoporosis in women (Jensen et al. 1985; Jensen and Christiansen 1988), and may reduce the benefits of hormonal replacement therapy (Komulainen et al. 2000). In a Finnish trial of osteoporosis prevention, smoking was associated with a nonresponse to hormonal therapy, as assessed by changes in BMD (Komulainen et al. 2000). Less consistent evidence for a blunted response to estrogen by smoking was reported from a Danish trial (Bjarnason and Christiansen 2000). Interestingly, although estrogen appears to be a critical hormone for male skeletal health (Slemenda et al. 1997; Khosla et al. 1998), smoking does not appear to modify the association between estradiol levels and bone density in men (Amin et al. 1999). Finally, smoking may increase the risk of fractures through reductions in physical performance capacity, thereby increasing the risk for falls (Nelson et al. 1994).

Bone Density in Young Men and Women

Epidemiologic Evidence

Increasingly refined measures of BMD have become available so that current studies use direct BMD measurements. Before such direct measurements were possible BMD was assessed using radiographs, with measurements typically focused on the widths of the cortical bones in sites such as the metacarpals. Direct quantitative assessments of the amount of mineral in various skeletal sites have now become possible with the advent of single and dual photon absorptiometry, followed by refinements such as single and dual x-ray absorptiometry, quantitative computed tomography, and quantitative ultrasonography. These techniques have all been used to generate the data summarized here.

In adults at any particular age bone mass is dependent on the peak mass achieved up to that age, and subsequent losses from the peak are attributable to aging and other factors. The pace of skeletal growth is rapid during infancy, slower during childhood, accelerated during puberty, and by 20 to 30 years of age the peak skeletal mass is attained (Kroger et al. 1992; Lu et al. 1996). Gains in BMD continue into the third decade after bone growth has ceased (Recker et al. 1992). After menopause, bone loss rates accelerate compared with premenopausal rates, and these rates are sustained or increase even more with aging (Ensrud et al. 1995). Age-related losses also occur in men (Jones et al. 1994). In the context of these age-related patterns, the role of smoking in the attainment of peak bone mass is reviewed along with studies of bone density and menopausal status. A literature search was conducted using the National Library of Medicine's PubMed system; the key words used were "bone mineral density," "bone density," "fracture," "smoking," and "cigarettes." In addition, all references from a key meta-analysis (Law and Hackshaw 1997) were also retrieved. Studies focusing on men mainly involve older age groups. The evidence on smoking and BMD comes primarily from cross-sectional and cohort studies. The cross-sectional studies assess the cumulative consequences of smoking on BMD growth and/or decline. Cohort studies can assess changes in BMD over time. Findings of the different types of studies are presented in Tables 6.15–6.17.

Table 6.15 Cross-sectional studies on the association between smoking status and bone density in women*

Study	Mean (range) age (years)	Smoking status	Site of bone density measurement
		Premenopausal	
Fehily et al. 1992	22 (20–23)	104 current smokers 78 never / former smokers	Radius
Välimäki et al. 1994	24 (20–29)	9 current smokers 47 never smokers	Femur
McCulloch et al. 1990	28 (20–35)	25 current smokers 76 never / former smokers	Calcaneus
Ortego-Centeno et al. 1994	28 (SD = 7)	47 current smokers 54 never / former smokers	Femur
Daniel et al. 1992	29 (20–35)	25 current smokers 27 never / former smokers	Femur
Mazess and Barden 1991	30 (20–39)	23 current smokers 195 never / former smokers	Femur, lumbar spine, and radius
Sowers et al. 1992	36 (22–54)	31 current smokers 77 never / former smokers	Radius
Law et al. 1997	37 (35–39)	28 current smokers 72 never smokers	Radius
	42 (40–44)	63 current smokers 115 never smokers	Radius
	47 (45–49)	50 current smokers 107 never smokers	Radius
	52 (50–54)	14 current smokers 79 never smokers	Radius
Hopper and Seeman 1994	42 (27–49)	9 current smokers 9 never smokers	Femur
Johnell and Nilsson 1984	49 (49)	186 current smokers 185 never / former smokers	Radius

**Note:* See Figure 6.2 for results. The order of the studies in this table reflects the order of the regression lines in Figure 6.2.
†BMD = Bone mineral density.
‡SD = Standard deviation.
§CI = Confidence interval.
ΔBMC = Bone mineral content.

Findings
No differences in BMD† between smokers (0.71 g/cm² [SD‡ = 0.07]) and nonsmokers (0.71 [0.06])
Mean BMD in g/cm² (SD) at hip = 0.914 (0.102) for smokers compared with 0.956 (0.100) for nonsmokers; adjusted for age, weight, and exercise
Mean BMD in g/cm² = 177.8 (54.1) for smokers compared with 190.6 (52.9) for nonsmokers
Femoral neck BMD in g/cm² (SD) for smokers = 0.796 (0.118), nonsmokers = 0.838 (0.123), p <0.05; lumbar spine for smokers = 1.025 (0.108), nonsmokers = 1.039 (0.106), p = not significant
Mean BMD in g/cm² (SD) = 1.16 (0.014) for smokers compared with 1.151 (0.014) for nonsmokers; adjusted for weight (p = 0.140)
Spine BMD was significantly lower for smokers compared with nonsmokers (t = 2.26, p <0.05)
Radial BMD loss in g/cm² (SD) = 0.71 (0.01) for smokers compared with 0.74 (0.008) for nonsmokers (p = 0.300)
Difference between current and nonsmokers = 0.43 (95% CI§, -0.73–1.59)
Study of twin pairs found that BMD was lower for the twin who smoked more heavily
Distal BMCΔ in mg/cm² = 320 (SD = 73) for smokers compared with 318 (77) for nonsmokers; proximal = 538 (68) for smokers compared with 533 (62) for nonsmokers; results were not significant

Table 6.15 Continued

Study	Mean (range) age (years)	Smoking status	Site of bone density measurement
		Postmenopausal	
Law et al. 1997	45 (39–49)	24 current smokers 56 never smokers	Radius
	52 (50–54)	31 current smokers 83 never smokers	Radius
	57 (55–59)	32 current smokers 135 never smokers	Radius
	62 (60–64)	27 current smokers 65 never smokers	Radius
Jensen and Christiansen 1988	50 (44–53)	56 current smokers 54 never / former smokers	Radius
Jensen et al. 1985	51 (44–56)	67 current smokers 69 never / former smokers	Radius
Slemenda et al. 1989	51 (45–57)	21 current smokers 63 never / former smokers	Radius and lumbar spine
McDermott and Witte 1988	53 (SD = 10)	24 current smokers 24 never smokers	Radius
		Premenopausal	
Guthrie et al. 1996	54 (48–57)	7 current smokers 39 never / former smokers	Femur
Cheng et al. 1991	54 (50–60)	25 current smokers 82 never / former smokers	Calcaneus
Krall and Dawson-Hughes 1991	59 (40–70)	35 current smokers 267 never / former smokers	Femur
Hopper and Seeman 1994	62 (50–73)	7 current smokers 7 nonsmokers	Femur

[†]BMD = Bone mineral density.
[‡]SD = Standard deviation.
[Δ]BMC = Bone mineral content.
[¶]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Findings
Difference in BMD† between current smokers and nonsmokers = -0.17 g/cm^2 (95% CI, -1.88–1.54)
No odds ratio was given for smoking
BMC$^\Delta$ (g/cm) = 38.2 (95% CI, 20.9–48.7) in smokers compared with 38.0 (95% CI, 24.9–58.9) in nonsmokers
For current smokers of >20 pack-years¶, midradius had a -0.0034 g/cm^2 (SD‡ = 0.169) change in bone mass/year, distal radius = -0.0071 (0.0180), and lumbar spine = -0.0261 (0.0476); for current smokers of <20 pack-years, midradius = -0.0023 (0.0135), distal radius = -0.0113 (0.0366), and lumbar spine = 0.0136 (0.0800); and for nonsmokers, midradius = -0.0072 (0.0111), distal radius = -0.0071 (0.0172), and lumbar spine = -0.0120 (0.0409)
BMC (g/cm) midradius = 0.89 (0.03) for smokers compared with 0.87 (0.02) for nonsmokers (p = 0.66); distal radius = 0.87 (0.03) for smokers compared with 0.87 (0.03) for nonsmokers (p = 0.98)
Smoking was associated with a lower BMD
BMD (g/cm^2) was lower among smokers (0.170 [SD = 0.025]) than nonsmokers (0.180 [0.029] p >0.05)
Mean BMD (g/cm^2) of current smokers = 0.611 (SD = 0.012) for radius, 0.787 (0.015) for femoral neck, and 1.084 (0.021) for spine; for current nonsmokers radius = 0.614 (0.005), femoral neck = 0.793 (0.007), and spine = 1.080 (0.009)
Study of twins discordant for tobacco use, by menopause status, BMD was lower for the twin who smoked more heavily

Table 6.15 Continued

Study	Mean (range) age (years)	Smoking status	Site of bone density measurement
		Premenopausal	
Sowers et al. 1985	62 (55–80)	119 current smokers 278 never smokers	Radius
Hansen et al. 1991	63 (59–67)	61 current smokers 60 never / former smokers	Femur
Egger et al. 1996	66 (63–68)	23 current smokers 99 never smokers	Femur and lumbar spine
Holló et al. 1979	68 (61–75)	41 current smokers 125 never smokers	Radius
Nguyen et al. 1994	70 (>60)	102 current smokers 765 never smokers	Femur and lumbar spine
Jensen 1986	70 (70)	77 current smokers 103 never smokers	Radius
Johansson et al. 1992	70 (70)	38 current smokers 200 never smokers	Calcaneus
Rundgren and Mellström 1984	70 (70)	43 current smokers 243 never smokers	Calcaneus
	75 (75)	49 current smokers 364 never smokers	Calcaneus
	79 (79)	19 current smokers 218 never smokers	Calcaneus
Bauer et al. 1993	71 (65–84)	485 current smokers 4,367 never smokers	Radius
Kiel et al. 1996	74 (68–98)	77 current smokers 340 never smokers	Femur
Cheng et al. 1993	75 (75)	10 current smokers 161 never smokers	Calcaneus
Hollenbach et al. 1993	76 (60–89)	42 current smokers 320 never smokers	Femur

[†]BMD = Bone mineral density.
[‡]SD = Standard deviation.
[Δ]BMC = Bone mineral content.

Findings
Mean BMD[†] = 0.633 (SD[‡] = 0.014) for smokers of 1–9,000 pack-days, and 0.637 (SD = 0.014) for >9,000 pack-days compared with 0.625 (SD = 0.005) for nonsmokers (findings were not significant); adjusted for age to 66 years and median muscle mass
Smokers had a lower BMD (g/cm^2) 0.69 (SD = 0.11) than nonsmokers 0.65 (0.09)
Mean (g/cm^2) change / decade of smoking = -0.015 (95% CI, -0.028 to -0.003) for lumbar spine and -0.004 (-0.012 to -0.003) for femoral neck; adjusted for age, weight, height, alcohol use, calcium intake, and physical activity
Smokers had a lower BMC[Δ] (0.68 g / cm [SD = 0.10]) than nonsmokers (0.72 [0.10]), $p < 0.05$
Lumbar spine BMD = 0.96 g/cm^2 (SD = 0.22) for current smokers, 1.03 (0.17) for former smokers, and 1.02 (0.19) for never smokers; femoral neck BMD = 0.73 (0.10) for current smokers, 0.78 (0.12) for former smokers, and 0.79 (0.13) for never smokers ($p < 0.05$ for current smokers vs. nonsmokers for both comparisons)
40.3% of smokers and 44.7% of nonsmokers had some type of fracture (hip, proximal, distal radius, vertebral, or long bones)
$r = 0.15$, $p < 0.01$ comparing current, former, and nonsmokers
Among 70-year-old current smokers, BMD (µm) = 784 (SD = 252) compared with former smokers (884 [280], $p < 0.05$) and nonsmokers (928 [273], $p < 0.001$); among current smokers aged 75 years, 759 (260) compared with former smokers (950 [282], $p < 0.05$) and nonsmokers (878 [268], $p < 0.01$); and among current smokers aged 79 years, 554 (258) compared with former smokers (748 [372], $p < 0.05$) and nonsmokers (807 [329], $p < 0.001$)
Percentage change in bone mass (g/cm^2) = -0.04 (95% CI, -0.9–0.8) for lifetime cigarettes smoked (per 20 pack-years)
Among estrogen users, current smokers had a lower BMD of the trochanter (0.589 g/cm^2) than nonsmokers (0.640, $p = 0.05$)
Current smokers had a lower mean BMD (0.114 g/cm^3 [SD = 0.023]) than nonsmokers (0.129 [0.036] $p > 0.05$)
Current smokers had a lower mean femoral neck BMD (0.608 [SD = 1.008]) than nonsmokers (0.632 [0.005] $p < 0.01$)

Table 6.16 Studies on the association between smoking status and bone density in men and women published since the 1997 meta-analysis by Law and colleagues

Study	Population/age (years)	Smoking status	Measurement/site
		Women	
Brot et al. 1997	433 perimenopausal Danish women aged 45–58 years; 87 were followed for 2 years	49% current smokers 39% never smokers 12% former smokers	A BMC* of the whole body was measured at enrollment and after 1 and 2 years
Takada et al. 1997	3,867 premenopausal and postmenopausal Japanese women aged 37–69 years	A dichotomous category for current smoking (yes/no), but no data were provided	BMD‡ at the distal radius 1/3 of the distance from the wrist to the elbow
Grainge et al. 1998	580 postmenopausal women aged 45–59 years	25.7% current smokers 74.3% nonsmokers at the time of the scan	BMD of the spine, hip, radius/ulna, and whole body
Smeets-Goevaers et al. 1998	5,896 perimenopausal white Dutch women aged 46–54 years	Never smokers; former or current smokers were said to be identified, but no data were provided	BMD of the spine
Cheng et al. 1999	200 white women aged 20–79 years	38% had a history of tobacco use (average 8.2 packs/year) 7% current smokers	BUA§ of the calcaneus
Gregg et al. 1999	393 women aged 45–53 years (7.4% white; 12.2% perimenopausal or postmenopausal)	9.2% current smokers	BUA and SOSΔ of the calcaneus; BMD of the spine and hip
Jones and Scott 1999	263 premenopausal women; mean age 33 ± 4.5 years	45% current smokers	BMD of the spine, hip, and whole body
Varenna et al. 1999	6,160 postmenopausal Italian women; mean age 54.5 ± 6.4 years	74.9% never smokers 5.0% former smokers 20.1% current smokers	BMD of the spine

*BMC = Bone mineral content.
†Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.
‡BMD = Bone mineral density.
§BUA = Broadband ultrasound attenuation.
ΔSOS = Speed of sound.

Findings
Smoking (pack-years[†]) was a significant and independent predictor of total BMC ($p < 0.001$)
The combined variable of no drinking (consumption of alcohol ≤3 days / week) and current smoking has a statistically significant negative effect on radial BMD among older (56–69 years) women ($p < 0.05$)
BMD was more strongly related to the number of months of smoking than to pack-years at all 5 sites ($p < 0.05$ at all sites except the femoral neck)
Increased risks for a low BMD (osteopenia and osteoporosis) were associated with smoking (odds ratio = 1.25 [95% confidence interval, 1.08–1.44])
Smoking was not associated with the BUA ($p > 0.05$)
Smoking was not significantly associated with the calcaneal BUA or SOS
Current smoking was associated with a significantly lower BMD at the hip and a lower BMD (not significant) at the spine and whole body
Smoking was not associated with BMD or a risk for osteoporosis

Table 6.16 Continued

Study	Population/age (years)	Smoking status	Measurement/site
		Women	
Kim et al. 2000	238 Korean women; mean age 24.2 ± 2.5 years scanned only as a reference population 552 postmenopausal Korean women; mean age 62.5 ± 8.2 years	Data were not reported	BUA[§] of the calcaneus
		Men	
Vogel et al. 1997	1,303 men of Japanese descent living in Hawaii; aged 61–82 years	35% never smokers 45% former smokers 20% current smokers	BMD[‡] of the calcaneus, and distal and proximal radius
Hagiwara and Tsumura 1999	1,736 Japanese men aged 20–64 years	35.5% nonsmokers 15.7% former smokers 48.8% current smokers	BMD of the calcaneus
Huuskonen et al. 2000	140 Finnish men aged 54–63 years	Mean pack-years = 19.0 (range 1–59.5)	BMD of the neck, trochanter, Ward's triangle, and L2–L4

[‡]BMD = Bone mineral density.
[§]BUA = Broadband ultrasound attenuation.

Findings
There was no association between a history of smoking and low quantitative ultrasound values after controlling for age and time since menopause
Current and former smokers had a 1.8–4.8% lower BMD in the calcaneus and distal radius
Men in the highest BMD quintile were younger, with a higher body mass index and a lower mean pack-year history than men in the lowest quintile
Correlation coefficient = 0.04, -0.01, 0.05, and -0.10 with pack-years for the neck, trochanter, Ward's triangle, and L2–L4 ($p > 0.05$), respectively

Table 6.17 Cohort studies on the association between smoking status and the risk of bone loss in men and women

Study	Population/age (years)	Smoking status	Measurement/site
Slemenda et al. 1989	84 perimenopausal and postmenopausal women followed for 3[illegible] years	Data were not reported	BMD* of the midradius, distal radius, and the lumbar spine
Krall and Dawson-Hughes 1991	320 postmenopausal women aged 40–70 years; 2-year calcium supplementation trial	55% never smokers 35% former smokers (>1 month before trial) 11% smoked during all or part of the trial	BMD of the radius, femoral neck, Os calcis, and the spine
Slemenda et al. 1992	111 male veterans of World War II or the Korean War born between 1916 and 1927, all twin pairs; 16-year follow-up	Monozygotic male twins (n = 57) had mean 10.9 ± 14.9 cigarettes / day; dizygotic twins (n = 54) had mean 14.4 ± 15.9 cigarettes / day	BMD of the radius
Sowers et al. 1992	217 women aged 22–54 years; 5-year follow-up	Mean lifetime packs of cigarettes = 2,447	BMD of the distal radius
Jones et al. 1994	626 (385 women, 241 men); average follow-up was 2.5 years	Women had a median of 9 pack-years of smoking; men had a median of 31 pack-years of smoking	BMD of the hip and the spine
Vogel et al. 1997	1,303 Japanese American men aged 51–82 years; average follow-up was 5 years	20% current smokers 45% former smokers 35% never smokers	BMD of the distal and proximal radius and the calcaneus
Burger et al. 1998	1,856 Dutch men (mean age, 66.7 years), 2,452 Dutch women (mean age 67.2 years); average follow-up was 2 years	Current smokers Men (23%) Women (19%)	BMD of the hip

*BMD = Bone mineral density.
†Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Findings
Heavy smokers (≥20 pack-years[†]) had significantly ($p < 0.05$) lower radial (midradius = 0.76 [standard deviation (SD) ±0.10] g/cm, distal radius = 0.83 [±0.12] g/cm^2) and vertebral (lumbar spine = 0.82 [±0.16] g/cm^2) BMD than nonsmokers (0.84 [±0.11], 0.91 [±0.13], and 0.94 [±0.15] g/cm^2, respectively); there were no significant differences between light smokers (<20 pack-years) and nonsmokers; there were no detectable effects of smoking on the rates of bone loss at any site
Adjusted mean (±SD) annualized rate of bone change from the radius was greater among smokers than nonsmokers (-0.914 [±2.624]%/year, n = 34, vs. 0.004 [±2.568]%/year, n = 278, respectively; $p = 0.05$); variables adjusted for include supplement type (placebo, citrate malate, or calcium carbonate), current alcohol status (user or nonuser), and caffeine intake; this same significant trend was observed at 3 other sites
-0.100 g/cm (standard error ±0.036) ($p = 0.007$) for cigarette smoking; the twin who smoked more lost more bone ($p = 0.005$); men with cigarette and alcohol use above median levels had the most rapid losses
In postmenopausal women, but not premenopausal women, smoking at baseline was associated with a lower BMD at follow-up
There were no differences in the rates of loss between current smokers and nonsmokers
Compared with never smokers, current smokers had significantly greater rates of bone loss: 29.4% from the calcaneus ($p < 0.001$) and 33.8% from the distal radius ($p < 0.01$); analyses were adjusted for age, height, weight, physical activity, and alcohol and thiazide use
Smoking was accompanied by a significantly higher rate of bone loss in both men and women (men, $p = 0.02$; women, $p = 0.01$); the association was stronger when not adjusting for body mass index

Table 6.17 Continued

Study	Population/age (years)	Smoking status	Measurement/site
Guthrie et al. 1998	224 women (74 premenopausal, 90 perimenopausal, and 60 postmenopausal); follow-up was 2 years	Premenopausal women 14% current smokers Early perimenopausal women 14% current smokers Late perimenopausal women 25% current smokers Postmenopausal women 15% current smokers	BMD* of the hip and the spine
Krall and Dawson-Hughes 1999	402 elderly men and women (32 smokers, 370 nonsmokers); 3-year placebo-controlled study	Smokers 42% men 53% women Nonsmokers 45% men 55% women	BMD at the femoral neck, total body, and the spine
Hannan et al. 2000	468 women, 273 men (mean age 74.5 years); average follow-up was 4 years	Current smokers Women (10%) Men (8%)	BMD of the hip, spine, and radius

*BMD = Bone mineral density.

Findings

Of the women who became postmenopausal during the study, 6 were current smokers and their mean annual change in spine BMD was slightly greater (-3.3%) than that of the 36 nonsmokers (-2.3%); p = 0.10

BMD losses (adjusted for baseline BMD, weight, age, gender, supplementation status, and dietary calcium intake) were higher in smokers than in nonsmokers at the femoral neck (-0.714 g/cm [standard error = (±0.285)%/year vs. 0.038 [±0.084]%/year, p <0.02]), and total body (-0.360 [±0.101]%/year vs. -0.152 [±0.030]%/year, p <0.05); there were no significant differences at the spine (0.260 [±0.252]%/year in smokers vs. 0.593 [±0.074]%/year in nonsmokers, p = 0.21)

Compared with women who had never smoked, female current smokers had no increase in bone loss; in men, current smokers had greater bone loss (4–5%) than never smokers

Peak Bone Mass

Because BMD increases rapidly during adolescence, initiating smoking around the time of puberty might reduce peak BMD. However, the effects of smoking on the attained level of peak bone mass are uncertain because there are limited data on the skeletal effects of smoking during adolescence. Furthermore, it is possible that relatively short exposures in this age group would have little effect on bone density measurements. One prospective cohort study of children and adolescents (aged 9 to 18 years) in Finland repeatedly ascertained lifestyle factors and followed participants for 11 years, at which time they underwent bone density testing (Välimäki et al. 1994). In men, but not in women, smokers had lower BMD measurements of the hip and spine than did nonsmokers after adjusting for covariates. A cross-sectional study of 15-year-old Swedish adolescents did not find an association between smoking and total body bone mineral content (Lötborn et al. 1999). Findings were similar in a cross-sectional study of 500 children aged 4 to 20 years in the Netherlands, but only 32 were smokers (Boot et al. 1997).

Data are available from studies of premenopausal women, starting from the ages at which peak BMD is reached. A meta-analysis of cigarette smoking, BMD, and the risk for hip fractures (Law and Hackshaw 1997) identified 10 cross-sectional studies of premenopausal women (Johnell and Nilsson 1984; McCulloch et al. 1990; Mazess and Barden 1991; Daniel et al. 1992; Fehily et al. 1992; Sowers et al. 1992; Hopper and Seeman 1994; Ortego-Centeno et al. 1994; Välimäki et al. 1994; Law et al. 1997). Additional study populations included menopausal and postmenopausal women (Table 6.15). As shown in Table 6.15, the mean ages of women in the study samples ranged from 22 to 76 years. Because absolute bone density units varied among studies according to the bone site assessed and the measurement technique used, the difference between the average BMD of current smokers and nonsmokers in each of the studies was recorded as a proportion of one between-person standard deviation. In combining the studies, each bone density difference was weighted by the inverse of its variance and was age-adjusted only.

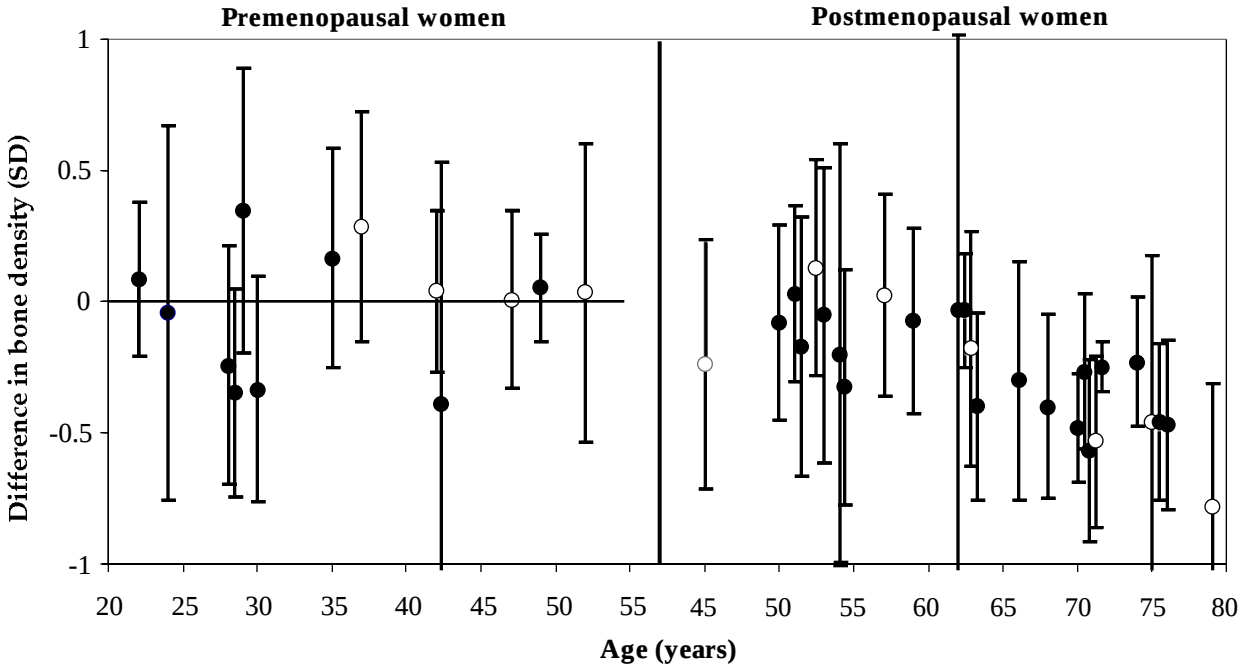
Bone densities were reported for current smokers compared with never smokers in most studies, but were reported for current compared with former and lifetime never smokers combined in a few studies. There was no evidence of a significant difference in BMD between smokers and nonsmokers in the premenopausal women (Figure 6.2). Two additional studies of premenopausal and postmenopausal women performed since the 1997 meta-analysis also show no significant differences in BMD between smokers and nonsmokers (Table 6.16) (Takada et al. 1997; Gregg et al. 1999); however, a study of premenopausal women from Australia did find a significantly lower BMD in female current smokers that was not found in the subgroup of female smokers who participated in sports (Jones and Scott 1999). Cross-sectional data from the Danish Osteoporosis Prevention Study showed lower BMD in current smokers compared with lifetime nonsmokers in perimenopausal women (Hermann et al. 2000). It is appropriate to consider these results unadjusted for other covariates in that adjusting for one of the most important risk factors for bone density—weight—actually may mask an association. Smoking-induced weight loss may represent an intervening variable in the causal chain between smoking and bone density reduction.

One study from Spain assessed smoking and BMD in healthy young males (Ortego-Centeno et al. 1997). In this study, male volunteers aged 20 through 45 years were measured for BMD in the lumbar spine and proximal femur; blood biochemical markers were also assessed. BMD was significantly lower for smokers of 20 or more cigarettes per day compared with nonsmokers. In multiple regression analyses considering all smokers, smoking was not significantly associated with measures of BMD. Interpretations of these findings are limited by the cross-sectional data and the small sample size.

Smoking Cessation and Bone Mineral Density Loss

Two prospective cohort studies assessed smoking cessation and BMD in men and women (Hollenbach et al. 1993; Kiel et al. 1996). In a study in Rancho Bernardo, California, Hollenbach and colleagues (1993) found that smoking cessation later in life was beneficial for men and women in halting BMD loss at hip sites (intertrochanter, total hip, femoral neck, and trochanter) where BMD is reduced in smokers. In men, smoking cessation was followed by a reduction in the rate of loss of the spinal BMD, and women experienced a significant decrease in the rate of BMD loss at the midradius after quitting. In the Framingham study, current or former smoking (past 10 years) was not associated with a lower BMD loss at any skeletal site among women who had not taken estrogen but it was in women who had (Kiel et al. 1996). Former male smokers who had quit for less than 10 years had a lower BMD than men who had quit for 10 or more years, independent of weight, alcohol consumption, or caffeine use.

Figure 6.2 Differences (95% confidence intervals), as a proportion of 1 standard deviation (SD), in bone mineral density between female smokers and nonsmokers according to age and menopausal status



Note: Fitted regression lines are shown. The 11 open circles refer to two studies (Rundgren and Mellström 1984; Law et al. 1997); the 28 solid circles refer to the other studies in the order listed in Table 6.15 (Fehily et al. 1992 through Johnell and Nilsson 1984 for premenopausal women, and Law et al. 1997 through Hollenbach et al. 1993 for postmenopausal women).
Source: Law and Hackshaw 1997, p. 843. Reprinted with permission.

Evidence Synthesis

Smoking, even at a young age, might increase risk for osteoporosis later in life if it reduces the peak bone mass attained, thereby compromising the peak from which decline begins. Only a few studies address smoking during adolescence, and the findings in women during the premenopausal years are conflicting, are not based on large studies, and do not provide strong evidence for an effect of smoking on BMD before menopause. For males, data are scant for this age range. Although an effect of smoking on BMD is plausible, the available evidence from observational studies is limited and inconsistent.

Conclusion

1. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and reduced bone density before menopause in women and in younger men.

Implications

The failure to demonstrate a causal relationship between smoking and bone density in young women does not detract from the basis for concern about smoking and osteoporosis in women. For women, smoking patterns established in younger years are likely to persist past menopause, and there is substantial evidence linking smoking to low bone density during menopause (see below). Future research should quantify the combined and cumulative effects of premenopausal and postmenopausal smoking on bone density. More research is needed in young men regarding the relationship between smoking and bone density.

Bone Density in Middle and Later Years of Life

Epidemiologic Evidence

In contrast to the findings for younger persons, findings of bone density studies performed in populations well beyond the years of peak bone mass demonstrate substantial differences between smokers and nonsmokers. As illustrated in Figure 6.2, based on the meta-analysis by Law and Hackshaw (1997), bone density was lower in smokers than in nonsmokers for postmenopausal women, and the difference increased linearly with age. For every 10-year increase in age, the bone density of smokers fell below that of nonsmokers by approximately 2 percent of the average bone density at the time of menopause, regardless of the skeletal site that was measured.

Since the publication of this meta-analysis, there have been additional studies of smoking and bone density in postmenopausal women and in men. Of four studies that did not demonstrate an association between smoking and bone density (Cheng et al. 1999; Varenna et al. 1999; Huuskonen et al. 2000; Kim et al. 2000), two had used quantitative ultrasound to measure bone status. Seven other studies did demonstrate statistically significant associations between smoking and BMD (Table 6.16) (Brot et al. 1997; Takada et al. 1997; Vogel et al. 1997; Grainge et al. 1998; Smeets-Goevaers et al. 1998; Hagiwara and Tsumura 1999; Hermann et al. 2000).

Data from cohort studies of older men and women also implicate smoking as a significant risk factor for bone loss (Table 6.17). Of the six studies that reported smoking data (three involving women and men, two involving women only, and one involving men only) (Sowers et al. 1992; Jones et al. 1994; Vogel et al. 1997; Burger et al. 1998; Guthrie et al. 1998; Hannan et al. 2000), three documented significantly more bone loss in female smokers than in female and male nonsmokers (Sowers et al. 1992; Burger et al. 1998; Guthrie et al. 1998), and three reported higher rates of loss among male smokers than among male nonsmokers (Vogel et al. 1997; Burger et al. 1998; Hannan et al. 2000). Interpretations of several of the studies are constrained by relatively small sample sizes and limited durations of follow-up.

Evidence Synthesis

Extensive and consistent data are available on BMD and smoking for perimenopausal and postmenopausal women and for older men. Data from cohort studies, which track changes in BMD over time, as well as from cross-sectional studies provide generally consistent evidence of increased rates of loss in postmenopausal women who smoke compared with nonsmokers. Smoking cessation appears to benefit BMD since limited data indicate higher rates of BMD loss for heavier smokers. Data are more limited for men. The 2001 Surgeon General's report (USDHHS 2001) found the evidence to be consistent for women and concluded that "Postmenopausal women who currently smoke have lower bone density than do women who do not smoke" (p. 321). There are a number of mechanisms that may underlie this finding.

Conclusions

1. In postmenopausal women, the evidence is sufficient to infer a causal relationship between smoking and low bone density.

2. In older men, the evidence is suggestive but not sufficient to infer a causal relationship between smoking and low bone density.

Implications

Smoking has an adverse effect on bone density in middle and later years of life; for every 10-year increase in age, the bone density of female smokers falls below that of nonsmokers by about a 0.14 standard deviation, or 2 percent of the average bone density at the time of menopause in women. Because a 1.0 standard deviation decrease in bone density doubles the risk of fracture, and because fracture incidence increases with age (Melton and Riggs 1987; Melton et al. 1987), the proportion of all fractures attributable to smoking would be expected to increase for smokers who continue smoking into older ages. Attempts to decrease smoking as early in life as possible are likely to reduce fractures that would be caused by smoking in old age.

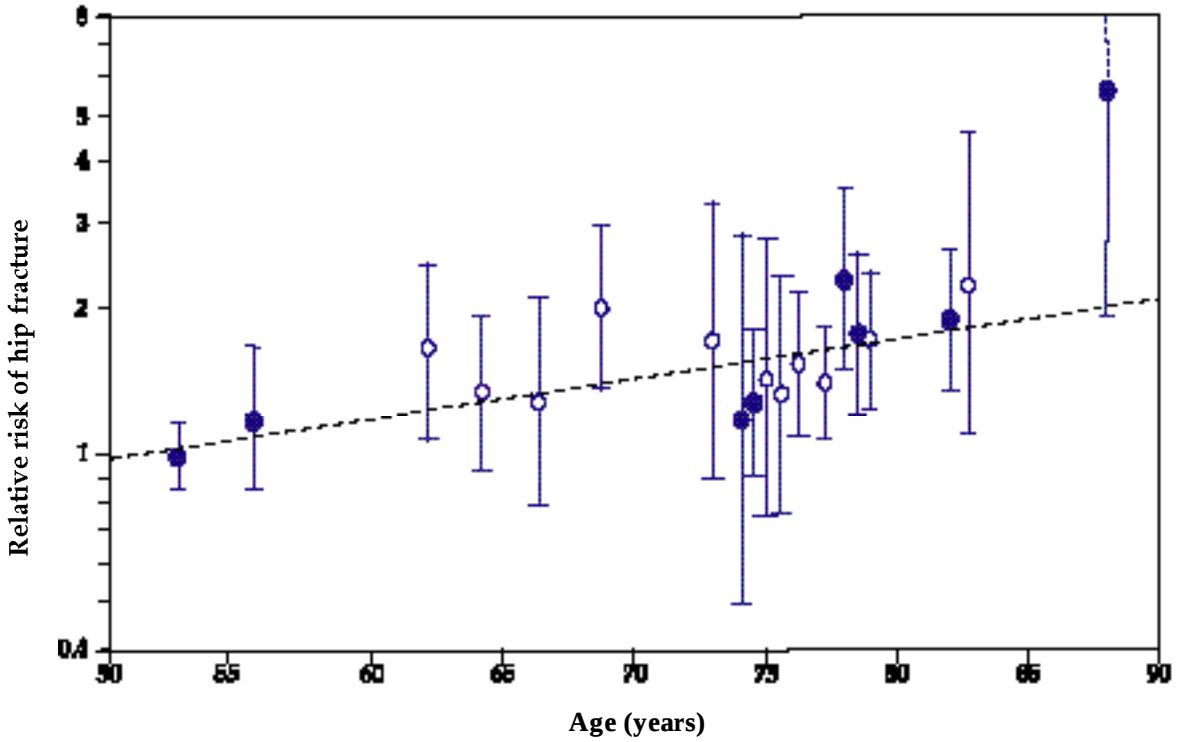
Because bone loss is relatively small over short periods of time, studies with longer durations of follow-up and minimal avoidable losses of participants at follow-up could add important information to the understanding of how smoking contributes to bone loss. Additional information is likely to come from studies of biochemical markers of bone turnover, which might further the understanding as to mechanisms whereby smoking accelerates bone loss.

Fractures

Epidemiologic Evidence

Hip fractures, the most frequently studied fractures in relation to smoking, account for a significant proportion of the morbidity and mortality attributed to osteoporosis. The meta-analysis by Law and colleagues (1997) reviewed 19 cohort and case-control studies of the risk of hip fractures in postmenopausal women according to whether they had COPDs. The studies differed with regard to the ages of the participants, duration of follow-up, and whether former smokers were included in the smoking or nonsmoking groups. Table 6.18 shows the characteristics of each of the 19 studies, demonstrating the range of ages at the time of the fracture. For the cohort studies, the duration of follow-up ranged from three years (Forsén et al. 1994) to 26 years (Kiel et al. 1992). Figure 6.3 shows the risk of hip fractures in smokers relative to nonsmokers according to age; the risks for smokers increased with increasing age. Major conclusions of the meta-analysis include (1) smoking has no material effect on bone density in premenopausal women; (2) postmenopausal bone loss is greater in smokers—an

Figure 6.3 Relative risk (95% confidence intervals) of hip fracture in smokers compared with nonsmokers in postmenopausal women according to age



Note: Each cohort study (8 solid circles) and case-control study (11 open circles) is in the same order as in Table 6.18. Fitted regression (dotted) line is shown.
Source: Law and Hackshaw 1997, p. 844. Reprinted with permission.

additional 0.2 percent of bone mass each year; (3) in comparisons of women who are current smokers with women who are nonsmokers, the risk of hip fracture is estimated to be 17 percent greater at 60 years of age, 41 percent greater at 70 years, 71 percent greater at 80 years, and 108 percent greater at 90 years; and (4) the estimated cumulative risk of hip fracture to 85 years of age in women is 19 percent in smokers and 12 percent in nonsmokers; to 90 years it is 37 percent and 22 percent, respectively. The data for men were much more limited but suggested similar consequences.

Since the publication of the meta-analysis by Law and colleagues (1997), some (Forsén et al. 1998; Burger et al. 1999; Kanis et al. 1999; Melhus et al. 1999; Baron et al. 2001) but not all subsequent studies of hip fracture (Fujiwara et al. 1997; Clark et al. 1998; Mussolino et al. 1998) have continued to show an association between smoking and an increased risk of hip fracture (Table 6.19). These studies have used various designs and have been carried out in diverse populations.

Data on the association between smoking and fractures at other sites are more limited (Table 6.20). Studies from the 1980s and early 1990s that examined fractures other than those of the hip rarely found an association with smoking, although more recent studies have demonstrated positive associations between smoking and vertebral fractures (Scane et al. 1999; Lau et al. 2000), ankle fractures (Honkanen et al. 1998), and the general categories of nonhip fractures (Jacqmin-Gadda et al. 1998) and of all fractures (Huopio et al. 2000).

Smoking Cessation and Hip Fractures

The association between smoking cessation and the risk of hip fractures was examined in several studies, including three prospective cohort studies with follow-up periods of 5 to 12 years (Forsén et al. 1998; Cornuz et al. 1999; Høidrup et al. 2000) and two case-control studies (La Vecchia et al. 1991; Cumming and Klineberg 1994). In men, successful smoking cessation of at least five years decreased the risk of hip fracture compared with continuing smokers (Høidrup et al. 2000), although other investigations found that this risk remained elevated for men and women smokers compared with lifetime nonsmokers (Cumming and Klineberg 1994; Forsén et al. 1998). Two studies also found no decrease in the risk for hip fractures in women after five years of smoking cessation (La Vecchia et al. 1991; Cornuz et al. 1999), and another found that no benefit from quitting for women, including premenopausal women, was observed until 10 years after cessation (adjusted RR = 0.7 [95 percent confidence interval (CI), 0.5–0.9] compared with current smokers) (Cornuz et al. 1999).

Evidence Synthesis

The evidence on smoking and fracture has been reviewed extensively in previous reports of the Surgeon General. The 1990 report considered evidence from eight case-control studies, noting that most showed an association with risk for fracture of the hip or vertebra. Five cohort studies, however, did not show a clear increase in risk and the report found the evidence to be inconclusive. Far more extensive data were available for the 2001 report, including substantially more studies of hip fracture in women. The case-control studies reviewed all indicated excess risk for hip fracture in smokers, with the RR ranging from 1.1 to 2.0. Six reports of cohort studies published subsequent to the 1990 report were also cited, all showing an increased risk for hip fracture in current smokers. The 2001 report (USDHHS 2001) concluded that "women who currently smoke have an increased risk for hip fracture compared with women who do not smoke" (p. 321).

This report extends the review of the 2001 report with additional studies and covers the evidence on men as well. The evidence consistently indicates an increased risk for women and men who smoke. Findings of some studies show a dose-response relationship between risk for hip fracture and the amount smoked. The RR tends to rise with age as would be expected, and the effect of smoking reflects sustained, additional bone loss beyond that associated with aging. The documented effects of smoking on BMD is consistent with the observational evidence on hip fracture.

For fracture sites other than the hip, the evidence has been less consistent. The 2001 Surgeon General's report found the evidence to be unclear. This report evaluated a number of studies for other sites, also finding the evidence to be mixed and limited in scope for any particular site.

Conclusions

1. The evidence is sufficient to infer a causal relationship between smoking and hip fractures.

2. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and fractures at sites other than the hip.

Implications

The RR of hip fractures in smokers increases with age, and hip fracture incidence increases with age, implying that the proportion of hip fractures attributable to smoking increases with age. Smoking is one of the major causes of fracture in older persons that can be prevented. Public health interventions aimed at helping smokers quit are likely to substantially reduce the number of hip fractures. Although hip fractures carry the greatest costs and risks of mortality and morbidity, other fractures also contribute to these outcomes. Further research is necessary to quantify the risks of these other fractures in smokers.

Table 6.18 Studies on the association between smoking and the risk of hip fractures in men and women used in the 1997 meta-analysis by Law and Hackshaw*

Study	Age at entry (years)	Mean age at fracture (years)	Number of persons (% smokers)	
			With fracture	Without fracture
Cohort studies				
Hemenway et al. 1988	34–59	53	662	68,056 (28)
Meyer et al. 1993	35–49	56	124	20,881 (37)
Holbrook et al. 1988	50–79	75	33	924
Kiel et al. 1992	28–62	75	167 (22)	2,243 (37)
Cummings et al. 1995	≥65	78	192	9,324 (10)
Forsén et al. 1994	≥50	78	220 (16)	14,598 (20)
Paganini-Hill et al. 1991	All ages	82	242 (13)	5,558 (13)
Case-control studies				
Wickham et al. 1989	≥65	88	44	1,375
La Vecchia et al. 1991	29–74	62	158 (11)	1,096 (6)
Williams et al. 1982	50–74	64	160 (60)	567 (53)

**Note:* The order of the studies in this table reflects the order of the regression lines in Figure 6.3.
†RR = Relative risk.
‡CI = Confidence interval.
§SD = Standard deviation.
ΔOR = Odds ratio.
¶ERT = Estrogen replacement therapy.

Findings

Compared with nonsmokers, RR[†] = 0.98 (95% CI[‡], 0.84–1.14) for former smokers, 0.95 (95% CI, 0.71–1.20) for current smokers of 1–14 cigarettes/day, 0.97 (95% CI, 0.79–1.20) for current smokers of 15–24 cigarettes/day, and 0.99 (95% CI, 0.78–1.25) for current smokers of ≥25 cigarettes/day

Compared with never smokers, the age-adjusted RR = 0.81 (95% CI, 0.45–1.46) for former smokers, 1.04 (95% CI, 0.71–1.53) for current smokers of 1–14 cigarettes/day, and 1.46 (95% CI, 0.81–2.64) for current smokers of ≥15 cigarettes/day

RR = 1.1 (not significant) for smokers compared with nonsmokers; adjusted for age, gender, body mass index (BMI), and alcohol use

Compared with never smokers, the age-adjusted RR = 1.08 (95% CI, 0.82–1.42) for ever smokers, 0.97 (95% CI, 0.68–1.39) for former smokers, 1.19 (95% CI, 0.84–1.69) for all current smokers, 1.16 (95% CI, 0.80–1.67) for light smokers (≤1 pack/day), and 1.45 (95% CI, 0.66–3.17) for heavy smokers (>1 pack/day)

Age-adjusted RR = 2.1 (95% CI, 1.4–3.3) for current smokers compared with never smokers

Incidence rates/1,000 person-years for current smokers compared with nonsmokers for men: 1.3 (SD[§] = 0.4) for ages 50–64 years, 3.4 (SD = 1.3) for 65–74 years, 10.3 (SD = 6.4) for ≥75 years; for women: 2.1 (SD = 1.4) for 50–64 years, 7.8 (SD = 3.5) for 65–74 years, and 23.9 (SD = 16.6) for ≥75 years

Compared with never smokers, the age-adjusted RR = 1.8 ($p < 0.001$) for current female smokers and 2.2 ($p < 0.05$) for current male smokers

Crude OR[Δ] = 5.6 (95% CI, 1.8–17.7) for current smokers compared with nonsmokers

Compared with never smokers, RR = 1.7 (95% CI, 1.0–3.0) for former smokers and 1.5 (95% CI, 1.0–2.1) for current smokers; adjusted for age, area of residence, education, BMI, menopausal status, ERT[¶], and alcohol use

Age-standardized OR for ≥1 year of estrogen use compared with obese (based on Ponderal index: height = inches/cubed root of weight [pounds]; obese = 9.6–12.5, average = 12.6–13.5, thin = 13.6–15.5) never smokers: obese ever smokers = 1.3 (95% CI, 0.4–4.5), average never smokers = 2.1 (95% CI, 0.7–5.9), average ever smokers = 2.1 (95% CI, 0.8–5.8), thin never smokers = 2.7 (95% CI, 0.5–14.0), and thin ever smokers = 6.4 (95% CI, 2.1–19.4)

Table 6.18 Continued

Study	Age at entry (years)	Mean age at fracture (years)	Number of persons (% smokers)	
			With fracture	Without fracture
Case-control studies				
Kreiger et al. 1982	45–74	66	98	801
Michaelsson et al. 1995	40–75	68	205 (18)	765 (10)
Kreiger et al. 1992	50–84	74	102 (29)	277 (17)
Grisso et al. 1994	≥45	75	109 (29)	169 (15)
Paganini-Hill et al. 1981	<80	75	83 (35)	166 (30)
Jaglal et al. 1993	55–84	75	381 (22)	1,138 (16)
Lau et al. 1988	All ages	76	400	800
Cooper et al. 1988	≥50	78	300 (48)	600 (37)
Cumming and Klineberg 1994	≥65	82	209	207

¶ERT = Estrogen replacement therapy.
**Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.
Source: Law and Hackshaw 1997.

Findings
No OR was given for smoking
Compared with never smokers, OR = 1.50 (95% CI, 1.10–2.05) for ever smokers, 1.17 (95% CI, 0.74–1.86) for former smokers of <20 pack-years**, 1.94 (95% CI, 0.96–3.92) for former smokers of ≥20 pack-years, 1.91 (95% CI, 1.12–3.26) for current smokers of <20 pack-years, and 1.82 (95% CI, 1.03–3.20) for current smokers of ≥20 pack-years
OR = 1.73 (95% CI, 0.90–3.32) for current smokers compared with never or former smokers; adjusted for age, dietary calcium, ovariectomy, ERT¶ (months), and Quetelet index (g/cm^2)
Compared with never smokers, OR = 1.2 (95% CI, 0.6–2.4) for former smokers, 1.3 (95% CI, 0.7–2.6) for all current smokers, 1.1 (95% CI, 0.5–2.4) for current smokers smoking <1 pack / day, and 2.0 (95% CI, 0.7–6.0) for those smoking ≥1 pack / day
Compared with never smokers, OR = 1.05 for current smokers of 1–10 cigarettes /day, and 1.96 for ≥11 cigarettes /day; adjusted for estrogen and ovarian status
Compared with zero pack-years, crude OR for 1–29 pack-years = 1.02 (95% CI, 0.72–1.43), 30–59 pack-years = 1.49 (95% CI, 1.01–2.21) and ≥60 pack-years = 1.43 (95% CI, 0.73–2.79)
RR = 1.3 (95% CI, 1.0–1.7) for current or former smokers compared with never smokers
RR = 1.7 (95% CI, 1.2–2.3) for ever smokers compared with never smokers
Compared with never smokers, OR for ever smokers = 1.6 (95% CI, 1.0–2.6), former smokers = 1.4 (95% CI, 0.8–2.5), and current smokers = 2.2 (95% CI, 1.1–4.6); adjusted for age, gender, and proxy status (when relevant)

Table 6.19 Studies on the association between smoking and the risk of hip fractures in men and women reported since the 1997 meta-analysis by Law and Hackshaw

Study	Design	Population
Fujiwara et al. 1997	Cohort	1,586 Japanese men, 2,987 Japanese women; mean age 58.5 ± 12.2 years; during and up to the 14-year follow-up, 55 incidents of hip fractures not attributable to traffic accidents were identified
Grisso et al. 1997	Case-control	356 men with radiologically confirmed hip fractures, 402 controls from 20 hospitals in Philadelphia, Pennsylvania, and 14 Kaiser Permanente hospitals in northern California
Clark et al. 1998	Case-control	45 Mexican men and 107 Mexican women with hip fractures, aged ≥45 years (mean age was 70.2 for men, 73.5 for women); 143 healthy controls (37 men, 106 women) without hip fractures, mean age was 68.9 for men, 71.1 for women
Forsén et al. 1998	Cohort	14,428 Norwegian men, 15,364 Norwegian women aged ≥50 years; during the 3-year follow-up, 421 new cases of hip fractures were identified
Mussolino et al. 1998	Cohort	2,879 white U.S. men aged 45–74 years; during the 22-year follow-up, 71 cases of hip fractures were identified
Turner et al. 1998	Cross-sectional	2,325 women aged ≥50 years from the Third National Health and Nutrition Examination Survey were queried about their history of a wrist or hip fracture
Burger et al. 1999	Cohort	2,193 Dutch men, 3,015 Dutch women aged ≥55 years; during a 4-year follow-up, 47 persons (14 men) experienced their first hip fracture
Cornuz et al. 1999	Cohort	116,229 female nurses (98% white) aged 34–59 years; during a 12-year follow-up, 377 hip fractures occurred because of low or moderate trauma
Høidrup et al. 1999	Cohort	6,159 postmenopausal Danish women; during a 15- to 17-year follow-up, 363 hip fractures were identified and validated
Kanis et al. 1999	Case-control	730 southern European men with hip fractures aged ≥50 years (mean age 73.9); 1,132 age-stratified controls

*OR = Odds ratio.
†CI = Confidence interval.
‡RR = Relative risk.

Findings
Smoking was not related to a risk for hip fractures
Men in the lowest quintile of body mass had an OR* = 3.8 (95% CI†, 2.3–6.4) compared with the highest quintile
Smoking was not associated with the risk of a hip fracture
Among the persons aged ≤75 years, the RR‡ of a hip fracture was elevated for current smokers (men = 5.0 [95% CI, 1.5–16.9]; women = 1.9 [95% CI, 1.2–3.1]); for former smokers, including those who had quit smoking >5 years previously, men = 4.4 (95% CI, 1.2–15.3); women = 1.3 (95% CI, 0.6–3.0)
Smoking was not significantly associated with hip fractures
The bivariate analysis showed that the percentage of former smokers in the wrist or hip fracture group was greater than in the nonfracture group; smoking was not associated with fractures in multivariate analyses
When adjusted for age and gender, current smoking was a statistically significant indicator of hip fracture risk (OR = 2.6 [95% CI, 1.4–5.1])
Current smokers experienced higher rates of hip fractures than never smokers; the risk increased with the number of cigarettes smoked daily; the age-adjusted RR of hip fracture was 1.3 (95% CI, 1.0–1.7) for all cigarette smokers and 1.6 (95% CI, 1.1–2.3) for those who smoked ≥25 cigarettes / day (p = 0.09 for trend); 10 years after quitting, the risk of a fracture was no longer significant
The use of hormone replacement therapy was associated with a lower risk for a hip fracture in former (RR = 0.55 [95% CI, 0.22–1.37]) and current (RR = 0.61 [95% CI, 0.38–0.99]) smokers but not in never smokers (RR = 1.10 [95% CI, 0.60–2.03])
A long history of smoking (>49 years) was associated with a significant increase in the risk of a hip fracture (RR = 1.44 [95% CI, 1.10–1.89]; p <0.01)

Table 6.19 Continued

Study	Design	Population
Melhus et al. 1999	Case-control	247 Swedish women with hip fractures and 873 controls, from a cohort study of 66,651 Swedish women aged 40–76 years
Høidrup et al. 2000	3 population studies in Copenhagen, Denmark	13,393 women and 17,379 men initially examined between 1964 and 1992, followed through 1997
Huopio et al. 2000	Cohort	3,068 Finnish women aged 47–56 years; during 3.6 years of follow-up, 295 (8.4%) sustained a fracture
Kato et al. 2000	Prospective cohort	6,250 postmenopausal women aged 34–65 years at baseline; average 7.6 years follow-up
Baron et al. 2001	Case-control	1,328 cases of postmenopausal women with a mean age of 72.5 years and low trauma hip fractures; 3,262 female controls of a similar age and residence

Findings
OR for hip fractures among current smokers was 2.1 (95% CI, 1.3–3.2); OR for hip fractures among current smokers with a low intake of vitamin E was 3.0 (95% CI, 1.6–5.4) and of vitamin C, 3.0 (95% CI, 1.6–5.6); OR decreased to 1.1 (95% CI, 0.5–2.4) and 1.4 (95% CI, 0.7–3.0) with high intakes of vitamins E and C, respectively; in current smokers with a low intake of vitamins E and C, OR increased to 4.9 (95% CI, 2.2–11.0)
RR = 1.36 (95% CI, 1.12–1.65) for female and 1.59 (95% CI, 1.04–2.43) for male current smokers compared with nonsmokers; adjusted for body mass index
Smoking was associated with an increased risk of any fracture (RR = 1.8 [95% CI, 1.1–2.7]) independent of low spine or hip bone mineral density, previous fracture history, and 23 chronic illnesses
RR = 71.6 per 105 woman-years (the time from the baseline [first] examination to the date of first post-menopausal fracture) for hip fractures; risks increased with increasing age, body height, and total fat intake, and were lower for obese and African American women
Current smokers had an increased risk for a hip fracture (OR = 1.66 [95% CI, 1.41–1.95]); the OR for a fracture was not significantly higher among former smokers (OR = 1.15 [95% CI, 0.97–1.37])

Table 6.20 Studies on the association between smoking and the risk of fractures at sites other than the hip in men and women

Study	Design	Population
	Vertebral fracture	
Aloia et al. 1985	Age-matched case-control	58 cases 58 controls Volunteer women Mean age 64 years United States
Kleerekoper et al. 1989	Case-control	266 cases 263 controls Postmenopausal women who were screened for an osteoporosis trial Aged 45–75 years United States
Cooper et al. 1991	Survey of general practice patients	1,012 women Aged 48–81 years United Kingdom 79 fractures
Santavirta et al. 1992	Population-based survey	27,278 females Aged ≥15 years Finland 105 fractures
Scane et al. 1999	Case-control	91 men with vertebral fractures 91 age-matched controls Aged 27–79 years (median, 64) United Kingdom
Lau et al. 2000	Cross-sectional	396 community-dwelling Chinese men Aged 70–79 years
	Distal forearm fracture	
Williams et al. 1982	Population-based case-control	184 cases 567 controls Aged 50–74 years United States
Kelsey et al. 1992	Cohort	9,704 women Aged ≥65 years United States 171 fractures over 2.2 years (mean)

*RR = Relative risk.
†CI = Confidence interval.
‡BMI = Body mass index.
§OR = Odds ratio.

Findings
Percentage of smokers ($p < 0.01$) Cases: 59% Controls: 30%
Percentage of current smokers ($p > 0.05$) Cases: 27% Controls: 20%
Smoking >10 cigarettes / day for >10 years was not related to a risk for fractures
RR* = 1.1 (95% CI†, 0.6–2.0) for current smokers; adjusted for age, history of trauma, tuberculosis, peptic ulcer, BMI‡, and occupation
Current smoking was associated with a significantly increased risk of a vertebral fracture (OR§ = 2.8 [95% CI, 1.2–6.7])
Heavy smoking was a significant risk factor for a vertebral deformity (OR = 6.5 [95% CI, 1.3–32.7])
There was a higher fracture risk in women smokers using estrogen
RR = 1.0 (95% CI, 0.96–1.0) for current smokers (10 cigarettes / day) compared with never smokers

Table 6.20 Continued

Study	Design	Population
	Distal forearm fracture	
Kreiger et al. 1992	Hospital case-control	Aged 50–84 years Canada 54 fractures
Mallmin et al. 1994	Population-based case-control	385 cases 385 controls Aged 40–80 years Sweden
Honkanen et al. 1998	Retrospective survey	12,192 women Aged 47–56 years Finland 345 fractures
Kato et al. 2000	Prospective cohort	6,250 postmenopausal women aged 34–65 years at baseline; average 7.6 years follow-up
	Proximal humerus fracture	
Kelsey et al. 1992	Cohort	9,704 women Aged ≥65 years United States 79 fractures over 2.2 years (mean)
	Ankle fracture	
Seeley et al. 1996	Cohort	9,704 women Aged ≥65 years 191 fractures over 5.9 years (mean)
Honkanen et al. 1998	Retrospective survey	12,192 women Aged 47–56 years Finland 210 fractures
	Foot fracture	
Seeley et al. 1996	Cohort	9,704 women Aged ≥65 years 204 fractures over 5.9 years (mean)
	Nonhip fracture	
Jacqmin-Gadda et al. 1998	Cohort	3,216 French men and women aged ≥65 years (mean age 74.8); during a 5-year follow-up, 265 persons (8.2%) reported 1 fracture, 19 (0.6%) reported 2 fractures, and 1 (0.03%) reported 3 fractures

‡BMI = Body mass index.

Findings
RR = 1.5 (95% CI, 0.9–2.6) for current smokers compared with former smokers or never smokers; adjusted for age and BMI‡
RR = 0.9 (95% CI, 0.5–1.6) for current smokers; adjusted for multiple factors including age, BMI, physical activity, and hormone use
Current smoking: RR = 0.9 (95% CI, 0.6–1.4); any smoking: RR = 0.6 (95% CI, 0.3–1.1), 1–10 cigarettes/day; RR = 1.4 (95% CI, 0.9–2.3), >10 cigarettes/day; adjusted for age, BMI, menopausal status, and chronic health disorders
RR = 334.7 per 10^5 woman-years (the time from the baseline [first] examination to the date of first post-menopausal fracture) for wrist fractures; risks increased with increasing age, body height, and total fat intake, and were lower for obese and African American women
RR = 1.2 (95% CI, 0.9–1.6) for current smokers (10 cigarettes/day)
There was no association with current smoking
Current smoking: RR = 2.2 (95% CI, 1.6–3.2); any smoking: RR = 1.6 (95% CI, 0.9–2.8), 1–10 cigarettes/day; RR = 3.0 (95% CI, 1.9–4.6) for >10 cigarettes/day; adjusted for age, BMI, menopausal status, and chronic health disorders
There was no association with current smoking
Current smoking was associated with a higher risk for nonhip fractures (OR = 1.68 [95% CI, 1.08–2.60]), but not for hip fractures (OR = 0.73 [95% CI, 0.24–2.20])

Dental Diseases

Diseases of the teeth and their supporting structures are a major public health issue with a significant impact on personal well-being. More than $60 billion were spent on oral health care in the United States in 2000, and each year acute oral conditions result in an estimated 1.6 million missed school days and 2.4 million lost workdays. Although there have been tremendous improvements in the oral health of the U.S. public during the past several decades, oral diseases and conditions remain highly prevalent. For example, recent national data indicate that 66 percent of persons aged 12 through 17 years and 94 percent of those aged 18 years and older have experienced dental caries in their permanent teeth (USDHHS 2000).

As the oral cavity is the first part of the human anatomy to be exposed to mainstream smoke in active smokers, researchers have long hypothesized that smoking could have a deleterious effect on the teeth and their supporting structures. However, research on this association was hampered for decades by (1) lack of consensus on case definitions for some diseases; (2) difficulty in measuring oral conditions and consequent use of indices of questionable validity; (3) some incorrect assumptions about disease etiology, pathogenesis, distribution, and natural history; and (4) limited capacity for epidemiologic investigations within the dental research community. As a result, until recently the literature was sparse and findings were not definitive.

Conclusions of Previous Surgeon General's Reports

The previous Surgeon General's reports on smoking and health did not include dental or periodontal effects of smoking, although oral cancer and related premalignant lesions have been addressed. During the past 15 years, however, there has been a substantial amount of research on smoking and oral health, and this topic was addressed in *Oral Health in America: A Report of the Surgeon General* (USDHHS 2000). This section reviews the epidemiologic evidence for smoking as a causal factor for the most common forms of nonmalignant oral disease; cancers of the oral cavity are covered in Chapter 2.

Periodontitis

The periodontium includes those hard and soft tissue structures that support the teeth: the gingiva, the cementum covering the root surfaces of the teeth, the periodontal ligament that attaches the tooth root surfaces to the adjacent alveolar bone supporting each tooth, and the alveolar bone. The gingiva covers the other periodontal structures and comprises attached and free gingiva. The attached gingiva extends from the bottom of the gingival sulcus to the mucogingival junction, where it is contiguous with the mucous membrane of the lip, cheek, and floor of the mouth. The free gingiva extends from the base of the gingival sulcus to the gingival margin.

In a healthy state, the gingival margin is approximately 0.5 to 2.5 mm coronal to the cemento-enamel junction (CEJ) (where the enamel on the crown of the tooth meets the root). The sulcus is 1 to 3 mm in depth and does not bleed when probed. The base of the sulcus is formed by the junctional epithelium, which joins the gingival connective tissue to the tooth surface. Healthy gingiva is usually pink in color, is well adapted to the teeth, has a stippled surface texture, and is tightly bound to the underlying alveolar bone and the roots of the teeth.

Based on the most recent classification system developed by the American Academy of Periodontology, there are at least eight categories of periodontal diseases and conditions (Armitage 1999). Of those, the two most common are gingivitis and chronic periodontitis. Gingivitis is defined as an inflammation of the gingiva in which the junctional epithelium remains on or near the enamel covering the crown of the tooth. It is characterized clinically by redness, gingival bleeding, edema or enlargement, and occasional gingival sensitivity and tenderness (Genco 1990a). Chronic periodontitis (previously called adult periodontitis) is an inflammation of the gingiva and the adjacent attachment apparatus that is characterized by loss of clinical attachment because of destruction of the periodontal ligament and loss of the adjacent supporting bone (Flemmig 1999). Clinical features of chronic periodontitis may include edema, erythema, gingival bleeding upon probing, periodontal pocketing, or suppuration.

The most common forms of both gingivitis and periodontitis involve bacterial infection. Severe forms of periodontitis often are associated with infection by specific bacteria that colonize the subgingival area (Genco 2000). Destruction of soft tissue and alveolar bone is thought to involve toxins and proteases produced by the bacteria as well as hyperresponsiveness and reactivity of various components of the immune system (e.g., the production of cytokines and prostaglandins). Smoking may play a role in the pathogenesis of periodontal diseases by altering immune function and tissue repair.

The understanding of the distribution and natural history of periodontitis has evolved over the past several decades. Previously, it was thought that virtually all persons were susceptible to severe disease if oral hygiene was inadequate. The disease was considered to progress in a linear fashion throughout life from gingivitis to periodontitis to bone loss to tooth loss, generally attacking the entire dentition and was nearly universal among adults (World Health Organization 1961). This concept was driven, in part, by epidemiologic indices that incorporated signs of both gingivitis and periodontitis, analytic methods that aggregated and averaged measurements within persons and populations, and assumptions about disease progression on the part of the early oral epidemiologists. In the current model of periodontal diseases, a small proportion of persons in most populations are considered to have severe periodontitis; periodontitis is usually preceded by gingivitis but few sites with gingivitis later develop periodontitis; periodontal tissues can undergo some degree of self-repair; and generalized forms of periodontitis are uncommon (American Academy of Periodontology 1996; Burt and Eklund 1999).

Based on current concepts of periodontitis, clinical or epidemiologic assessment of the disease involves detailed measurements of various signs of soft tissue or bone destruction at two to six sites per tooth either on all teeth or on selected teeth. Among the most common measurements is probing pocket depth (PPD), which is measured by inserting a calibrated probe into the gingival sulcus and recording the distance in millimeters from the gingival margin to the base of the gingival sulcus (if healthy) or pocket (if diseased). Because the pathogenesis of periodontitis involves destruction of the junctional epithelium at the base of the sulcus, a PPD greater than 4 mm may indicate disease (Genco 1990b). Another common parameter is the clinical attachment level (CAL), which is measured as distance in millimeters from the CEJ to the base of the gingival sulcus or pocket. It is a direct measure of the position of the periodontal epithelial attachment of a tooth relative to its ideal position at the CEJ. Many cross-sectional studies have used the terminology "loss of periodontal attachment" (LPA) to describe this same parameter, although more recent studies tend to reserve the use of the term LPA for longitudinal assessments of change in the CAL between two points in time. The longitudinal change in CAL is sometimes called relative attachment loss, particularly when computer-linked electronic periodontal probes are used to record the measurements from a fixed reference point such as a cusp tip. Examples of all of these parameters and terms are found in the epidemiologic literature on the association between smoking and periodontal destruction. Because periodontal destruction may occur without deep pocket formation, PPD alone will underestimate disease and may not be sufficient as the prime indicator of disease (Goodson 1990). Intraoral radiographs have been used to assess alveolar bone loss from periodontitis, but this approach can have low sensitivity and may underestimate true bone loss (Goodson 1990; Eickholz and Hausmann 2000; Pepelassi et al. 2000). In addition, radiography often is not logistically feasible or acceptable to examinees during large-scale field epidemiologic studies. At this time, change in the CAL is considered the prime indicator of periodontal destruction.

Biologic Basis

Microbiology

It is possible that cigarette smoking affects periodontal health by altering the quantity or composition of bacterial dental plaque. Although some studies found that smokers had more visible bacterial plaque than nonsmokers (Sheiham 1971; Bastiaan and Waite 1978; Lavstedt et al. 1982; Preber and Bergström 1985), many other studies reported no significant differences in mean plaque levels or rates of plaque accumulation (Alexander 1970; Swenson 1979; Bergström 1981, 1990; Feldman et al. 1983; Macgregor et al. 1985; Bergström and Eliasson 1987a,b; Lie et al. 1998). Cross-sectional differences in plaque levels between smokers and nonsmokers may be due to differences in oral hygiene practices rather than to smoking per se (Preber and Kant 1973; Andrews et al. 1998). However, the presence of specific bacterial species in periodontal plaque may be more important than the quantity of visible plaque and debris on the teeth in the pathogenesis of severe periodontitis (Genco 1996). Some evidence indicates that smokers may be more likely than nonsmokers to harbor specific periodontal pathogens. A study of adults exhibiting a wide range of

periodontal conditions (Zambon et al. 1996) found that subgingival infection with *Bacteroides forsythus* was more common in current smokers even after adjusting for disease severity, with a dose-response relationship between the amount of smoking and infection. Current smokers were also more likely than former or lifetime nonsmokers to have subgingival infection with *Actinobacillus actinomycetemcomitans*. Consistent with those findings, a study of dental clinic patients found that plaque samples from smokers were 11 times more likely than samples from nonsmokers to test positive for one of three periodontal pathogens (Kazor et al. 1999). In a study of young adults with early-onset periodontitis (Kamma et al. 1999), 11 postulated periodontal pathogens were detected more frequently and in greater numbers in the subgingival plaque from smokers than from nonsmokers. Smoking may increase the likelihood of infection with periodontal pathogenic microorganisms even among persons with no clinical signs of disease. In a study of young adults who did not have periodontitis (Shiloah et al. 2000), smokers were 18 times more likely than nonsmokers to have at least one of eight periodontal pathogens in their subgingival plaque. Several studies, however, reported no differences in the plaque bacteria between smokers and nonsmokers (Preber et al. 1992; Stoltenberg et al. 1993). Additional evidence suggests that smoking may act synergistically to potentiate the effects of toxins produced by periodontal pathogenic bacteria (Sayers et al. 1999).

Immune Function

There is substantial evidence that smoking affects both localized and systemic components of the immune system, although the links between these effects and periodontal disease remain to be established. Smoking increases the number but impairs the functions of polymorphonuclear leukocytes (PMNs, or neutrophils), peripheral blood cells that represent the first line of defense against microorganisms (Noble and Penny 1975; Barbour et al. 1997). Either an impairment of the PMN's ability to neutralize periodontal infections or an overstimulation of potentially tissue-destructive processes can lead to periodontal destruction (American Academy of Periodontology 1999). For example, smoking can impair PMN chemotaxis, phagocytosis, and oxidative burst (Eichel and Shahrik 1969; Kenney et al. 1977; Ryder et al. 1998). Impaired phagocytosis has been implicated in refractory periodontitis (MacFarlane et al. 1992). Smoking also appears to compromise the function of macrophages, which play a vital role in both humoral and cell-mediated immunity, and of B lymphocytes, the major cell type involved in the humoral immune system. Exposure to cigarette smoke also appears to have an immunosuppressive effect on T lymphocytes, which may reduce antibody response to periodontal bacteria (Barbour et al. 1997). Smokers may have a decreased production of antibodies specific to periodontal pathogens, especially IgG2 (Quinn et al. 1998). Recent evidence suggests that levels of cytokines in gingival crevicular fluid, which are secreted by mononuclear cells and are associated with collagen destruction and bone resorption, may be increased in smokers (Boström et al. 1998a,b). Furthermore, there may be a synergistic interaction between smoking and the genotype for a specific cytokine, IL-1, in the development of severe periodontitis (Kornman and di Giovine 1998).

Gingival Blood Flow and Soft Tissue Effects

It has long been hypothesized that the peripheral vasoconstrictive effect of tobacco smoke and nicotine reduces gingival blood flow and thereby impairs the delivery of oxygen and nutrients to gingival tissue. There is some evidence of reduced blood flow in gingival tissues (Clarke et al. 1981; Clarke and Shephard 1984) and reduced size and altered morphology of capillaries in oral mucosa and gingival tissues (Johnson et al. 1989) following exposure to tobacco smoke or nicotine. However, more recent evidence appears contradictory (Baab and Öberg 1987; Johnson et al. 1991). Smokers tend to exhibit less gingival bleeding than nonsmokers, even with control for bacterial plaque levels (Preber and Bergström 1985, 1986; Bergström and Preber 1986; Bergström 1990; Danielsen et al. 1990; Newbrun 1996). However, this reduced gingival bleeding may be related more to the suppression of an inflammatory response than to reduced gingival blood flow.

Nicotine can be stored in and released from periodontal fibroblasts, possibly affecting their morphology and ability to attach to root surfaces (Raulin et al. 1988; Hanes et al. 1991; James et al. 1999). In addition, nicotine may inhibit the growth of gingival fibroblasts and their production of collagen and fibronectin, components of the gingival extracellular matrix involved in the structure and attachment of gingiva (Tipton and Dabbous 1995). Thus, it is possible that smoking impairs the ability of periodontal tissues to repair damaged junctional epithelium. Smoking impairs

wound healing and compromises the prognosis following surgical and nonsurgical periodontal therapy (Preber and Bergström 1990; Ah et al. 1994; Newman et al. 1994; Rosenberg and Cutler 1994; Preber et al. 1995; Tonetti et al. 1995; Grossi et al. 1996, 1997; Kaldahl et al. 1996; Kinane and Radvar 1997; Trombelli and Scabbia 1997; Boström et al. 1998b; Machtei et al. 1998; Renvert et al. 1998; Palmer et al. 1999; Papantonopoulos 1999; Söder et al. 1999). One study that employed statistical modeling of longitudinal changes in the CAL concluded that diminished capacity for repair, rather than direct tissue damage, probably was the major mechanism involved in smoking-associated periodontal destruction (Faddy et al. 2000).

Epidemiologic Evidence

Epidemiologic studies of smoking and periodontitis have employed a variety of case definitions for disease, using various combinations of PPD, CAL or LPA, and alveolar bone loss. Some studies used indices for "periodontal disease" that are no longer considered valid indicators for the prevalence of disease in populations (Burt and Eklund 1999). Other studies employed indices that originally were intended for use in population-based treatment planning and not for etiologic studies, such as the Community Periodontal Index of Treatment Needs (Ainamo et al. 1982). Some studies did not use a case definition for disease, but instead assessed mean levels of one or more clinical parameters among exposed and unexposed groups, or described the proportion of the study population that exceeded various measurement thresholds (e.g., ≥4 mm LPA). Some studies, primarily conducted before the 1970s, provided no case definition other than diagnosis by the examiner. Despite the numerous problems measuring the disease, published epidemiologic and clinical studies consistently show a moderate to strong degree of association between smoking and periodontitis.

To identify epidemiologic studies of smoking and periodontitis, the National Library of Medicine's PubMed database was searched for English language publications from 1965–2000, using the following Medical Subject Headings (MeSH) key words: "smoking," "tobacco," "periodontal diseases," and "periodontitis." These terms also were searched as title words. The smoking and health database maintained by the Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, CDC, was also searched using those terms as key words. Reference lists from published studies, review articles, and textbooks were examined to identify additional studies.

Tables 6.21 through 6.23 summarize the findings from 6 case-control studies, 52 cross-sectional studies, and 12 cohort studies conducted between 1959 and 2000. The case-control studies consistently found that persons with periodontitis were more likely than controls without periodontitis to be smokers, although not all studies separated current smokers from former smokers in their analyses. These studies generally controlled for potential confounders in either the selection of a control group or in their analyses. Cross-sectional studies that attempted to estimate parameters such as the odds ratio (OR) consistently reported moderate to strong degrees of association between smoking and periodontitis under a wide range of case definitions (Beck et al. 1990; Horning et al. 1992; Haber et al. 1993; Stoltenberg et al. 1993; Grossi et al. 1994, 1995; Sakki et al. 1995; Tomar et al. 1995; Ahlberg et al. 1996; Dolan et al. 1997a; Norderyd and Hugoson 1998; Shizukuishi et al. 1998; Wakai et al. 1999; Tomar and Asma 2000). Consistent with the findings from case-control and cross-sectional studies, cohort studies reported RR estimates for smoking and onset or progression of periodontitis of 1.4 to more than 10, using a wide range of outcome measures. Of the cross-sectional studies that examined the relationship separately for current smokers and former smokers, current smokers were more likely than former smokers to have periodontitis (Haber et al. 1993; Dolan et al. 1997a; Wakai et al. 1999; Tomar and Asma 2000). Two case-control studies (Haber and Kent 1992; Gelskey et al. 1998) and several cross-sectional studies (Grossi et al. 1994, 1995; Norderyd and Hugoson 1998; Wakai et al. 1999; Tomar and Asma 2000) reported a significant dose-response relationship between the number of cigarettes smoked per day and disease status. Two of these studies used cigarette-years[2] or pack-years as the measure for exposure (Grossi et al. 1994, 1995), which combined quantity and duration of smoking to characterize the exposure. One study reported a significant dose-response relationship between the duration of smoking and disease risk (Tomar and Asma 2000). That study also found a significant inverse relationship between the number of years since quitting smoking and the odds of having periodontitis.

[2]Cigarette-years = The number of years of smoking multiplied by the number of cigarettes smoked per day.

Nearly all other reviewed studies reported either mean measures of PPD or CAL/LPA or radiographically demonstrated alveolar bone loss by smoking status, or they reported the percentage of persons with some specified number or percentage of sites exceeding some threshold on one or more of these clinical parameters. With only one exception (Preber et al. 1980), all cross-sectional and cohort studies that measured differences in mean CAL/LPA or mean PPD found a worse periodontal status among smokers than among nonsmokers. That 1980 study (Preber et al. 1980), however, was conducted with young military recruits whose duration of smoking must have been relatively short because of their age.

Evidence Synthesis

The available epidemiologic literature is highly consistent in showing a moderate to strong association between cigarette smoking and periodontal destruction. The association is robust across a wide range of case definitions, populations, and study designs. There is also evidence of a dose-response relationship between smoking intensity and risk for periodontitis. Both number of cigarettes smoked and duration of smoking are positively associated with disease risk. The risk of periodontitis appears to decrease after smokers stop smoking, with a decreasing risk as the duration of successful cessation increases. Although only a few prospective cohort studies have been carried out, they consistently found that smokers were more likely than nonsmokers to experience the onset or progression of disease. The association cannot be explained by confounding.

The mechanisms involved in smoking-associated periodontal destruction are still not fully understood. However, available evidence supports several hypotheses. An immune mechanism is plausible because smoking affects many elements of the human immune system. The effects of smoking on local and systemic immune factors may make the smoker more susceptible to bacterial infection. In addition, substantial evidence indicates that smoking impairs the regeneration and repair of periodontal tissues. The evidence is inconsistent in suggesting that smoking quantitatively or qualitatively alters the microflora of subgingival plaque.

Conclusion

1. The evidence is sufficient to infer a causal relationship between smoking and periodontitis.

Implications

Smoking intervention should be a major component of prevention and treatment of periodontitis. A recent study (Tomar and Asma 2000) concluded that more than 50 percent of the cases of adult periodontitis in the United States are attributable to cigarette smoking. In light of this conclusion, and because more than one-half of U.S. adult smokers visit a dentist each year (Tomar et al. 1996), the dental care community has both the opportunity and the professional obligation to counsel patients who smoke to quit. The dental office may also provide an opportune setting for tobacco use prevention efforts among young people (Hovell et al. 1996). Unfortunately, a lack of awareness and inadequate skills may be barriers to further involvement by dentists and dental hygienists (Secker-Walker et al. 1994; Dolan et al. 1997b).

Further research is needed to achieve a greater understanding of the mechanisms involved in smoking-associated periodontitis. In addition, more behavioral research is needed to enhance the willingness and ability of dentists and dental hygienists to intervene in their patients' use of tobacco and to counsel younger patients against tobacco use. Educational research should identify effective methods for training students of dentistry and dental hygiene, as well as licensed clinicians, to become competent at counseling their patients to stop using tobacco and assisting patients who want to quit (Tomar et al. 1996; Barker and Williams 1999; Cabana et al. 1999).

Dental Caries

Dental caries is an infectious, communicable, multifactorial disease in which bacterially produced acids dissolve the hard enamel surface of a tooth (Featherstone 1999). Unchecked, the bacteria may then penetrate the underlying dentin and progress into the soft pulp tissue, which is rich in blood and nerve tissue. Dental caries commonly results in loss of tooth structure and discomfort. Untreated dental caries commonly progresses to incapacitating pain and a bacterial infection that leads to pulpal necrosis, tooth extraction, and loss of dental function, and can progress to an acute systemic infection. The major etiologic factors for this disease are thought to be specific bacteria in dental plaque (particularly *Streptococcus [S.] mutans* and *S. lactobacilli*) on susceptible tooth surfaces and the availability of fermentable carbohydrates.

Most epidemiologic studies conducted during the past 60 years have used some variation of the decayed, missing (due to caries), or filled permanent teeth (DMFT) index (Klein et al. 1938) to measure the frequency of dental caries. Until the mid-1980s the proportion of the population with dental caries was rarely used to estimate disease prevalence in industrialized populations because the disease was nearly universal. The DMFT index is more a measure of disease severity than of disease prevalence; it is simply the sum of the number of permanent teeth (T) that are decayed (D), missing due to dental caries (M), or filled (F). This index, if applied to the number of coronal (i.e., enamel-covered) tooth surfaces (S), is designated the DMFS. The M component is often omitted in adult studies because of the inherent uncertainty as to why a tooth is missing. Thus, some studies report DFT or DFS scores. Other studies report the components of DMFT individually, such as DS, FS, and MS. Nearly all studies aggregate DMF data by reporting the population mean. The number of root surfaces affected by caries is almost always scored and reported separately from coronal caries, and usually is designated as RDFS or RDS (the M component is not reported for root-surface caries).

Biologic Basis

There are several hypothesized mechanisms that may underlie the association between smoking and dental caries. As discussed in the section on smoking and periodontitis, evidence is inconsistent in showing that smoking per se alters either the bacterial profile in the gingivi or the rate of formation of dental plaque (Alexander 1970; Swenson 1979; Bergström 1981, 1990; Feldman et al. 1983; Macgregor et al. 1985; Bergström and Eliasson 1987a,b; Lie et al. 1998). Differences in oral care behavior between smokers and nonsmokers provide an indirect explanation. Perhaps the most consistent explanation is that smokers tend to practice less frequent or less effective oral hygiene and plaque removal (Preber and Kant 1973; Macgregor and Rugg-Gunn 1986; Andrews et al. 1998).

Several studies concluded that smoking might lower the pH or reduce the buffering capacity of saliva (Heintze 1984; Parvinen 1984), impairing the function of saliva as a protective factor against enamel demineralization (Edgar and Higham 1996). In contrast, one review concluded that smoking increases salivary flow rate (Macgregor 1989), raising pH and increasing salivary calcium concentration (ten Cate 1996). These factors would tend to favor enamel remineralization, but benefit would come only if the flow rate increase were sustained. Another comprehensive review concluded that smoking has a minor effect on saliva flow rate and its chemical composition, at least in terms of factors thought to affect dental cariogenesis (Christen et al. 1991). In sum, an effect of smoking on salivary function does not appear to be a key mechanism in causing dental caries.

The association between smoking and root-surface caries suggested by several studies may be due, in part, to the periodontal effects of smoking. The loss of periodontal attachment and subsequent exposure of root surfaces are necessary conditions for root-surface caries to occur (Burt et al. 1986; Stamm et al. 1990). Persons who experience a loss of periodontal attachment attributable to smoking may also be at greater risk for subsequent root-surface caries.

Epidemiologic Evidence

To identify the epidemiologic studies on smoking and dental caries, the National Library of Medicine's PubMed database was searched for English language publications from 1965–2000. The following MeSH key words were used: "smoking," "tobacco," "dental caries," and "tooth demineralization." These terms also were searched as title words. The smoking and health database maintained by CDC's Office on Smoking and Health was also searched using the same terms as key words. Reference lists from published studies, review articles, and textbooks were sources for additional studies.

Table 6.24 summarizes 12 cross-sectional studies and 3 cohort studies published between 1952 and 1999. Most cross-sectional studies used some variation of the DMF index to measure caries prevalence; all but two (Hart et al. 1995; Tomar and Winn 1999) found that smokers experienced more coronal dental caries than nonsmokers, as measured by mean DS, DFS, DMFS, or DMFT. In general, differences between smokers and nonsmokers in mean DMFT or DMFS were small, even in studies in which the differences were reported to be "statistically significant." The largest differences in numbers of carious lesions were reported in studies that used DMFS (Ludwick and Massler 1952; Ainamo 1971; Zitterbart et al. 1990; Axelsson et al. 1998). None of those studies, however, appeared to limit the "missing" component of DMFS to those tooth surfaces lost due to caries. Consequently, these studies may mix caries caused by smoking with the advanced periodontal destruction that can cause tooth loss in adults.

Few of the studies on the association between smoking and dental caries controlled for potential confounding factors. Although the observed association between smoking and dental caries may reflect a causal relationship, it is also possible that it reflects factors common to both smoking and the risk of dental caries. For example, in industrialized nations both dental caries (USDHHS 2000) and cigarette smoking (Giovino et al. 1995) are more prevalent among groups with lower socioeconomic status (SES) than among higher SES groups. SES is a strong correlate of factors that affect dental caries status, such as diet, use of dental services, and oral hygiene practices (USDHHS 2000). None of the studies adjusted for SES or other potential confounding factors in examining the association between smoking and dental caries. Several literature reviews do suggest that the association between smoking and dental caries may reflect the tendency for smokers to practice less effective dental hygiene and plaque removal (Macgregor 1989; Christen et al. 1991; Kassirer 1994; Andrews et al. 1998).

Few studies adjusted for other notable correlates of both smoking and dental caries in their analyses. The DMF index is a cumulative, irreversible index. As persons experience decayed or filled permanent tooth surfaces or lose teeth over their lifetimes, their DMFT or DMFS scores will increase. Therefore, DMFT and DMFS can be associated strongly with age even if age per se is not a risk factor for incidence of dental caries. Few studies, however, adjusted for age in their analyses. Several studies provided age-specific mean caries scores (Ludwick and Massler 1952; Zitterbart et al. 1990; Axelsson et al. 1998) or age-specific significance testing of differences in means (Hirsch et al. 1991), which revealed an inconsistent association between smoking and caries within age groups. In the one study that used a nationally representative sample of U.S. adults and adjusted for age and race or ethnicity, DFT and DMS were actually slightly lower among male smokers than among those who had never used tobacco (Tomar and Winn 1999).

Two studies attempted to investigate a dose-response relationship between smoking and dental caries (Ludwick and Massler 1952; Ainamo 1971). Although smokers in the highest category of cigarettes smoked per day had experienced slightly higher DMFT, DMFS, or DS than those in the lowest dose categories, the relationship was not consistent. The first study presented age-specific comparisons of mean DMFT and DMFS by the number of cigarettes smoked per day, which showed no clear pattern within age strata. The second study did not present age-stratified or age-adjusted estimates, which potentially could present difficulties in interpreting the association between a disease index that is cumulative with age and an exposure that probably was increasing with age in the study population (aged 18 through 26 years).

Smoking may be associated more with root-surface caries than with coronal caries. Two cohort studies (Ravald et al. 1993; Locker 1996) and two cross-sectional studies (Locker 1992; Tomar and Winn 1999) reported higher mean RDFS or RDS scores among smokers, but in one cohort study (Locker 1996) smoking was not found to be a significant predictor of root-surface caries in multiple logistic regression modeling.

Evidence Synthesis

Few studies have investigated the association between cigarette smoking and dental caries. The available literature is fairly consistent in suggesting that smokers may experience slightly more decayed, missing, or filled coronal tooth surfaces. In addition, smokers generally experienced more decayed or filled root surfaces than nonsmokers. However, many of the published studies did not address potential confounders of these associations. It is therefore possible that the observed associations could reflect in part the presence of other factors associated with both smoking and dental caries. Evidence for a dose-response relationship is sparse and inconsistent. Studies that examined whether quitting smoking reduced the risk of caries development were not identified.

There is little evidence for a biologic mechanism that would explain the role of smoking in the development of coronal dental caries. Methodologic considerations limit the interpretation of findings from epidemiologic studies. The few lines of investigation undertaken have been inconsistent in identifying either bacterial or salivary effects that would be expected to increase this risk.

Some evidence suggests that smoking may indirectly increase the risk for root-surface caries. The mechanism probably involves an increased exposure of root surfaces of teeth secondary to loss of periodontal attachment. This relationship may reflect the impact of smoking on periodontium and the subsequent exposure of tooth root surfaces to the oral environment.

Conclusions

1. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and coronal dental caries.

2. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and root-surface caries.

Implications

To better characterize the relationship between cigarette smoking and dental caries, future investigations will need to control for potential confounding factors. These studies should be of the cohort design to allow for assessments of the effect of smoking on carious lesion formation and to determine whether smoking cessation reduces disease incidence. Investigations into an association between smoking and root-surface caries will need to apply indices that take into account the number of root surfaces at risk, such as the Root Caries Index (Katz 1980), or control for root surface exposure in trying to identify whether smoking acts through a direct or indirect mechanism.

The increased risk for root-surface caries may be due to smoking-associated periodontal destruction and subsequent exposure of root surfaces of teeth to the oral environment. Because of the causal relationship between smoking and periodontitis as well as with many other diseases, and because more than one-half of U.S. adult smokers visit a dentist each year, the dental care community has both the opportunity and the professional obligation to counsel patients who smoke to quit.

Table 6.21 Case-control studies on the association between smoking and periodontitis

Study	Number of cases/ controls	Case definition	Sources of cases/ controls	Findings		
				Smoking status	Odds ratio	95% confidence interval
Preber and Bergström 1986	260/ 1,769	Moderate to severe periodontitis; advanced periodontitis (mean PPD* >4.5 mm)	Dental school periodontal clinic/ population-based sample	Current smokers		
				Moderate to severe periodontitis	2.1	1.7–2.7
				Advanced periodontitis	2.4	1.7–3.5
Bergström and Eliasson 1987b	134†	PPD ≥4 mm on ≥1 site	Periodontal patients/ population-based sample	Current smokers		
				Men	2.8†	NR‡
				Women	2.1†	NR
				Total	2.5†	NR
Haber and Kent 1992	196/209	Moderate periodontitis (20–50% bone loss on ≥1 surface); advanced periodontitis (>50% bone loss on ≥1 surface)	Periodontal offices/ general dental practices	Never smoked	1.0	
				Ever smoked (moderate or advanced disease)	2.6	1.6–3.9
				Current smokers (moderate or advanced disease)	3.3	1.8–5.8
				≤10 cigarettes/ day	1.0	0.4–2.5
				>10 cigarettes/ day	5.4	2.8–10.6
				≤10 years' duration	1.0	0.2–6.5
				>10 years' duration	4.3	1.6–12.1
				Moderate disease	1.8	0.9–3.7
				Advanced disease	6.1	2.9–12.8
MacFarlane et al. 1992	31/12	Refractory periodontitis: persistent failure of conventional treatment including root planing, surgery, and antibiotics	Private periodontal practices and dental school graduate periodontal clinics/ laboratory personnel	Current smokers (odds ratio estimate calculated from reported raw data by adding 0.5 to each cell; 0 smokers in the control group)	203.6	9.8–4, 242.4

*PPD = Probing pocket depth.
†Odds ratio estimates in this study were based on comparisons with smoking prevalence in a general population survey in Stockholm, Sweden. However, periodontal health was not examined in this "control" group.
‡NR = Data were not reported.

Table 6.21 Continued

Study	Number of cases/ controls	Case definition	Sources of cases/ controls	Findings		
				Smoking status	Odds ratio	95% confidence interval
Gelskey et al. 1998	205/205	≥1 tooth with alveolar bone loss >3 mm, or ≥1 tooth with PPD* ≥7 mm	Dental school clinic	Never smoked	1.0	NR
				Ever smoked	1.8	1.1–2.9
				Cigarette-years§		
				Aged 35–87 years		
				1–300	1.2	0.7–1.8
				301–500	1.8	0.9–2.7
				>500	3.8	2.9–4.7
				Aged 35–54 years		
				1–300	1.0	0.3–1.7
				301–500	3.2	2.1–4.2
				>500	4.3	6.2–8.5
				Aged 55–87 years		
				1–300	1.7	0.7–3.9
				301–500	1.1	0.01–4.0
				>500	2.2	0.01–7.6
Quinn et al. 1998	270/193	≥2 mm loss of periodontal attachment on ≥1 tooth	Clinical Research Center for Periodontal Diseases, Virginia	Blacks		
				Former smokers	1.0Δ	NR
				Current smokers	2.1Δ	0.9–5.1
				Whites		
				Former smokers	1.0Δ	NR
				Current smokers	4.0Δ	2.1–7.6

*PPD = Probing pocket depth.
§Cigarette-years = Number of years of smoking multiplied by the number of cigarettes smoked per day.
ΔCrude odds ratio estimates were calculated from data reported in the paper.

Table 6.22 Cross-sectional studies on the association between smoking and periodontitis

Study	Population	Findings	Comments
Arno et al. 1959	728 male factory workers and staff Aged 21–45 years Norway	No quantitative results were reported	Mean alveolar bone loss appeared to increase with more cigarettes / day in graphic plots of deviations from the sample mean; the analysis of variance verified with a significant degree of certainty that the difference could not be due to chance (mean and test scores were not reported)
Brandtzaeg and Jamison 1964	206 male army recruits Aged 19–25 years Norway	Mean Periodontal Index score Nonsmokers 0.71 <10 cigarettes / day 0.79 ≥10 cigarettes / day 1.05 Mean Oral Hygiene Index score Nonsmokers 1.22 <10 cigarettes / day 1.45 ≥10 cigarettes / day 1.59	An association between smoking and the Periodontal Index score was not statistically significant in the analysis of covariance
Solomon et al. 1968	2,182 male and 5,009 female dental clinic and hospital patients Aged 20–79 years United States (New York)	Prevalence of periodontal disease was consistently higher among ever smokers than among never smokers for both men and women (e.g., aged 40 years: white men, 75 vs. 50%; white women, 65 vs. 50%)	Periodontal disease included both gingivitis and periodontal disease with or without pocket formation; smoking was strongly associated with periodontal disease in the age-stratified Cochran's test for both men and women
Summers and Oberman 1968	Probability sample of 154 men and 170 women Aged ≥20 years (mean or range not reported)	Multiple correlation coefficients for cigarette use and the Periodontal Disease Index score by gender Men 0.591 Women 0.551	The Periodontal Disease Index was used to measure periodontal disease; cigarette smoking was measured in packs per day; it is unclear if former smokers were included in this multiple correlation analysis
Ainamo 1971	167 male military recruits Aged 18–26 years Finland	Mean LPA* by daily smoking habit Cigarettes / day — LPA 0 — 0.049 1–9 — 0.069 10–20 — 0.072 >20 — 0.108	LPA was measured clinically on 4 surfaces of all erupted teeth

Note: Unless otherwise defined, current, former, and never refer to smoking status.
*LPA = Loss of periodontal attachment.

Table 6.22 Continued

Study	Population	Findings	Comments
Preber et al. 1980	134 male army conscripts Aged 19–27 years Sweden	There were no significant differences between smokers (n = 81) and nonsmokers (n = 53) in mean bone level or PPD[†]	PPD was clinically assessed on 6 teeth (1st molars, upper right central incisor, lower left central incisor); radiographic assessments were of lower incisors only
Bergström and Floderus-Myrhed 1983	164 twin pairs, selected from twin registry, discordant on smoking Aged 39–78 years Sweden	Mean alveolar bone index High-exposed twins 1.09 Low-exposed twins 0.94 Number of teeth lost High-exposed twins 11.3 Low-exposed twins 9.6	Alveolar bone index was based on a 5-category ordinal scale of radiographic bone loss, with no information on quantity or duration of smoking; the low-exposed group included both nonsmokers and twins with a lifetime exposure to smoking considered to be less than the twin
Feldman et al. 1983	862 men Mean age of nonsmokers = 47.9 years; mean age of smokers = 43.8 years United States	Mean PPD (mm) Smokers 0.73 Nonsmokers 0.56 Mean bone loss Smokers 0.70 Nonsmokers 0.42	Adjusted for age in the analysis of variance; the nonsmoking group included former smokers
Ismail et al. 1983	Population-based sample of 2,948 persons Aged 25–74 years United States	Mean Periodontal Index score by smoking status Current smokers 1.6 Former smokers 1.1 Never smoked 1.0	An association between Periodontal Index scores and current smoking remained significant after adjusting for the Oral Hygiene Index score, race, gender, education, poverty index, frequency of toothbrushing, age, and income in a multiple linear regression model

[†]PPD = Probing pocket depth.

Table 6.22 Continued

Study	Population	Findings	Comments
Markkanen et al. 1985	Population-based sample of 2,019 men and 2,349 women Aged ≥30 years Finland	Prevalence (%) of PPD† 4–6 mm Men Current smokers 51.6 Nonsmokers 51.7 Women Current smokers 50.8 Nonsmokers 50.8 Total Current smokers 51.3 Nonsmokers 51.2 Prevalence of PPD >6 mm Men Current smokers 33.1 Nonsmokers 30.6 Women Current smokers 20.5 Nonsmokers 19.3 Total Current smokers 29.6 Nonsmokers 24.2	Nonsmokers included former smokers; periodontal status was measured by the Periodontal Treatment Need System (PTNS), classifying each quadrant of the mouth by the highest score within that quadrant and each person according to the highest quadrant score; there were no significant differences between smokers and nonsmokers in periodontal pocketing when stratified by gender; smoking was not a significant correlate of the PTNS score in a log-linear model that also included gender, age, and the number of dentate quadrants
Bergström and Eliasson 1987a	203 male and 32 female professional musicians Aged 21–60 years Sweden	Alveolar bone height (% of root length) Aged 21–40 years Smokers 84.4 Nonsmokers 86.3 Aged 41–50 years Smokers 79.2 Nonsmokers 83.1 Aged 51–60 years Smokers 68.0 Nonsmokers 76.1 Total Smokers 77.9 Nonsmokers 82.3	Radiographically determined alveolar bone height was significantly lower in smokers than in nonsmokers across age groups and plaque index scores; there were no significant differences in plaque levels between smokers and non-smokers; former smokers were excluded from the analysis
Bergström and Eliasson 1987b	208 male and 34 female professional musicians Aged 21–60 years Sweden	Mean number of periodontal pockets ≥4 mm Aged 21–40 years Smokers 27.3 Nonsmokers 13.4 Aged 41–60 years Smokers 39.9 Nonsmokers 31.0 Total Smokers 36.0 Nonsmokers 21.8	The mean number of periodontal pockets was significantly greater in smokers than in nonsmokers across age groups and plaque index scores

†PPD = Probing pocket depth.

Table 6.22 Continued

Study	Population	Findings	Comments
Levy et al. 1987	Population-based sample of 477 dentate adults Aged ≥65 years United States (Iowa)	Multiple linear regression coefficient for proportion of teeth that were periodontally healthy by the number of cigarettes smoked Males -0.203 Females -0.088 (not statistically significant)	Periodontally healthy teeth were defined as PPD† ≤3 mm with no gingival bleeding; other variables in the models for males were the number of teeth, age, Parkinson's disease, ever smoked a pipe, exercise level, and proportion of teeth with calculus and with recession; for females: the number of teeth; age; and proportion of teeth with coronal decay, calculus, and recession
Beck et al. 1990	Population-based sample of 381 blacks and 308 whites Aged ≥65 years United States (North Carolina)	OR‡ estimates (95% CI§) for tobacco use and severe LPA Whites Unadjusted 6.7 (3.2–14.0) Adjusted 6.2 (2.6–14.5) Blacks Unadjusted 2.8 (1.7–4.7) Adjusted 2.9 (1.6–5.1)	Severe LPA* was defined as ≥4 periodontal sites with LPA ≥5 mm, and ≥1 of those sites with PPD ≥4 mm; it is unclear if tobacco use included forms other than cigarettes; the prevalence of smoking or other forms of tobacco use was not provided; logistic models for whites included tobacco use, education, dentate status of sibling, most recent dental visit, periodontal plaque bacteria levels, the presence of dental caries, a perceived worsening of finances, and a perceived bother by things in life; for blacks, models included tobacco use, education, reported bleeding gums, most recent dental visit, bacteria levels, socioeconomic status, morning cough, and perceived financial status

*LPA = Loss of periodontal attachment.
†PPD = Probing pocket depth.
‡OR = Odds ratio.
§CI = Confidence interval.

Table 6.22 Continued

Study	Population	Findings	Comments
Goultschin et al. 1990	154 male and 190 female hospital workers Aged 17–74 years Israel	Mean number of sextants affected, based on CPITN[Δ] scores 0 Smokers 0.32 Nonsmokers 0.84 1 Smokers 0.55 Nonsmokers 1.01 2 Smokers 1.52 Nonsmokers 1.32 3 Smokers 2.46 Nonsmokers 1.71 4 Smokers 0.47 Nonsmokers 0.61	The mean number of affected sextants did not differ significantly between smokers and nonsmokers for CPITN scores 2 and 4; adjusted for age and gender
Hansen et al. 1990a	Population-based sample of 156 persons Aged 35 years Norway	Mean number of quadrants with ≥1 site with PPD[†] ≥5 mm Smokers 0.397 Nonsmokers 0.395	No significant difference in the mean number of quadrants affected
Bergström et al. 1991	210 female dental hygienists Aged 24–60 years Sweden	Mean alveolar bone loss (mm) Current smokers 1.71 Former smokers 1.55 Never smoked 1.45 Mean alveolar bone loss (mm) in current smokers by cigarettes / day ≤10 1.60 >10 2.06 Mean alveolar bone loss (mm) in current smokers by duration of smoking (years) ≤15 1.39 >15 1.89	Bone loss was assessed radiographically for interdental septum of right posterior teeth; associations between bone loss and cigarette habits were consistent within age strata; smoking was a significant predictor of bone loss in multiple linear regression models that included age
Horning et al. 1992	1,520 male and 263 female dental patients United States	OR (95% CI) for moderate or advanced periodontitis Smokers 1.8 (1.2–2.7)	This logistic regression model included age, ethnicity, gender, and smoking status; it is unclear if former smokers were included in the analysis

[†]PPD = Probing pocket depth.
[Δ]CPITN = Community Periodontal Index of Treatment Needs.

Table 6.22 Continued

Study	Population	Findings	Comments
Locker 1992; Locker and Leake 1993	Population-based sample of 702 dentate adults Aged ≥50 years Canada (Ontario)	Mean LPA* (mm) Current smokers 3.7 Former smokers 2.9 Never smoked 2.7 Sites (%) with LPA ≥2 mm Current smokers 84.7 Former smokers 77.6 Never smoked 72.3 Sites (%) with LPA ≥5 mm Current smokers 30.2 Former smokers 15.9 Never smoked 13.8 Prevalence of severe LPA Current smokers 34.4 Former smokers 20.4 Never smoked 13.1	Severe LPA was defined as the upper 20th percentile of distribution of LPA in the full study population (≥3.8 mm)
Haber et al. 1993	132 patients with insulin-dependent diabetes mellitus from diabetes clinics; 95 HMO¶ patients	OR (95% CI) of periodontitis by diabetes and smoking status No diabetes Current smokers 8.6 (2.7–27.8) Former smokers 2.1 (1.1–4.2) Never smoked (referent) Diabetes Current smokers 6.9 (2.6–18.5) Former smokers 1.8 (0.8–4.2) Never smoked (referent)	Case definition of periodontitis: ≥1 site with PPD† ≥5 mm and LPA ≥2 mm; Mantel-Haenszel summary OR estimates were adjusted for age
Stoltenberg et al. 1993	63 smokers (mean age 48 years) and 126 nonsmokers (mean age 49 years) matched for age, gender, and plaque and calculus levels HMO patients United States (Minnesota)	Mean PPD (mm) Smokers 3.12 Nonsmokers 2.94 Prevalence (%), OR, and 95% CI for having mean PPD ≥3.5 mm Smokers 24 5.3 (2.0–13.8) Nonsmokers 6 (referent) Prevalence (%) of ≥1 site with PPD ≥3.5 mm Smokers 76.2 Nonsmokers 59.5	It is unclear if former smokers were included in the study; smokers also had a higher prevalence than nonsmokers of ≥1 site with PPD ≥4.5 mm or ≥5.5 mm

*LPA = Loss of periodontal attachment.
†PPD = Probing pocket depth.
¶HMO = Health maintenance organization.

Table 6.22 Continued

Study	Population	Findings	Comments
Wouters et al. 1993	Population-based sample of 378 men and 345 women Aged ≥20 years Sweden	Age-standardized mean interproximal alveolar bone height as a percentage of root length, by smoking status Current smokers 77.0 Former smokers 81.5 Never smoked 83.1	Current smoking (but not former smoking) was significantly associated with mean interproximal alveolar bone heights in a multiple linear regression model that included gender, age, urban/rural residence, level of education, frequency of dental and dental hygiene visits, number of tooth surfaces, plaque and calculus scores, and the presence of defective dental restorations
Grossi et al. 1994	Population-based sample of 741 women and 685 men Aged 25–74 years United States (New York)	OR (95% CI) for smoking and LPA* Pack-years** 5.3–15.0 2.05 (1.47–2.87) 15.1–30.0 2.77 (1.91–4.02) 30.1–150.0 4.75 (3.28–6.91)	This stepwise ordinal logistic regression analysis used the mean LPA as a dependent variable (5 ordinal categories), and included age, gender, education, diabetes status, anemia, allergy, and plaque bacteria levels
Linden and Mullally 1994	Random sample of 82 regular dental attenders Aged 20–33 years Northern Ireland	Mean PPD† (mm) Current smokers 2.9 Nonsmokers 2.6 Mean number of pockets ≥4 mm Current smokers 14.6 Nonsmokers 5.8 Mean LPA (mm) Current smokers 1.2 Nonsmokers 0.7 Mean number of LPA sites ≥2 mm Current smokers 21.8 Nonsmokers 9.3	Nonsmokers included never smokers and those who had quit ≥2 years before examination

*LPA = Loss of periodontal attachment.
†PPD = Probing pocket depth.
**Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Table 6.22 Continued

Study	Population	Findings	Comments
Söder et al. 1994	Population-based sample of 840 men and 841 women Aged 31–40 years Sweden	Prevalence (%) of teeth (≥1) with PPD† ≥5 mm by smoking status Current smokers 23.1 Former smokers 18.7 Never smoked 10.1 Mean number (%) of teeth with PPD ≥5 mm by smoking status Current smokers 1.4 (5.3) Former smokers 0.9 (3.4) Never smoked 0.4 (1.6)	Smoking was a highly significant correlate of the number of teeth with PPD ≥5 mm in a multiple linear regression model that also included gender, most recent dental visit, debris and calculus index scores, and the number of teeth
Grossi et al. 1995	Population-based sample of 696 women and 665 men Aged 25–74 years United States (New York)	OR (95% CI) for smoking and alveolar bone loss Pack-years >0–5.2 1.48 (1.02–2.14) 5.3–15.0 3.25 (2.33–4.54) 15.1–30.0 5.79 (4.08–8.27) 30.1–150.0 7.28 (5.09–10.31)	This stepwise ordinal logistic regression analysis, with mean alveolar bone loss as a dependent variable (4 ordinal categories), also included age, gender, race, education, kidney disease, allergy, and plaque bacteria levels
Martinez-Canut et al. 1995	340 male and 549 female periodontal patients with mild to moderate periodontitis Aged 21–76 years Spain	Mean PPD (mm) by cigarettes / day 0 3.36 1–10 3.47 11–20 3.68 ≥21 3.69 Mean GR†† (mm) by cigarettes / day 0 0.48 1–10 0.43 11–20 0.68 ≥21 0.81 Mean LPA (mm) by cigarettes / day 0 3.84 1–10 3.72 11–20 4.36 ≥21 4.50	The number of cigarettes smoked per day was significantly associated with log transformed mean GR, PPD, and LPA* in ANOVA‡‡ models that also included age and gender

*LPA = Loss of periodontal attachment.
†PPD = Probing pocket depth.
††GR = Gingival recession.
‡‡ANOVA = Analysis of variance.

Table 6.22 Continued

Study	Population	Findings	Comments
Sakki et al. 1995	Population-based sample of 266 men and 261 women Aged 55 years Finland	Periodontal sites (%) at risk for PPD† ≥3 mm Never smoked 8.4 Ever smoked 15.3 OR for periodontitis (95% CI) Ever smoked 1.73 (1.11–2.68)	Current and former smokers were not separated; in this multiple logistic regression model, persons with disease were defined as those in the upper one-third of the distribution of the percentage of sites with PPD ≥3 mm; dietary habits, alcohol intake, and toothbrushing frequency were also included
Schenkein et al. 1995	431 male and 335 female periodontal patients and their family members Aged 5–80 years United States (Virginia)	Prevalence (%) of current smoking by disease classification Localized juvenile periodontitis (LJP) 20 Generalized early-onset periodontitis (GEOP) 43 Adult periodontitis 38 Healthy 16 Mean number of teeth with LPA* ≥5 mm by disease and smoking status GEOP Current smokers 49.0 Not current 36.8 GEOP (probands) Current smokers 62.7 Not current 49.8 Adult periodontitis Current smokers 16.2 Not current 8.2	Current smoking was determined by serum cotinine analysis; former smoking was not measured; case definitions differed for probands and family members; means were adjusted for age and plaque index scores; among persons with LJP, the mean LPA and mean number of teeth with LPA ≥2 mm or ≥5 mm did not differ between smokers and nonsmokers
Söder et al. 1995	85 men and 59 women with at least 1 PPD site ≥5 mm, selected from population-based sample Aged 31–40 years Sweden	Mean PPD (mm) by smoking status Current smokers 3.0 Nonsmokers 2.8 Number of PPD sites at ≥5 mm Current smokers 15.4 Nonsmokers 11.6 Mean alveolar bone height (%) Current smokers 76.9 Nonsmokers 80.2	There was no control group; all subjects had disease; response rate was 50% among persons with disease identified in a population-based survey; it is unclear if nonsmokers included former smokers

*LPA = Loss of periodontal attachment.
†PPD = Probing pocket depth.

Table 6.22 Continued

Study	Population	Findings	Comments
Tomar et al. 1995	416 male and 58 female HIV[§§]-infected military personnel Aged 18–49 years United States	Unadjusted OR (95% CI) for having ≥1 LPA* site ≥5 mm Current smokers 2.6 (1.5–4.8) Former smokers 2.4 (1.2–4.9) Never smoked 1.0 (referent) Adjusted OR (95% CI) for having ≥1 LPA site ≥5 mm Current smokers 2.0 (1.1–3.5) Former smokers 1.0 (referent)	This multiple logistic regression model included age, stage of HIV disease, gender, retirement status, gingival cratering or ulceration, AZT[ΔΔ] use, and the presence of oral candidiasis
Ahlberg et al. 1996	483 male industrial workers Aged 38–65 years Finland	Adjusted OR (95% CI) for having PPD[†] ≥4 mm Smokers 2.1 (1.3–3.5)	Used the CPITN[Δ]; persons who had quit smoking <6 months before the study were considered smokers; all others were nonsmokers; this logistic regression model included education, access to subsidized dental care, toothbrushing frequency, most recent dental visit, and age
Alpagot et al. 1996	71 female and 46 male dental patients Aged 18–70 years United States (Minnesota)	Pearson correlation coefficients, pack-years Mean LPA (mm) 0.23 Mean PPD (mm) 0.27	An association between pack-years of smoking and the mean LPA or mean PPD was statistically significant in stepwise multiple linear regression models that also included age, enzyme levels in gingival crevicular fluid (β-glucuronidase, neutrophil elastase, myeloperoxidase), and plaque bacteria levels (*Fasibacterium nucleatum*, *Prevotella intermedia*, *Porphyromonas gingivalis*, *Eikenella corrodens*, and *Actinobacillus actinomycetemcomitans*)

*LPA = Loss of periodontal attachment.
[†]PPD = Probing pocket depth.
[Δ]CPITN = Community Periodontal Index of Treatment Needs.
[§§]HIV = Human immunodeficiency virus.
[ΔΔ]AZT = Azidothymidine or zidovudine, a medication used to treat HIV infections.

Table 6.22 Continued

Study	Population	Findings	Comments
Bridges et al. 1996	118 men with diabetes (46 with type I, 72 with type II) and 115 age-matched men without diabetes, from outpatient clinics Aged 24–78 years United States (Kentucky)	Pearson correlation coefficients for smoking and periodontal parameters Mean PPD† (mm) Diabetic 0.23 Nondiabetic 0.25 Mean LPA* (mm) Diabetic 0.34 Nondiabetic NR¶¶	The mean PPD and LPA were described as higher among smokers with diabetes than among other groups, but the data were not reported; smoking was reported to be significantly associated with the mean PPD and LPA in a multiple linear regression model, but regression parameters were not reported; smoking included cigarettes, cigars, and pipes; the prevalence of tobacco use was not reported
González et al. 1996	79 persons with established periodontitis, including 30 current smokers, 34 former smokers, 15 never smokers Aged 25–64 years United States (New York)	Correlation coefficients between serum cotinine levels and periodontal measures Mean LPA (mm) 0.498 Mean crestal bone height (mm) 0.473	None
Mullally and Linden 1996	100 periodontal patients 50 current smokers (mean age 44 years) and 50 never smokers (mean age 46 years) Northern Ireland	Persons (%) with furcation involvement of ≥1 molar Current smokers 74 Never smoked 40 Molars with furcation involvement (%) Current smokers 39 Never smoked 16	Maxillary and mandibular 1st and 2nd molars were assessed radiographically; furcation involvement was defined as the area of radiolucency at furcation of the roots of at least 1 molar; molars with fused roots were excluded from the analysis

*LPA = Loss of periodontal attachment.
†PPD = Probing pocket depth.
¶¶NR = Data were not reported.

Table 6.22 Continued

Study	Population	Findings	Comments
Dolan et al. 1997a	Population-based sample of 471 adults Aged ≥45 years United States (Florida)	Prevalence (%) of teeth (≥1) with ≥7 mm LPA* Current smokers 49 Former smokers 33 Never smoked 37 OR (95% CI) for teeth (≥1) with ≥7 mm LPA Current smokers 1.9 (1.2–2.9) Former smokers 1.1 (0.8–1.6) Never smoked (referent) Teeth / person with 4–6 mm LPA (mean %) Current smokers 42 Former smokers 36 Never smoked 35 Teeth / person with ≥7 mm LPA (mean %) Current smokers 21 Former smokers 10 Never smoked 8	Estimates of prevalence and extent of LPA were significantly higher among current smokers but were not adjusted for other factors; OR estimates were adjusted for diabetes status, use of dental care services, tooth-brushing, flossing, and use of toothpicks
Hildebolt et al. 1997	Convenience sample of 155 postmenopausal women Aged 41–71 years United States (Missouri)	Correlation between pack-years and LPA = 0.16 ($p < 0.07$) Parameter estimates for least square linear regression model: Intercept 1.01 Age 0.02 Years menopausal 0.02 Current smokers 2.22 Age*** current smokers -0.04	There was a significant association between age and current smoking status; pack-years of smoking were not significantly associated with the mean LPA among current smokers

*LPA = Loss of periodontal attachment.
***Age was retained in the model because of its interaction with current smokers.

Table 6.22 Continued

Study	Population	Findings	Comments
Imaki et al. 1997	1,611 male factory workers Aged 20–59 years Japan	Persons (%) with PPD[†] ≥4 mm by plaque bacteria levels, age, smoking status, and cigarettes / day Low plaque levels Aged 20–39 years Current smokers 15.1 1–20 14.3 ≥21 16.9 Former smokers 12.8 Never smoked 17.4 Aged 40–59 years Current smokers 43.7 1–20 40.5 ≥21 47.3 Former smokers 31.6 Never smoked 32.0 High plaque levels Aged 20–39 years Current smokers 49.7 1–20 49.3 ≥21 50.5 Former smokers 43.4 Never smoked 29.3 Aged 40–59 years Current smokers 84.8 1–20 81.3 ≥21 88.5 Former smokers 82.5 Never smoked 72.3	Used the CPITN[Δ]; periodontal pocketing was significantly more prevalent among smokers than nonsmokers, and among persons with high plaque levels
Taani 1997	Convenience sample of 998 dental patients Aged 20–60 years Jordan	Prevalence (%) of PPD ≥4 mm by age and smoking status Aged 20–34 years Smokers 17.0 Nonsmokers 7.5 Aged 35–44 years Smokers 21.7 Nonsmokers 18.8 Aged 45–60 years Smokers 27.9 Nonsmokers 25.7	Nonsmokers included both never smokers and those who had quit ≥2 years earlier; periodontal status was measured by the CPITN

[†]PPD = Probing pocket depth.
[Δ]CPITN = Community Periodontal Index of Treatment Needs.

Table 6.22 Continued

Study	Population	Findings		Comments
Axelsson et al. 1998	Population-based sample of 536 men and 557 women Aged 35, 50, 65, and 75 years Sweden	Mean number of missing teeth		Former smokers were excluded from the analysis; the mean number of missing teeth was significantly higher among smokers for all ages except 35 years; the mean percent of molars with furcation involvement was higher for all age groups except 75 years; the LPA* was measured at mesial surfaces of all teeth
		Aged 35 years		
		Smokers	2.0	
		Nonsmokers	1.6	
		Aged 50 years		
		Smokers	6.3	
		Nonsmokers	4.8	
		Aged 65 years		
		Smokers	13.8	
		Nonsmokers	10.3	
		Aged 75 years		
		Smokers	18.8	
		Nonsmokers	13.0	
		Molars with furcation involvement (mean %)		
		Aged 35 years		
		Smokers	6.3	
		Nonsmokers	2.7	
		Aged 50 years		
		Smokers	28.3	
		Nonsmokers	14.5	
		Aged 65 years		
		Smokers	42.0	
		Nonsmokers	22.3	
		Aged 75 years		
		Smokers	60.0	
		Nonsmokers	33.5	
		Mean LPA (mm)		
		Aged 35 years		
		Smokers	1.1	
		Nonsmokers	0.7	
		Aged 50 years		
		Smokers	2.4	
		Nonsmokers	1.5	
		Aged 65 years		
		Smokers	3.1	
		Nonsmokers	2.3	
		Aged 75 years		
		Smokers	4.0	
		Nonsmokers	2.7	

*LPA = Loss of periodontal attachment.

Table 6.22 Continued

Study	Population	Findings	Comments
Gunsolley et al. 1998	Dental patients 142 nonsmokers and 51 smokers without periodontitis Mean age = 30.9 years United States (Virginia)	Mean LPA* (mm) Smokers 0.28 Nonsmokers 0.17 Teeth with ≥1 LPA site ≥2 mm (mean %) Smokers 17.0 Nonsmokers 9.9 Teeth with ≥1 LPA site ≥5 mm (mean %) Smokers 1.5 Nonsmokers 0.4	Analysis of covariance; covariates included age, race, gender, and mean plaque index score
Norderyd and Hugoson 1998	Population-based sample of 283 women and 269 men Aged 20–70 years Sweden	OR (95% CI) for severe generalized periodontitis by cigarettes / day 1–9 1.12 (0.19–6.62) ≥10 11.84 (4.19–33.50)	Severe generalized periodontitis was defined as alveolar bone loss of one-third or more of the root length affecting the majority of teeth; this multiple logistic regression model included age, plaque index score, and the number of cigarettes smoked per day
Persson et al. 1998	416 dental patients Aged 15–94 years United States (Washington)	Smokers were more likely than nonsmokers to have severe vertical alveolar bone defects, and smokers had more vertical defects	Alveolar bone defects were assessed radiographically; χ^2 and ANOVA[‡‡] test results were reported, but the prevalence or number of bone defects among smokers and nonsmokers was not reported
Shizukuishi et al. 1998	252 male and 58 female factory workers Aged 20–59 years Japan	OR (95% CI) for moderate or deep periodontal pockets Current smokers 2.1 (1.2–3.8)	Miller's modified CPITN[Δ] was used to assess periodontal status; disease was defined as the upper 25% of the population distribution; this logistic model included age, gender, alcohol intake, frequency of tooth-brushing, and the use of the interdental cleaners; the reference group included former and never smokers

*LPA = Loss of periodontal attachment.
[Δ]CPITN = Community Periodontal Index of Treatment Needs.
[‡‡]ANOVA = Analysis of variance.

Table 6.22 Continued

Study	Population	Findings	Comments
Kamma et al. 1999	40 male and 20 female dental patients with early onset periodontitis Aged 22–35 years Greece	Mean number (%) of periodontal sites with PPD† >5 mm Smokers 76.3 (54.1) Nonsmokers 57.5 (39.6) Mean PPD (mm) per diseased site Smokers 6.9 Nonsmokers 5.9 Mean LPA* (mm) per diseased site Smokers 7.6 Nonsmokers 6.5	There was no control group
Liede et al. 1999	Random sample in 1992 and 1993 of 409 male participants in an ongoing cancer prevention trial who had ≥15 teeth and smoked ≥5 cigarettes / day at baseline (1985–1988) Aged 55–70 years Finland	Mean PPD Current smokers 0.76 Former smokers 0.43 Sites (%) with gingival suppuration Current smokers 2.0 Former smokers 0.4 Persons (%) with moderate or severe radiographic alveolar bone loss Current smokers 43 Former smokers 28	Former smokers had quit for ≥6 months before the periodontal examination; gingival suppuration and the loss of alveolar bone remained significantly lower among former smokers than among current smokers in multiple logistic regression models
Mullally et al. 1999	21 male and 50 female periodontal patients Aged <35 years; mean age = 28 years (minimum age not specified) Northern Ireland	Alveolar bone loss (mean %) Current smokers 31.7 Never smoked 25.0	The early onset of periodontitis was defined as persons with teeth (≥1) with ≥30% radiographic bone loss, aged <35 years, with no medical conditions or drug therapies known to affect periodontium; smoking was not significantly associated with the mean percent of bone loss in this ANOVA‡‡ model that included age and disease status (generalized vs. localized); there was no control group

*LPA = Loss of periodontal attachment.
†PPD = Probing pocket depth.
‡‡ANOVA = Analysis of variance.

Table 6.22 Continued

Study	Population	Findings	Comments
Wakai et al. 1999	517 male and 113 female participants in a multiphasic health examination Aged 23–83 years Japan	Adjusted OR (95% CI) for "periodontal disease" by smoking status Current smokers (cigarettes / day) 0–19 2.3 (1.2–4.3) 20–39 3.3 (2.1–5.1) ≥40 3.6 (2.0–6.7) Former smokers 1.4 (0.9–2.1) Never smoked 1.0 (referent)	This ordinal logistic regression model with CPITN[Δ] scores as outcomes was adjusted for age, gender, fasting plasma glucose, and dental debris index; a dose-response relationship was highly significant
Kerdvong-bundit and Wikesjö 2000	77 male and 43 female dental patients (60 current smokers and 60 never smokers) Aged 31–60 years Thailand	Mean PPD[†] (mm) by smoking status Current smokers 5.1 Never smoked 2.1 Mean LPA* (mm) by smoking status Current smokers 4.8 Never smoked 1.5 Persons (%) with PPD ≥4 mm by smoking status Current smokers 87 Never smoked 20 Persons (%) with LPA ≥4 mm by smoking status Current smokers 77 Never smoked 19	Mandibular molars buccal sites only
Machuca et al. 2000	304 male military recruits Mean age 19 years Spain	Mean PPD (mm) by smoking status Current smokers 1.68 Nonsmokers 1.56 Mean LPA (mm) by smoking status and cigarettes / day Current smokers 1.82 <5 1.83 5–20 1.82 >20 1.79 Nonsmokers 1.63	It is unclear if nonsmokers included former smokers

*LPA = Loss of periodontal attachment.
[†]PPD = Probing pocket depth.
[Δ]CPITN = Community Periodontal Index of Treatment Needs.

Table 6.22 Continued

Study	Population	Findings	Comments
Tomar and Asma 2000	Population-based sample of 6,460 men and 7,190 women Aged ≥18 years United States	Adjusted OR for periodontitis and smoking Current smokers (all) 4.0 (3.2–4.9) Cigarettes / day ≤9 2.8 (1.9–4.1) 10–19 3.0 (2.1–4.1) 20 4.7 (3.5–6.4) 21–30 5.1 (3.5–7.5) ≥31 5.9 (4.0–8.6) Former smokers (all) 1.7 (1.3–2.2) Years since quitting 0–2 3.2 (2.2–4.8) 3–5 2.3 (1.3–4.1) 6–10 2.0 (1.2–3.2) ≥11 1.2 (0.8–1.6) Never smoked 1.0 (referent)	Periodontitis was defined as 1 or more periodontal sites with both PPD† ≥4 mm and LPA* ≥4 mm; there were strong dose-response relationships for current smokers (cigarettes / day and duration) and former smokers (years since quitting)

*LPA = Loss of periodontal attachment.
†PPD = Probing pocket depth.

Table 6.23 Cohort studies on the association between smoking and periodontitis

Study	Population	Follow-up (years)	Outcome	Findings
Bolin et al. 1986	170 men and 179 women Aged 18–65 years at baseline Sweden	10	Loss of interproximal alveolar bone	Mean bone loss (% of root length) by baseline smoking status and cigarettes smoked / day, standardized for plaque level Current 1–9 cigarettes / day 5.1 10–20 cigarettes / day 5.5 >20 cigarettes / day 5.6 Nonsmokers 4.0 Unclear if nonsmokers included former smokers
Feldman et al. 1987	483 men from the Veterans Administration Normative Aging Study United States (Boston)	6	6-year change in mean PPD*, tooth mobility, and radiographic alveolar bone loss	Mean change in PPD by baseline smoking status Smokers 0.167 Nonsmokers -0.079 Mean change in tooth mobility Smokers 0.360 Nonsmokers 0.253 Mean change in alveolar bone level Smokers 0.287 Nonsmokers 0.172
Ismail et al. 1990	167 adults Aged 5–60 years at baseline United States (Michigan)	28	Change in mean LPA† ≥2 mm	OR‡ = 14.2 (95% CI§, 4.1–48.7) for smoking (assessed at baseline); this multiple logistic regression model also included year of birth and amount of tooth mobility
Bolin et al. 1993	170 men and 179 women Aged 18–65 years at baseline Sweden	10	Loss of interproximal alveolar bone	Mean bone loss (% of bone height / root length) by baseline and follow-up smoking status and by baseline cigarettes / day Smokers 6.0 1–9 cigarettes / day 5.2 10–20 cigarettes / day 6.0 >20 cigarettes / day 6.3 Former smokers (stopped smoking during the 10-year period) 4.4 Nonsmokers 3.9

*PPD = Probing pocket depth, measured in millimeters.
†LPA = Loss of periodontal attachment.
‡OR = Odds ratio.
§CI = Confidence interval.

Table 6.23 Continued

Study	Population	Follow-up (years)	Outcome	Findings
Brown et al. 1994	611 community-dwelling persons Aged ≥65 years at baseline United States (North Carolina)	1.5	2 or more sites with incident LPA[†] ≥3 mm	OR = 3.4 (95% CI, 1.6–7.5) among white adults who smoked cigarettes regularly; this logistic regression model included levels of *Porphyromonas gingivalis*, most recent medical care, and feelings of depression
McGuire and Nunn 1996	100 treated periodontal patients Aged 22–71 years at baseline United States (Texas)	5	5-category clinical prognosis score	OR = 1.9 (95% CI, 1.2–3.1) for smoking and a worsening prognosis
Beck et al. 1997	540 persons Aged ≥65 years at baseline United States (North Carolina)	5	At least 1 periodontal site with LPA ≥3 mm	RR[Δ] = 1.6 (95% CI, 1.2–2.0); analysis was conducted at the level of the periodontal site; referent group included both never and former smokers; this logistic regression model also included *Porphyromonas gingivalis* status, number of missing teeth, tooth type, periodontal site type, educational attainment, and most recent dental visit
Machtei et al. 1997	44 women and 35 men with established periodontitis Aged 25–66 years at baseline United States (New York)	1	Increased periodontal breakdown (mean bone loss exceeding 2 standard deviations based on radiographic examination)	OR = 5.41 (95% CI, 1.50–19.5) for smoking and increased periodontal breakdown Sites that experienced loss of clinical attachment (mean %) Smokers 8.35 Nonsmokers 6.00 Mean clinical attachment loss (mm) Smokers 0.27 Nonsmokers 0.09 Mean bone height loss (mm) Smokers 0.24 Nonsmokers 0.12 Sites with bone height loss (mean %) Smokers 15.4 Nonsmokers 11.4

[†]LPA = Loss of periodontal attachment.
[Δ]RR = Relative risk.

Table 6.23 Continued

Study	Population	Follow-up (years)	Outcome	Findings
Elter et al. 1999	697 community-dwelling persons Aged ≥65 years at baseline United States (North Carolina)	7	At least 1 site with incident LPA† ≥3 mm	RR = 1.4 (95% CI, 1.1–1.7) among whites and 1.9 (95% CI, 1.6–2.2) among blacks for current smoking; multivariable Poisson regression models included a number of site-level and person-level variables
Machtei et al. 1999	415 persons with little or no periodontal disease Aged 25–75 years at baseline United States (New York)	2–5	Mean LPA ≥1.95 mm	Mean annual LPA (mm) Smokers 0.19 Nonsmokers 0.10 Sites experiencing LPA (mean %) Smokers 5.28 Nonsmokers 3.75 Smoking also was a strong predictor of annual changes in PPD* in multiple linear regression models
Norderyd et al. 1999	Population-based sample of 357 persons Aged 20, 30, 40, 50, and 60 years at baseline Sweden	17	6 or more sites with radiographic alveolar bone loss >20%	OR = 12.0 (95% CI, 4.5–32.1) for smoking and bone loss
Faddy et al. 2000	456 university staff members Aged 18–65 years Australia	3	4 or more sites with PPD ≥4 mm	Current smokers had a 28% higher rate of disease regression than nonsmokers of the same age and gender; used Markov chain models to model transition probabilities of changes in disease state

*PPD = Probing pocket depth, measured in millimeters.
†LPA = Loss of periodontal attachment.

Table 6.24 Cross-sectional and cohort studies on the association between smoking and dental caries

Study	Population	Design	Results
Ludwick and Massler 1952	2,577 male navy enlistees Aged 17–21 years United States	Cross-sectional	Mean DMFS* by mean number of cigarettes / day Cigarettes / day — DMFT† — DMFS 0 — 9.5 — 20.4 5 — 9.1 — 20.5 10 — 9.8 — 21.7 15 — 9.75 — 21.2 ≥20 — 10.2 — 23.0 A statistically significant difference was reported in DMFT and DMFS means between those smoking ≤5 cigarettes / day and those smoking ≥15 cigarettes / day
Ainamo 1971	167 army recruits Aged 18–26 years Finland	Cross-sectional	Mean DS‡ and DMFS by cigarettes / day Cigarettes / day — DS — DMFS 0 — 13.8 — 36.4 1–9 — 20.7 — 51.7 10–20 — 19.9 — 41.5 >20 — 23.3 — 58.5 F-test — p <0.05 — p <0.01
Modéer et al. 1980	232 schoolchildren Aged 13–14 years Sweden	Cross-sectional	The number of cigarettes / day was a significant correlate of the number of decayed tooth surfaces ($\beta = 0.311$; $p < 0.01$) and filled tooth surfaces ($\beta = 0.309$; $p < 0.05$) in this stepwise multiple linear regression ($R^{2§} = 0.22$)
Zitterbart et al. 1990	95 male dental patients Aged 18–52 years (34 current smokers and 61 never smokers) United States (Illinois)	Cross-sectional	Mean DS and DMFS by smoking status DS — DMFS Current smokers — 3.9 — 24.6 Never smoked — 2.4 — 19.4 In analysis of variance modeling, smoking was significantly associated with the number of untreated decayed tooth surfaces and the number of missing surfaces; dose-response relationships were seen between daily cigarette use and both MS$^{\Delta}$ and DMFS; it is unclear if missing tooth surfaces were limited to those lost due to dental caries

*DMFS = Decayed, missing (due to caries), or filled coronal permanent tooth surfaces.
†DMFT = Decayed, missing (due to caries), or filled permanent teeth.
‡DS = Decayed coronal permanent tooth surfaces.
§R^2 = Prediction values.
$^{\Delta}$MS = Missing tooth surfaces.

Table 6.24 Continued

Study	Population	Design	Results
Hirsch et al. 1991	1,122 male and 1,023 female dental patients Aged 14–19 years Sweden	Cross-sectional	Mean DMFT† by smoking status (but not adjusted for age) Smokers 9.0 Nonsmokers 7.0 The text suggests that smoking was significantly associated with DMFT across age groups, but data were not presented
Källestål 1991	Population-based sample 283 persons aged 16 years and 287 persons aged 18 years Sweden	Cross-sectional	Among persons aged 18 years, smokers had more DFS¶ than nonsmokers ($p < 0.05$), but data were not presented
Locker 1992	Population-based sample 907 persons Aged ≥50 years Canada (Ontario)	Cross-sectional	Mean DS‡, FS**, and RDS†† by smoking status Current smokers: DS 1.2, FS 18.7, RDS 1.2 Former smokers: DS 0.8, FS 22.1, RDS 0.6 Never smoked: DS 0.7, FS 25.6, RDS 0.6
Jette et al. 1993	Population-based sample of community-dwelling persons Aged 70–96 years United States (New England)	Cross-sectional	Current smokers were significantly more likely than never smokers to have current coronal or root surface decay; prevalence of current decay was not specified
Ravald et al. 1993	27 periodontal patients Aged 47–79 years Sweden	Cohort, 12-year follow-up	Compared with nonsmokers, smokers experienced higher median (8 vs. 1) and mean (14 vs. 7) numbers of new RDS following periodontal treatments
Thomas et al. 1994	Population-based sample 300 persons Aged ≥60 years India	Cross-sectional	Mean decayed or missing teeth, by smoking status Smokers 16.8 Nonsmokers 13.0
Hart et al. 1995	Convenience sample 200 dental patients Aged 14–88 years United States (Tennessee)	Cross-sectional	No significant difference in mean DMFT between smokers (23.9) and nonsmokers (21.2); not age-adjusted; unclear if missing teeth included only those missing due to dental caries

†DMFT = Decayed, missing (due to caries), or filled permanent teeth.
‡DS = Decayed coronal permanent tooth surfaces.
¶DFS = Decayed or filled coronal permanent tooth surfaces.
**FS = Filled coronal permanent tooth surfaces.
††RDS = Decayed root surfaces.

Table 6.24 Continued

Study	Population	Design	Results
Locker 1996	Population-based sample 493 persons (of 699 in the baseline survey) Aged ≥50 years at baseline Canada (Ontario)	Cohort, 3-year follow-up	Mean RDFS[‡‡] and RDS[††] increments by smoking status Current or former smokers: RDFS 0.75, RDS 0.36 Never smoked: RDFS 0.47, RDS 0.24 Persons (%) experiencing RDFS or RDS increments (≥1) by smoking status (RDS differences were not statistically significant) Current or former smokers: RDFS 31.6, RDS 19.0 Never smoked: RDFS 24.0, RDS 12.7 Smoking was not a significant predictor of RDFS or RDS increments in this multiple logistic model
Drake et al. 1997	Noninstitutionalized population-based sample 234 blacks, 218 whites Aged ≥65 years United States (North Carolina)	Cohort, 3-year follow-up	Blacks who smoked cigarettes or cigars were more likely than black nonsmokers to experience new DFS[¶] (odds ratio = 2.5 [95% confidence interval, 1.1–5.3]) in this stepwise logistic regression model; smoking was not significant among whites
Axelsson et al. 1998	Population-based sample Aged 35 years (n = 155) Aged 50 years (n = 510) Aged 65 years (n = 310) Aged 75 years (n = 310) Sweden	Cross-sectional	Mean DMFS* by age and smoking status Aged 35 years Current smokers 48.9 Never smoked 38.1 Aged 50 years Current smokers 84.4 Never smoked 76.7 Aged 65 years Current smokers 98.8 (not significant) Never smoked 93.0 Aged 75 years Current smokers 114.6 Never smoked 100.2 Largest difference at ages 50, 65, and 75 years was in the number of MS[Δ]; at 35 years, smokers had a higher mean DFS than never smokers (39.3 vs. 31.2); MS were not limited to those missing teeth due to caries

*DMFS = Decayed, missing (due to caries), or filled coronal permanent tooth surfaces.
[Δ]MS = Missing tooth surfaces.
[¶]DFS = Decayed or filled coronal permanent tooth surfaces.
[††]RDS = Decayed root surfaces.
[‡‡]RDFS = Decayed or filled root surfaces.

Table 6.24 Continued

Study	Population	Design	Results
Tomar and Winn 1999	Population-based sample 6,945 dentate men Aged ≥18 years United States	Cross-sectional	Mean DFT[§§], DFS[¶], and RDFS[‡‡] by smoking status, adjusted for age, race, and ethnicity DFT DFS RDFS Current smokers 6.3 16.0 2.3 Never smoked 7.0 17.4 1.1 DFT and DFS differences were not statistically significant; current smokers were not significantly more likely than men who had never used tobacco to have ≥1 RDFS in multiple logistic regression models

[¶]DFS = Decayed or filled coronal permanent tooth surfaces.
[‡‡]RDFS = Decayed or filled root surfaces.
[§§]DFT = Decayed or filled permanent teeth.

Erectile Dysfunction

Erectile dysfunction, defined as the persistent inability to attain and maintain penile erection adequate for satisfactory sexual performance (National Institutes of Health [NIH] Consensus Development Panel on Impotence 1993), has recently received considerable attention as a major medical issue in the United States. Additional emphasis has been given to this condition with increasing recognition of its profound impact on quality of life (Wagner et al. 2000). Epidemiologic data, though sparse, indicate its importance as a public health problem. The prevalence of erectile dysfunction in 1992 was estimated to be 18 percent among men 50 through 59 years of age according to the National Health and Social Life Survey, a United States probability sample of men and women aged 18 through 59 years (Laumann et al. 1999). Among men 40 through 70 years of age, prevalence estimates of complete erectile dysfunction during 1987–1989 exceeded 10 percent and estimates of at least mild erectile dysfunction exceeded 50 percent, according to the Massachusetts Male Aging Study (Feldman et al. 1994). Incidence estimates of erectile dysfunction during 1995–1997, derived from longitudinal results of the Massachusetts Male Aging Study, approach 26 cases per 1,000 men annually (Johannes et al. 2000).

Many conditions have been implicated as causes of erectile dysfunction, including hormonal derangement, psychogenic influences, neurologic disorders, and vascular impairment, which may all interfere with the basic physiologic mechanisms involved in penile erection. Vascular impairment, which commonly refers to disease states that hamper penile blood flow, warrants particular attention for several reasons. Most importantly, vascular diseases are commonly associated with presentations of erectile dysfunction. Objectively demonstrable erectile dysfunction has been found in patients with myocardial infarction, coronary bypass surgery, cerebral vascular accidents, peripheral vascular disease, and hypertension (Melman and Gingell 1999). Furthermore, reports of patients with vasculogenic erectile dysfunction have suggested predisposing vasculopathic risk factors, which include cigarette smoking, fatty diets, adverse serum lipid levels, hypertension, physical inactivity, and obesity (Goldstein and Hatzichristou 1994). Several large epidemiologic studies have explored the extent to which these factors impair erectile function (Feldman et al. 1994; Derby et al. 2000b; Feldman et al. 2000; Johannes et al. 2000). The results of these studies also imply that modifications of risk factors may reduce the occurrence of erectile dysfunction.

Among widespread concerns about adverse health effects associated with cigarette smoking is the growing belief that this activity adversely affects sexual health and, in particular, erectile function. It is plausible that cigarette smoking exerts atherogenic effects on penile circulation relevant to erectile function, akin to effects on coronary circulation associated with heart disease (Fried et al. 1986; Raichlen et al. 1986). Furthermore, cigarette smoking cessation may afford a preventive strategy for reducing erectile dysfunction rates. However, each of these hypotheses requires a critical examination of the evidence regarding the effects of smoking on penile erection. This chapter summarizes and evaluates current observational and experimental data linking cigarette smoking and tobacco use with erectile dysfunction, including the pathophysiologic concepts.

Conclusions of Previous Surgeon General's Reports

This topic has received some coverage in prior Surgeon General's reports. The 1964 report (U.S. Department of Health, Education, and Welfare [USDHEW] 1964) included a discussion on masculinity in relation to COPD. The discussion drew from an investigation that defined the "element of masculinity as indicated by external morphologic features," and contended that "weakness of the masculine component is significantly more frequent in smokers than in nonsmokers, and most frequent in heavier smokers" (USDHEW 1964, pp. 383–4). This vaguely described element merely relates to the theme of male sexual prowess, as erectile ability or lack thereof was not directly assessed. The Advisory Committee to the Surgeon General recognized the tentative nature of the conclusions and the need for further confirmation. The 1990 report carried out a comprehensive review of sexual activity and performance, and sperm density and quality (USDHHS 1990). This review did not lead to specific conclusions, reflecting limitations of the available data and their inconsistency. This section reviews the issue of male sexual function, examining the influence of cigarette smoking on penile erection, one specific component of male sexual function.

Biologic Basis

Direct biologic evidence establishing plausible mechanisms for the effects of cigarette smoking on penile erection certainly would strengthen the premise that cigarette smoking constitutes a risk factor for erectile dysfunction. One possible mechanism is smoking-induced endothelial dysfunction of the penile vasculature. This hypothesis is supported by recent investigations into the physiology of penile erection affirming that the endothelium of the blood vessels supplying the penis, as well as that lining the lacunar spaces within the penis, releases vasoactive substances that contribute to the control of penile smooth muscle relaxation required for penile erection (Lue and Tanagho 1987).

Saenz de Tejada and colleagues (1989) probed whether smoking affects penile vasculature endothelium as part of an investigation of the consequences of diabetes mellitus on endothelial function in the penis in men with erectile dysfunction. Using isolated strips of human corpora cavernosa of the penis, the investigators compared isometric tension results from men with and without diabetes who were smokers (having at least a five pack-year history of cigarette smoking) or nonsmokers. The findings indicate that a history of smoking was not associated with a worsened impairment of endothelium-mediated relaxation responses. The study did not assess responses of tissue from smokers independently while controlling for other possible erectile dysfunction risk factors, nor did it carry out a subset analysis of responses from smokers specified to have had large amounts of cigarette smoke exposure. These limitations restrict the conclusions that can be drawn concerning the effects of smoking on endothelial function in the penis.

In a study of rats, Xie and colleagues (1997) examined the long-term effects of smoking on the endothelial synthesis of nitric oxide in the penis. Nitric oxide is now known to be the principal vasoactive mediator of penile erection (Burnett 1997). Nitric oxide is released by endothelial cells in response to direct cholinergic stimulation and in response to dynamic factors of changing penile blood flow. In the study, rats were passively exposed to cigarette smoke in 60-minute sessions once per day, five days per week, for eight weeks. Immunoblot analyses of the protein expression of endothelial nitric oxide synthase (eNOS) in penile tissue from the exposed rats did not reveal any diminution of eNOS expression compared with tissue from control rats. However, these investigators confirmed that overall nitric oxide synthase enzymatic activity (which combines neuronal and endothelial sources) and specifically the protein expression of the neuronal form of nitric oxide synthase in the penis were both markedly reduced following passive exposure to cigarette smoke in rats as compared with rats not exposed to smoke. Their findings mainly suggest that smoking selectively impairs neuronal mechanisms, in particular the neuronally based nitric oxide signal transduction pathway associated with penile erection. But the relevance of the rat model for humans is uncertain.

The investigation by Saenz de Tejada and colleagues (1989) also evaluated whether smoking affects the neurogenic mechanisms responsible for penile erection. The overall finding was that the impairment of neurogenically mediated relaxation of penile smooth muscle from smokers (combining results from men with and without diabetes) was not different from the impairment observed in nonsmokers (both men with and without diabetes). However, these conclusions have the same limitations as those concerning endothelial effects observed in this study (see above). An in vitro investigation of neuromuscular transmission in human corpus cavernosum also studied nicotine and found that the actions of this agent are both contractile and relaxant (Adaikan and Ratnam 1988). If erectile dysfunction results from exogenously administered nicotine during cigarette smoking, it may be due to the acute vasoactive modulatory effects of this agent on the penile vasculature.

Epidemiologic Evidence

Observational Data

This section explores the association between cigarette smoking, as well as other forms of tobacco use, and the occurrence of erectile dysfunction based on a review of available observational data. A literature search was conducted using the National Library of Medicine's PubMed system and was supplemented with professional knowledge of other resources. The critical feature of the observational data is the necessary reliance on self-reporting and other subjective instruments (e.g., logs, questionnaires, and sexual function inventories) to determine tobacco exposure and erectile performance, rather than quantitative measurements of these variables. A single-item assessment (e.g., "Do you experience difficulty getting and/or maintaining an erection that is rigid enough for satisfactory sexual intercourse?") has gained prominence particularly for population-based epidemiologic studies (Derby et al. 2000a). This assessment has been

useful as a single, direct practical tool to ascertain the presence of erectile dysfunction, whereas clinical questions are impractical (Derby et al. 2000a). This data collection methodology does introduce the possibility of information bias, probably toward underreporting. Differential underreporting by smoking status would bias estimates of the effects of smoking; however, the findings do prove insightful as to its probable significance within the general population. Furthermore, aspects of compromised sexual function are fundamentally issues of a subjective nature, wherein patient self-reporting may accurately serve as the main, or even the sole, criterion for establishing the existence and severity of the problem.

Case Series

Cigarette smoking has been linked to erectile dysfunction in several clinical reports, most qualifying as observational case series. As such, they are limited by not having true comparison groups, but they are reviewed here because they are often cited and data from more formal studies are limited. Wabrek and colleagues (1983) found that approximately 50 percent of 120 men referred for evaluation and management of erectile dysfunction to a hospital-based medical sexology program were smokers, counting users of cigarettes, cigars, or pipes. Virag and colleagues (1985) confirmed a 64 percent rate of cigarette smoking, defined as tobacco use exceeding 15 cigarettes per day for at least 15 years, among 440 men referred for clinical evaluation of erectile dysfunction. Bornman and Du Plessis (1986) similarly observed a 62 percent cigarette smoking rate, based on approximately 25 cigarettes per day for more than 20 years among 300 men screened at an andrology clinic. An attempt to provide comparative information was made by Condra and colleagues (1986), who studied 178 men with erectile dysfunction referred for clinical evaluation and found that 51.4 percent were current smokers and 81 percent were current or former cigarette smokers. These rates exceeded the 38.6 percent and 58.3 percent rates, respectively, ascertained in the general population using concurrent survey data. A recently published meta-analysis of smoking prevalence in men with erectile dysfunction also included a comparative assessment that controlled for age distribution, time period, and geographic location (Tengs and Osgood 2001). This meta-analysis, which consisted of 19 clinical studies published in the last 20 years with data on current smoking, revealed that 40 percent of the combined total of 3,819 men with erectile dysfunction were current smokers compared with 20 percent of men in the general population (Tengs and Osgood 2001).

Population-Based Studies

More valid appraisals of the effects of cigarette smoking on erectile dysfunction have been obtained through cross-sectional, random surveys of a sample population (Table 6.25). The Vietnam Experience Study of 1985–1986, which surveyed 4,462 U.S. Army Vietnam-era veterans aged 31 through 49 years, found erectile dysfunction prevalence rates of 2.2 percent among nonsmokers, 2.0 percent among former smokers, and 3.7 percent among current smokers ($p = 0.005$). The association (OR = 1.5 [95 percent CI, 1.0–2.2]) was maintained even after adjustments for comorbidity factors including vascular disease, psychiatric problems, hormonal factors, substance abuse, marital status, race, and age (Mannino et al. 1994).

Additional recent studies support the direct association between cigarette smoking and erectile dysfunction. A cross-sectional study assessing the prevalence of erectile dysfunction in 2,010 men aged over 18 years in Italy in 1996–1997 showed that smoking was associated with an increased risk of the condition (Parazzini et al. 2000). Although the study was controlled for multiple variables including age, marital status, SES, and chronic diseases, it found an increased risk of erectile dysfunction for current smokers (OR = 1.7 [95 percent CI, 1.2–2.4], $p < 0.05$) and for former smokers (OR = 1.6 [95 percent CI, 1.1–2.3], $p < 0.05$) in comparison with lifetime nonsmokers (Parazzini et al. 2000). The Krimpen Study, a community-based study conducted in Rotterdam, the Netherlands, between 1995 and 1998 that surveyed 1,688 men aged 50 to 78 years, also confirmed that smokers professed significant erectile dysfunction (adjusted OR = 1.6 [95 percent CI, 1.1–2.3], $p < 0.05$) to a greater extent than nonsmokers (Blanker et al. 2001). A cross-sectional study of erectile dysfunction prevalence conducted in Spain in 1998–1999, consisting of 2,476 men aged 25 to 75 years, demonstrated that cigarette smoking was significantly associated with erectile dysfunction (adjusted OR = 2.5 [95 percent CI, 1.64–3.80], $p < 0.05$) (Martin-Morales et al. 2001).

Another recent study supports the direct association between cigarette smoking and erectile dysfunction (Bacon et al. 2001). The Health Professionals Follow-up Study, a prospective cohort study of heart disease and cancer among U.S. male health professionals (Rimm et al. 1991; Ascherio et al. 1996), surveyed 34,282 men aged 53 through 90 years in 2000. The study showed an increased probability of erectile dysfunction among current smokers compared with nonsmokers (OR = 1.3 [95 percent CI, 1.1–1.6], $p < 0.05$), while controlling for age, marital status, and chronic diseases (Bacon et al. 2001).

Table 6.25 Cross-sectional studies on the association between smoking and the risk of erectile dysfunction (ED)

Study	Population	Smoking status	ED rate (%)	p value
Feldman et al. 1994*	Boston, Massachusetts, residents aged 40–70 years; studied during 1987–1989	Never and former smokers Current smokers	9.3 11.0	>0.200
Mannino et al. 1994*	U.S. veterans aged 31–49 years; studied during 1985–1986	Never smokers Current smokers Former smokers	2.2 3.7 2.0	0.005†
Feldman et al. 2000‡	Boston, Massachusetts, residents aged 40–70 years; studied during 1987–1996	Never and former smokers Current smokers	14 24	0.010
Parazzini et al. 2000*	Italian men aged ≥18 years; studied during 1996–1997	Never smokers Current smokers Former smokers	24.2 35.6 40.2	NR§
Bacon et al. 2001*	U.S. male health professionals aged 53–90 years; data gathered in 2000	Never smokers Current smokers Former smokers	22.4 27.9 26.2	NR
Blanker et al. 2001*	Dutch men aged 50–78 years; studied during 1995–1998	Never and former smokers Current smokers	NR NR	NR
Martin-Morales et al. 2001*	Spanish men aged 25–95 years; studied during 1998–1999	Never and former smokers Current smokers	NR NR	NR

*Prevalence study.
†Significant results.
‡Incidence study.
§NR = Data were not reported.

Evidence against an independent association between cigarette smoking and erectile dysfunction comes from the baseline phase of the Massachusetts Male Aging Study, a community-based survey conducted from 1987–1989 of 1,290 men aged 40 through 70 years living in the Boston, Massachusetts, area (Feldman et al. 1994). The probabilities of complete erectile dysfunction were 11 percent in smokers and 9.3 percent in nonsmokers, including both former smokers and those who had never smoked (p >0.20) (Feldman et al. 1994). However, the longitudinal phase of the Massachusetts Male Aging Study, extending over a nine-year median interval, showed the comorbidity-adjusted rate of incident erectile dysfunction to be significantly higher among cigarette smokers (24 percent) than nonsmokers (14 percent) (OR = 1.97 [95 percent CI, 1.07–3.63], p = 0.03) (Feldman et al. 2000). The classification of erectile dysfunction was based on an algorithm derived by the discriminant analysis of 13 questions.

Kleinman and colleagues (2000) reanalyzed the baseline data from the Massachusetts study using new methods for classifying erectile dysfunction. One method corresponded to the approach used by Feldman and colleagues (2000), based on responses from men attending a urology clinic to an original

questionnaire and to an additional global question for self-rating erectile dysfunction. Another analysis was based on responses to an expanded follow-up questionnaire. Cross-sectional analyses of predictors of erectile dysfunction were carried out in the 1987–1989 baseline data. With the clinic-based method for classification, current smoking was not associated with erectile dysfunction (OR = 0.95 [95 percent CI, 0.72–1.22]) while with the study-based method it was (OR = 1.39 [95 percent CI, 1.07–1.80]).

Disease Correlates

Type of Tobacco Exposure. The prospective analysis of the Massachusetts Male Aging Study examined various types of tobacco exposures to identify associations with erectile dysfunction. The odds of incident erectile dysfunction were more than doubled both for passive exposure to cigarette smoke, if present both at home and at work (adjusted OR = 2.07 [95 percent CI, 1.04–4.13]) (p = 0.04), and for cigar smoking (adjusted OR = 2.45 [95 percent CI, 1.09–5.50]) (p = 0.03). Passive exposure at home or at work alone did not increase the odds of incident erectile dysfunction in nonsmokers, but each increment of exposure did increase the estimated likelihood of erectile dysfunction in smokers (Feldman et al. 2000).

Dose-Response. The relationship between the amount of tobacco exposure and the extent of erectile dysfunction has been subjected preliminarily to epidemiologic analyses. Several population-based studies further explored the effects of measures of exposure on erectile dysfunction. The Vietnam Experience Study did not show any relationship between the number of cigarettes smoked daily or the number of years smoked and erectile dysfunction among currently smoking veterans (Mannino et al. 1994). Similarly, the baseline phase of the population-based Massachusetts Male Aging Study did not reveal any dependence of packs per day or lifetime pack-years smoked on reported erectile dysfunction among current smokers (Feldman et al. 1994). By contrast, an Italian cross-sectional study showed an increased erectile dysfunction risk with duration of the behavior, based on an OR of 1.6 (95 percent CI, 1.1–2.3) for men smoking 20 or more years and an OR of 1.2 (95 percent CI, 1.0–2.4) for men smoking less than 20 years (Parazzini et al. 2000).

Risk Factor Covariates and Effects of Medication. The combined effects (i.e., synergistic or additive interactions) of cigarette smoking and other risk factors in the development of erectile dysfunction have been analyzed. Goldstein and colleagues (1984) examined clinical characteristics in 19 potent patients who underwent pelvic irradiation for prostate cancer, finding that 14 out of 15 who displayed diminished erectile capacity were cigarette smokers, whereas only 1 out of 4 who preserved erectile capacity was a cigarette smoker. The strong association of cigarette smoking with erectile impairment in this study led the investigators to propose a synergistic role of smoking, and conceivably other vasculopathic risk factors, with the radiation effects associated with radiation-induced erectile dysfunction (Goldstein et al. 1984). In the baseline phase of the Massachusetts Male Aging Study, Feldman and colleagues (1994) found that cigarette smoking did not constitute an independent risk factor for erectile dysfunction; however, in that same study, the association of erectile dysfunction with certain risk factors was greatly amplified in current cigarette smokers. This amplification was demonstrated for persons having erectile dysfunction with treated heart disease (from 21 percent for current nonsmokers to 56 percent for current smokers), treated hypertension (from 8.5 to 20 percent), and untreated arthritis (from 9.4 to 20 percent), and for those persons receiving various medications including cardiac drugs (from 14 to 41 percent), antihypertensive medications (from 7.5 to 21 percent), and vasodilators (from 21 to 52 percent). Similarly, in an Italian cross-sectional study, smoking increased the adjusted ORs for erectile dysfunction associated with diabetes by 13 percent and with hypertension by 39 percent (Parazzini et al. 2000).

Effects of Smoking Cessation. The hypothesis that cigarette smoking adversely affects erectile function would seemingly be strengthened by epidemiologic evidence demonstrating that smoking cessation leads to erectile function recovery. Forsberg and colleagues (1979) presented the case reports of two cigarette smokers aged 20 and 27 years with erectile dysfunction whose erectile function returned in concordance with improved penile vascular testing results following smoking cessation. Elist and colleagues (1984) determined that 8 (40 percent) out of 20 men with erectile dysfunction who had smoked one to two packs of cigarettes per day for at least 15 years recovered functional erections after abstaining from cigarette smoking for six weeks. In this study, seven responders (35 percent) were confirmed by objective testing criteria to have recovered normal erectile activity from baseline abnormal levels.

Population-based reports add additional perspectives to the premise that modifying cigarette smoking behavior affects the occurrence of erectile dysfunction. One study in this regard is the Vietnam Experience Study of 1985–1986, which determined that the prevalence of erectile dysfunction among former smokers was comparable to that among nonsmokers, and the prevalence rates were significantly lower than those found in current smokers (Mannino et al. 1994). Similarly, the longitudinal phase of the Massachusetts Male Aging Study determined that incident erectile dysfunction was no more likely among former smokers than among nonsmokers, in contrast to current smokers (Feldman et al. 2000). Results from the Health Professionals Follow-up Study also suggest that former smokers carry a lower risk of erectile dysfunction than current smokers, although this risk for former smokers still exceeds that of nonsmokers (Bacon et al. 2001).

From these population-based study results, one might further conclude that the discontinuation of smoking results in a recovery of functional erection status. However, this simple conclusion is challenged by recent results from the prospective evaluation of men participating in the Massachusetts Male Aging Study who discontinued smoking during the almost nine-year follow-up period of this study. This latter analysis found that the covariate-adjusted incidence of erectile dysfunction was not significantly reduced after smoking discontinuation ($p = 0.28$). Important considerations of this investigation are that the men who quit smoking had begun smoking at an early age (mean age 16.6 years) and had accumulated a high lifetime exposure to tobacco smoke before quitting (mean pack-years 39.4). The data provide a refined understanding of the effects of cigarette smoking cessation on erectile dysfunction: smoking cessation in middle age after a significant lifetime exposure to cigarette smoke may fail to modify erectile dysfunction occurrence, because long-term vascular effects of smoking conceivably persist after smoking cessation (Derby et al. 2000b).

Clinical Data

This section examines the link between tobacco exposure and erectile dysfunction based on objective clinical criteria. The erectile dysfunction specialty has developed quantitative measurements that serve as indices of erectile function, including physiologic and anatomic descriptions of the physical state of the penis. Numerous investigations have applied these methodologies to ascertain the effects of cigarette smoking and other forms of tobacco use on penile erection.

Penile Tumescence Studies

Nocturnal penile tumescence (NPT) monitoring provides a noninvasive diagnostic technique to quantify erection physiology objectively during the naturally occurring cycle of sleep-related penile erections. These spontaneous episodes of tumescence normally accompany rapid eye movement (REM) sleep and are diminished in men with presumably organic erectile dysfunction (Karacan et al. 1978; Allen and Brendler 1992). Several early investigations of the objective basis for vasculogenic erectile dysfunction applied NPT monitoring. Elist and colleagues (1984) confirmed NPT-monitored abnormalities in 20 smokers with erectile dysfunction, among whom 7 (35 percent) displayed normal NPT-monitored results after six weeks of smoking cessation. Virag and colleagues (1985) determined that smokers comprised 72 percent of patients with abnormal NPT results but only 32 percent of patients with normal NPT results. In a study of 168 men who smoked one or more packs per day (heavy smokers) and 632 men who smoked less than one pack per day (light smokers), Karacan and colleagues (1988) found that sleep-related penile erection rigidity was significantly lower at each decade of life after 30 years of age in heavy smokers compared with light smokers, and the duration of maximal tumescence was significantly lower for heavy smokers aged less than 30 years and 51 through 60 years compared with age-equivalent light smokers. In an investigation of 314 smokers with erectile dysfunction, Hirshkowitz and colleagues (1992) confirmed a significant inverse correlation between sleep-related penile erection rigidity and the number of cigarettes smoked per day ($r = -0.12$; $p = 0.04$). These investigators also showed that the duration of maximal tumescence was significantly shorter at the penile base ($p \leq 0.05$), and the duration of detumescence (which refers to the decline from full erection to penile flaccidity) was also shorter ($p = 0.06$) among men who smoked 40 or more cigarettes per day compared with men who smoked 1 to 19 per day and 20 to 39 per day ($p = 0.14$).

Penile Vascular Hemodynamics

Impaired blood flow to the penis can be assessed using various measurement techniques. One widely used early technique to assess arterial vascular competence within the penis was the Doppler ultrasound of arterial pulsations in the flaccid, unstimulated organ. Although this method is no longer applied, the findings of these studies may still be relevant with respect to the pathogenesis of smoking-related vascular

disease of the penis. With the values obtained, the penile-brachial index (PBI) can be calculated (the PBI refers to the ratio of penile to brachial systolic blood pressures). Reduced PBI values have been associated with impairment of the erectile process (Kempczinski 1979). Using this technique, Wabrek and colleagues (1983) did not find a significant association between cigarette smoking and abnormal PBI values. Virag and colleagues (1985) also did not find an independent smoking effect on PBI, although a synergistic effect was observed with smoking in combination with other arterial risk factors such as diabetes, hyperlipidemia, and hypertension. In contrast, Condra and colleagues (1986) demonstrated significantly lower PBI values among smokers than among nonsmokers. This same study also noted that the amount of time smoked correlated with abnormal PBI values: smokers with normal PBI values had smoked for a mean duration of 19.95 years while those with abnormal PBI values had smoked for a mean duration of 26.55 years. DePalma and colleagues (1987) likewise found that cigarette smoking carried a significantly higher probability of abnormal (49 percent) than normal (28 percent) vascular laboratory findings including PBI, which was not observed for age, hypertension, diabetes, or prior myocardial infarction. Hirshkowitz and colleagues (1992) confirmed consistent PBI reductions among 314 cigarette smokers with erectile dysfunction, finding significant correlations between the number of cigarettes smoked per day and the magnitude of these reductions for the left dorsal artery ($r = -0.14$; $p = 0.01$) and right cavernosal artery ($r = -0.13$; $p = 0.03$) of the penis.

The vascular evaluation of the penis has more recently employed a pharmacologic stimulus in combination with penile duplex ultrasonography to characterize the penile arteries. This application followed the discovery that a pharmacologic stimulus to induce an artificial erection provides an improved assessment of the physiologic responsiveness of these arteries over that provided during the resting state (Abber et al. 1986). Using this technique and applying a combined set of ultrasonographic parameters to establish normal vascular findings, Shabsigh and colleagues (1991) showed a consistent, nearly statistically significant difference in vascular impairment in smokers compared with nonsmokers. Kadioğlu and colleagues (1995) also observed that penile vascular parameters were abnormal to a greater extent among smokers than among nonsmokers, although the differences were not statistically significant.

In summary, PBI testing suggests deleterious effects of smoking on the "resting state" circulation of the penis, and sonographic evaluation of the penis following pharmacostimulation additionally demonstrates apparent deleterious effects of smoking on dynamic blood flow changes in the penis.

Penile Vascular Morphology

Arteriographic studies have been conducted in patients with erectile dysfunction to characterize the vascular anatomy of the penis. Investigations have been carried out among cigarette smokers to confirm the presence and location of arteriographic lesions. Virag and colleagues (1985) calculated a 67.8 percent rate of arteriographic abnormalities among patients in whom organic erectile dysfunction had been established by NPT monitoring, of whom 86 percent were smokers. Bähren and colleagues (1988) similarly showed that 82 percent of their patient group with arteriographically proven peripheral arteriosclerotic lesions were heavy smokers. In a study by Forsberg and colleagues (1989), men with erectile dysfunction underwent screening studies of penile blood flow to identify abnormalities. Using both pharmacostimulation and angiography in 17 men, this study found significant distal penile vessel lesions; 14 (82 percent) of the men were identified as smokers. Rosen and colleagues (1991) carried out a comprehensive evaluation of penile circulation in cigarette smokers with erectile dysfunction, finding that smoking represented a significant independent risk factor in the development of atherosclerotic lesions in the internal pudendal and common penile arteries. These investigators also determined that the number of pack-years smoked was independently associated with hemodynamically significant atherosclerotic disease in the hypogastric cavernous arterial bed supplying the penis (for each 10 pack-years smoked, RR = 1.31 [95 percent CI, 1.05–1.64]).

Histopathology

The effects of cigarette smoking on erectile tissue were investigated by Mersdorf and colleagues (1991), who confirmed degenerative tissue changes (including a decrease in smooth muscle content, sinusoidal endothelium, nerve fibers, and capillaries, and an increase in collagen density) in erectile tissue of smokers. These tissue alterations are consistent with tissue alterations seen in other vascular diseases.

Experimental Data

This section reviews experiments carried out to test the effects of cigarette smoking on erectile function (Table 6.26). These experimental approaches controlled cigarette smoking exposures and provided the possibility for a rigorous evaluation of the consequences for erectile ability. The value of the information was enhanced when experiments involved robust scientific methodology (e.g., a random allocation of people to experimental and control groups, the use of different control groups, and the application of blinding procedures to reduce bias).

Human Studies

Perhaps the first reported study to experimentally evaluate the hypothesized association between cigarette smoking and erectile dysfunction was performed by Gilbert and colleagues (1986), who made polygraphic recordings of penile erection responses in smokers during the viewing of erotic videos. Several aspects of this study are noteworthy: (1) the study population consisted of 42 male self-reported heterosexual cigarette smokers in good health, aged 18 through 44 years; (2) participants were assigned to high-nicotine exposure (0.9 mg nicotine per cigarette smoked), low-nicotine exposure (0.002 mg nicotine per cigarette smoked), or control (sucking on a hard mint candy) groups randomly selected and unknown to the experimenter; (3) at enrollment, a counterdemand was issued to the effect that nicotine enhanced sexual potency, to militate against contaminating hypotheses held by the participants about the effects of smoking on erections; (4) smoking abstention was required for two hours before the experiment; (5) baseline erotic videos were shown for participant acclimation; and (6) concomitant measures of cardiovascular response were obtained. The study found that smoking two, but not one, high-nicotine cigarettes significantly decreased the rate of penile diameter increase compared with the other conditions during the erectile stimulus ($p < 0.001$). It also determined that high-nicotine cigarettes caused significantly more vasoconstriction and heart rate increase than did low-nicotine cigarettes, which did not differ from control conditions ($p < 0.001$).

In another experiment undertaken to assess the acute effects of cigarette smoking exposure on penile erection, Glina and colleagues (1988) studied the interference of smoking on vasoactive drug-induced erectile responses monitored by intracavernous pressure recording. Study design features were as follows: (1) 12 chronic cigarette smokers, aged 22 through 65 years, were enrolled; (2) subjectively reported erectile function status of the participants at enrollment was not stated; (3) smoking was prohibited on test days; (4) each participant underwent pharmacostimulation consisting of intracavernous injection of 100 mg papaverine hydrochloride at baseline (without smoking) and one week later immediately after nicotine exposure (smoking two cigarettes containing 1.3 mg nicotine per cigarette); and (5) intracavernous pressure measurements were performed 20 minutes following pharmacostimulation by the same experimenter. The study found that all men obtained an erection by clinical judgment at baseline compared with only four (33 percent) after smoking, corresponding to a significant decrease in mean intracavernous pressures from 85.83 mm Hg at baseline to 53.50 mm Hg after smoking. As part of an earlier, larger investigation of the use of papaverine injections to test diagnostically for erectile dysfunction, Abber and colleagues (1986) described a similar experiment involving a chronic smoker with erectile dysfunction who displayed an acutely worsened erectile response immediately following smoking a cigarette compared with his baseline results.

In a visual depiction of the effects of cigarette smoking on arterial flow to the penis, Levine and Gerber (1990) described their pelvic arteriographic study of a 38-year-old man with a 25 pack-per-year smoking history who presented for evaluation of erectile dysfunction. Whereas a complete baseline evaluation including pelvic arteriographic studies showed no abnormalities, repeat pelvic arteriography immediately after the patient smoked two cigarettes revealed a decrease in the caliber of the entire pudendal artery and nonvisualization of the deep penile artery. The investigators suggested that acute vasospasm was responsible for the observed effects.

Further experimental evidence of the deleterious effects of cigarette smoking on erectile function was recently documented in an acute smoking cessation study by Guay and associates (1998). Ten men, 32 to 62 years of age who had at least a current 30 pack-year smoking history and were smoking one pack of cigarettes or more per day, were enrolled in a study monitoring NPT and rigidity by a home RigiScan® technique. The study required monitoring of sleep-related penile erections on two successive nights, the first night following a usual day of smoking and the second night following discontinuation of smoking for one 24-hour interval. An additional component of the study involved repeat monitoring in four men who did not smoke for one month although they were administered transdermal nicotine patches (21 mg) during this time. The study results show that erectile parameters improved to a statistically significant degree in men who

Table 6.26 Experimental studies on the association between smoking and erectile dysfunction

Study	Population	Study design	Stimulus	Outcome
		Human studies		
Gilbert et al. 1986	42 smokers aged 18–44 years	Randomized controlled trial	Visual sexual stimulation	High-nicotine cigarettes reduced the amount of penile diameter increase
Glina et al. 1988	12 smokers aged 22–65 years	Acute experiment	Erection pharmaco-stimulation	Two cigarettes reduced intracavernous pressure measurements
Guay et al. 1998	10 smokers aged 32–62 years	Acute experiment	Sleep-related erections	Cigarette smoking discontinuation improved erectile parameters
		Animal studies		
Juenemann et al. 1987	Dogs	Acute experiment	Cavernous nerve electrostimulation	Cigarette smoke inhalation reduced erectile parameters
Xie et al. 1997	Rats	Chronic experiment	Cavernous nerve electrostimulation	Cigarette smoke inhalation did not alter erection parameters

had stopped smoking for 24 hours, with further observed improvements in those not smoking and wearing nicotine patches for one month. The investigators concluded that eliminating cigarette smoking improves erectile function although factors contained in cigarette smoke other than nicotine primarily exert the damaging effects.

Animal Studies

Animal models have provided another useful approach for investigating the association between cigarette smoking and erectile dysfunction. The study by Juenemann and colleagues (1987) using an in vivo canine model represents a comprehensive, well-controlled investigation that combined stimulatory and monitoring techniques relevant to the physiology of erection. The methodology involved monitoring arterial inflow, intracavernous pressure, and venous outflow of the penis during cavernous nerve stimulation of erection alone, and with regulated penile perfusion before and after acute inhalation of cigarette smoke (1.4 mg nicotine per cigarette). Following smoking exposure (one to six cigarettes), compared with nonsmoking baseline conditions, peak arterial inflow was significantly diminished, peak intracavernous pressure was significantly diminished and could not be maintained, and venous outflow was not significantly restricted. Measurable serum nicotine and cotinine levels, obtained in the dogs following smoking exposure and used as markers, were consistent with concentrations found in human smokers, whereas no changes in arterial blood gases or systemic blood pressure were observed throughout the investigation. The investigators concluded that smoking exerts a localized deleterious effect on the neurovascular mechanisms required for penile erection, with a particular impairment of the veno-occlusive mechanism associated with maintenance of penile erections.

In a rat model, Xie and colleagues (1997) evaluated the long-term effects of cigarette smoking on penile erection. The methodology involved monitoring in vivo neurostimulated erections after exposing rats to a constant influx of cigarette smoke in an enclosed cage for a 60-minute session once per day, five days per week, for eight weeks. The investigation surprisingly found increases in intracavernous pressures in

smoke-exposed rats compared with controls. However, the rats exposed to cigarette smoke also developed systemic hypertension. Intracavernous pressures standardized to systemic blood pressures in rats exposed to cigarette smoke did not differ from intracavernous pressures found in controls. The investigators explained their findings on the basis of tobacco smoke-associated vasoconstriction, and they conceded that vascular damage commonly associated with long-term cigarette smoking is inappreciable in the rat model, which is resistant to atherosclerosis.

Evidence Synthesis

Available evidence indicates that cigarette smoking constitutes a risk factor for erectile dysfunction. However, the causal basis for this relationship must be carefully evaluated. With regard to the consistency of the relationship, both case series and population-based studies evaluating rates of erectile dysfunction among smokers provide support. The population-based studies afford a more accurate observational basis for this assessment than do uncontrolled case series, although the paucity of these studies hampers reaching a definitive conclusion. The strength of the relationship also rests on limited available information, but is similarly supported by observational evidence showing that a variety of tobacco exposures (including active and passive cigarette smoking and cigar smoking) is associated with erectile dysfunction. Consideration of a dose-response relationship is supported by a few observational and experimental investigations that have shown an increased risk of erectile dysfunction associated with increased exposures to cigarette smoking. The temporality of the relationship seems likely, with a few observational studies showing some evidence of erectile dysfunction following exposure to tobacco smoke. Intriguingly, preliminary observational findings demonstrate that cigarette smoking cessation apparently leads to a recovery of erectile function only if the discontinuation occurs after a limited extent of lifetime smoking.

Coherence of the relationship is supported by several biologic studies that have proposed plausible mechanisms for the deleterious effects of cigarette smoking on erections. The acute deleterious effects of smoking on erectile function result at least in part from nicotine carried in cigarette smoke. The nicotine pharmacologically induces vasospasm of penile arteries, and hence alters the dynamics of local blood flow required for penile erection. The chronic deleterious effects of smoking on erectile function result from impaired vascular physiology of the erectile tissue, as evidenced by degenerative morphologic changes in tissue of smokers. Although the exact mechanism of the impairment remains unclear, early studies in animals point to damaging effects on tissue-dependent erection regulatory factors. In sum, several lines of evidence contribute toward the inference of a causal relationship between cigarette smoking and erectile dysfunction. However, because the scope of observational and experimental evidence remains limited and incomplete, it seems reasonable to consider the evidence to be suggestive but insufficient to establish a causal relationship at this time.

Conclusion

1. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and erectile dysfunction.

Implications

The clinical studies and basic scientific research summarized in this section suggest a relationship between cigarette smoking and erectile dysfunction. A strong inference that smoking causes erectile dysfunction requires more evidence to confirm initial findings and to fill in gaps in the knowledge base. Additional observational studies of sufficient size and with well-validated outcome measures are needed. More basic scientific studies to identify biologic mechanisms for the deleterious effects of smoking on penile erections also are necessary. In the meantime, current knowledge about the problem still prompts recommendations for smoking cessation and avoidance to limit the risk of erectile dysfunction. Promoting nonsmoking to prevent erectile dysfunction seems clinically appropriate. There may be significant public health benefits by reducing morbidity rates of this increasingly recognized, widespread condition.

Eye Diseases

Diseases of the visual system, and possible subsequent visual loss, represent substantial social and economic concerns to the U.S. public. In the last three decades, Gallup polls have consistently indicated that blindness is second only to mental incapacity as the disability Americans fear most (National Advisory Eye Council [NAEC] 1998). There is ample reason for concern. An estimated 3.4 million Americans aged 40 years and older have visual impairment and 1 million of these people are legally blind. Because most vision loss results from eye disease associated with advancing age, and the "baby boom" population in the United States is aging, the public health impact of this problem is projected to double by 2030 (Prevent Blindness America 2002).

The economic consequences of eye disease for the U.S. population are huge. For example, sight-restoring cataract surgery was the most frequently performed surgical procedure among Medicare beneficiaries, at an estimated annual cost of $3.4 billion in 1991 (Steinberg et al. 1993). Altogether, the economic impact of visual disabilities and disorders was estimated at more than $38.4 billion in 1995 (NAEC 1998). Thus, substantial contributions to the social and economic welfare of the public are possible by finding and controlling the causes of these eye diseases, particularly the factors that present the opportunity to prevent the disease or loss of sight.

Conclusions of Previous Surgeon General's Reports

Epidemiologic investigation into risk factors for eye disease did not begin in earnest until the 1970s, bolstered by the establishment of the National Eye Institute (NEI) in 1968. Reports of the Surgeon General on smoking and health published before 2001 did not include eye disease as a topic simply because there were scant data indicating that smoking was related to ocular morbidity, although a compelling biologic basis did exist for postulating such associations. At least two of the three leading causes of visual loss worldwide, cataract and age-related macular degeneration (AMD), probably are due, at least in part, to smoking.

Cataract

Cataract is the leading cause of blindness worldwide and a leading cause of visual loss in the United States (Thylefors et al. 1995; Muñoz et al. 2000). Currently, the most common and effective means of restoring vision is through surgical removal of the opacified lens and insertion of an artificial lens into the eye. According to NEI, about 1.35 million cataract operations are performed annually in the United States for Medicare beneficiaries (NAEC 1998), at an estimated cost of $3.4 billion in 1991 (Steinberg et al. 1993). If risk factors that either delay the onset or slow the progression of cataracts could be identified, major socioeconomic gains would be realized. The research findings that link cigarette smoking to cataract, specifically nuclear cataract, have identified one of the few modifiable risk factors for cataract.

The ocular lens is a normally transparent organ having a purely optical function. The lens, situated behind the pupil, focuses radiant energy on the retina to produce an image, much like the lens of a camera. The shape of the lens changes, or accommodates, in response to the distance of the viewed object to focus a sharp image onto the retina.

The transparency of the lens is a function of its peculiar characteristics. The lens itself is composed of a central core, or nucleus, of inert, protein-filled, former epithelial cells. The interior proteins are highly structured to ensure transparency. The lens grows by the constant addition of protein-filled, elongated, former epithelial cells that have differentiated into lens fibers that do not have a nucleus or other organelles. Of interest in this process is that the lens contains every fiber cell ever incorporated into it, including cells formed in the embryo stage through those formed very recently. These cells must maintain transparency throughout the life of an individual to ensure visual clarity, yet this central core is metabolically inert and cannot renew itself. Thus, the central lens is severely restricted in its ability to repair damage. The outermost layer of the lens is composed of a layer of epithelial cells, which are responsible for most of the metabolic activity of the lens. These cells are the source of new cells, as the old cells differentiate into fiber cells and are displaced toward the nucleus. These newest lens fibers make up the lens cortex, which surrounds the nucleus.

The loss of lens transparency is termed lens opacity, and lens opacification becomes increasingly common with advancing age. When the opacity becomes sufficiently dense or extensive or both so as to interfere with vision, the lens opacity is called a cataract. There are three main types of lens opacity or cataract, which are distinct in terms of risk factors, location in the lens, and epidemiologic pattern: nuclear, cortical, and posterior subcapsular lens opacity (West and Valmadrid 1995). The different types of opacities also can occur together in the lens, resulting in a "mixed" opacity.

The frequency of each type of lens opacity in the population increases with age and varies by racial or ethnic group. In one population-based study of 2,520 older Americans (West et al. 1998), aged 65 to 69 years, 32 percent of whites had nuclear, 15 percent had cortical, and 8 percent had posterior subcapsular cataract in at least one eye; comparable figures for African Americans were 20 percent, 42 percent, and 4 percent, respectively. At least 4 percent of the study participants in that age group had undergone cataract surgery as well.

Biologic Basis

Several hypotheses have been advanced to explain a possible association of smoking and cataract. Given the plethora of aromatic compounds and trace metals in cigarette smoke that are capable of damaging lens proteins, it is difficult to know which mechanism is likely to be the most important. Harding (1995) has postulated that cadmium, lead, thiocyanate, and aldehydes from cigarette smoke lead to lens damage. Investigators analyzing blood and lenses from cataract surgery patients have shown significant accumulations of cadmium in the blood and lenses of smokers compared with lenses of nonsmokers, with cadmium in lenses proportional to the amount smoked (Ramakrishnan et al. 1995; Cekic 1998).

Harding (1991) also has suggested that the damage to the lens may be from thiocyanate, which can cause carbamylation of crystallins (lens proteins) and enzymes. Smokers do have elevated thiocyanate levels in their blood, but levels in lenses have not been measured.

Others suggest that smoking may cause cataract through an indirect route, by lowering antioxidants (Taylor et al. 1995). However, the role of antioxidants in protecting against cataractogenesis still is controversial. Few studies have determined the level of antioxidants in the lens and the relationship between lens levels and blood or serum levels. One of the better studied antioxidants is vitamin C, which appears to be concentrated in the lens, and ocular levels of vitamin C are sensitive to plasma levels of this vitamin (Taylor et al. 1997). A review of research linking vitamin C and cataract found studies that reported a protective effect of vitamin C, an increased risk with serum levels of vitamin C, and no association at all; the conflicting results do not provide evidence of an association (West and Valmadrid 1995). In one study, smokers compared with nonsmokers had lower serum values of vitamin C, and in another, both smokers and nonsmokers had similar blood and lens levels of vitamin C (Kallner et al. 1981; Ramakrishnan et al. 1995). At present, the antioxidant pathway for lens damage from smoking requires more corroborative research.

Epidemiologic Evidence

The relevant articles for this section on eye diseases were identified initially through a search in PubMed from 1966 through 2000 by using the following search terms: "lens opacity," "cataract," "lens," "nuclear lens opacity," "cortical lens opacity," "posterior subcapsular lens opacity," "age-related macular degeneration," "senile macular degeneration," "age related maculopathy," "choroidal neovascularization," "drusen," "geographic atrophy," "atrophic macular degeneration," "diabetic retinopathy," "diabetic eye disease," "glaucoma," "intraocular pressure," "Graves' ophthalmopathy," "thyroidopathy," "eye pathology," and "eye disease." These terms were searched with the Boolean operator "and" followed by the terms "cigarette," "smoking," and "tobacco" in appropriate combinations. All articles were reviewed, and their bibliographies were reviewed for relevant articles not captured by the search strategy. The final selection of articles for citation in this section was made in consideration of the adequacy of the research or review and the relevance to the topic. The selection of eye diseases for review was based on the public health importance of the disease and the availability of research relevant to an association with smoking.

Several key methodologic issues should be addressed in any research on risk factors for cataract. First, there are different types of cataract, with largely unique risk factors for each type. Early research on risk factors often did not differentiate cataract type, making interpretation difficult because the mix of cataract types was unknown. For example, a surgical series of cataract patients is likely to be heavily weighted for posterior subcapsular cataract, whereas a population-based series will have few posterior subcapsular cataract cases. Surgical notes, or ophthalmologist

notes, of the cataract type may lead to misclassification, as only the major cataract type usually is recorded. Ideally, studies on cataractogenesis would use one of several reliable, valid grading schemes for documentation of the presence and severity of lens opacity types.

The second methodologic issue is that each type of lens opacity has a different impact on the visual system. Research that defines cataract to include a visual acuity criterion effectively excludes asymptomatic, early lens changes or may include substantial numbers of persons with lens opacity not yet affecting acuity in the control group. Such research is less desirable from an etiologic standpoint.

Finally, issues of bias and confounding must be addressed with any research. Selection bias in clinic-based, case-control studies of cataract can be problematic, because controls sometimes have eye problems that may share risk factors in common with cataract. In population-based studies, patients with bilateral cataract surgery often are excluded from the analyses, because the type of cataract or date of surgery may be unknown. If the risk factor of interest drives progression of cataract, the exclusion of bilateral surgical cases will result in an underestimation of the risk. Potential confounders for the relationship of smoking and nuclear or posterior subcapsular cataract include age, race, gender, steroid use, and possibly alcohol use.

Ten epidemiologic studies reviewed have found an association between smoking and nuclear opacity and four found an association between smoking and posterior subcapsular opacity (Table 6.27). The studies reporting an association between nuclear cataract and smoking were carried out in diverse populations using different methodologies and different lens grading systems (Flaye et al. 1989; West et al. 1989a, 1995; Leske et al. 1991, 1998; Christen et al. 1992; Hankinson et al. 1992; Klein et al. 1993b; Cumming and Mitchell 1997; Hiller et al. 1997). The association with smoking generally was consistent (with most RRs ranging between 2 and 3); a dose-response relationship with the amount smoked was found. Four prospective cohort studies have found an association with smoking at baseline and subsequent risk of developing new nuclear opacities, surgery for nuclear opacities, or progression of existing nuclear opacities (Christen et al. 1992; West et al. 1995; Hiller et al. 1997; Leske et al. 1998).

Smoking has been less consistently associated with an increased risk of posterior subcapsular opacity. Two prospective cohort studies have found an increased risk, between 2.5- and 3-fold, associated with heavy smoking (smoking 20 or more cigarettes per day and smokers of 65 or more pack-years) (Christen et al. 1992; Hankinson et al. 1992). Two cross-sectional, population-based studies found a weaker association, and one reported an association only among men (Klein et al. 1993b; Cumming and Mitchell 1997). Two other population-based surveys did not find any association with posterior subcapsular cataract (Flaye et al. 1989; Hiller et al. 1997).

One limitation of population-based studies of risk factors for posterior subcapsular cataract is the rarity of that cataract type, making it difficult to acquire enough cases to precisely characterize risk. Another limitation is that posterior subcapsular cataract is highly visually disabling, and generally progresses quickly, so while it is overrepresented in surgical series it may be underrepresented in population-based studies because affected persons already have had cataract surgery (West et al. 1998). Thus, prospective cohort studies on posterior subcapsular cataract in populations are likely to provide more compelling data about the association.

The three studies that found no association between smoking and cataract deserve comment. The case-control study in India (Mohan et al. 1989) was hospital-based and relied on patients from one center. The possibility of selection bias, especially in terms of cases with vision loss and controls without vision loss and their COPDs, must be considered. The case-control study in Italy (Italian-American Cataract Study Group 1991) had a design similar to the study in India but used cases and controls from three clinics covering the population in Parma, Italy. This broader coverage reduced the possibility for selection bias. However, the recruitment rates of cases of posterior subcapsular cataract and nuclear cataract were lower than expected; the smoking data were not shown for this study, so an assessment of the power to detect an increased risk associated with smoking could not be done. The third study (Bochow et al. 1989), a case-control study of risk factors for posterior subcapsular cataract, did not evaluate the association of smoking with other cataract types. The controls included patients with nuclear cataract alone or with AMD, which may have increased the prevalence of smoking in the comparison group. Thus, the three studies that did not find an association between smoking and cataract have limitations that may have introduced bias toward the null.

There are no clinical trials of smoking cessation and determinations of either reduced risk of onset or progression of lens opacities. Six studies examined

the risk in former smokers, and the data in general support a lower risk of progression or development of cataract after cessation. The mechanism is likely to be a reduction in the smoking-related dose of injurious agents to the lens rather than any reversal of the cataractogenic process. A cross-sectional survey looked in detail at time since smoking cessation and reported that cessation of 10 or more years reduces the risk of nuclear opacity (West et al. 1989a). In two large prospective cohort studies, former smokers at baseline had no increased risk of new nuclear opacities (Christen et al. 1992) or new cataract surgery (Hankinson et al. 1992). The 13-year follow-up study among male physicians of self-reported development of visually significant cataract found a lower risk among former smokers compared with current smokers (Christen et al. 2000). The prospective data are compatible with previous work showing that ongoing smoking drives progression. Other researchers who found similar risks for former smokers as for current smokers did not evaluate risk by years since cessation (Cumming and Mitchell 1997; Hiller et al. 1997). Studies of risk for cataract among smokers using low-yield cigarettes or low-tar products have not been reported.

Evidence Synthesis

Substantial evidence based on cross-sectional and prospective cohort studies now has accrued linking nuclear, and possibly posterior subcapsular, cataract to cigarette smoking. There is a dose-response relationship and evidence that former smokers have a lower risk of cataract and of progression of cataract compared with current smokers. On the basis of the epidemiologic studies, researchers now are investigating the mechanisms by which smoking may damage the lens, by using animal and lens cell culture models. The laboratory data are not yet sufficiently mature to inform the discussion of smoking and cataract, in part because there are few animal models of age-related cataract; most require an external insult to initiate the cataractogenic process. However, smokers are exposed to a number of agents that may cumulatively damage the lens, which lacks reparative capacity.

Conclusions

1. The evidence is sufficient to infer a causal relationship between smoking and nuclear cataract.

2. The evidence is suggestive but not sufficient to infer that smoking cessation reduces the risk of nuclear opacity.

Implications

There is moderate evidence to suggest that smoking also may be associated with an increased risk of posterior subcapsular opacities as well, but more research is needed before a causal association can be inferred for this cataract type. The difficulty the lens has in repairing damage suggests that opacification at the time of smoking cessation is likely to be irreversible. Studies of cataract in clinical trials of smoking cessation would provide more definitive evidence for any protective effect, although feasibility would be constrained by the need for large populations.

Age-Related Macular Degeneration

AMD is the leading cause of blindness in whites aged 65 years and older in the United States (Sommer et al. 1991; Muñoz et al. 2000). There currently is no well accepted treatment to prevent or halt the progression of atrophic AMD, the most common form of AMD. Treatment to halt vision loss from the less common, severe form of AMD, exudative (neovascular) AMD, often is short lived, as neovascularization (new blood vessel formation) often recurs. A recent large-scale clinical trial has provided evidence that antioxidant supplements plus zinc may delay the progression of some signs of AMD (Age-Related Eye Disease Study Research Group 2001). Otherwise, no preventive therapy for AMD is available, so considerable attention has focused on identifying risk factors for this disease.

The macula is a component of the retina at the center of the optical axis; it contains the fovea, a highly specialized area of the retina responsible for high-resolution vision. The retina consists of neural tissues, including the photoreceptors that convert energy from visible light into electrical signals sent on to the brain for processing. The photoreceptors—rods and cones—have high metabolic requirements and replace their outer segments daily. The metabolic functions of the retina are supported by the retinal pigment epithelium, which phagocytizes an estimated 2,000 outer segment membranes daily. This high rate of activity is made possible by the exchange of nutrients (and removal of waste) through the retinal blood supply, the choriocapillaris. There is a blood retinal barrier to this exchange, which is formed by both the retinal pigment epithelium and its anchor, Bruch's membrane (lamina basalis choroideae). Thus, the complex of the retinal pigment epithelium, Bruch's membrane, and the choriocapillaris serve as the nutritional source for the

sensory retina. Changes in each of the tissues in this complex have been hypothesized to result in AMD. However, the pathogenesis of AMD, indeed the differentiation of changes in early AMD from those of normal aging, is uncertain (Sarks and Sarks 1994).

AMD is an umbrella designation for a variety of degenerative changes in the macula. The degeneration is characterized in its early stages by pigmentary disturbances and atrophic changes. The late stages of AMD are characterized by widespread atrophy of the retinal pigment epithelium, loss of photoreceptors (atrophic AMD), and, less commonly, exudative AMD. With exudative AMD, new, unstable blood vessels develop in the choroid and grow under or through the retinal pigment epithelium via breaks in Bruch's membrane. Leakage from these neovascular membranes may lead to detachment of the retinal pigment epithelium, hemorrhage, and formation of a disciform scar. The late stages are associated with vision loss, classically loss of central vision, the part of vision responsible for activities such as reading and close work.

Morphologic changes associated with AMD include basal laminar deposits at the level of the retinal pigment epithelium, thickening of Bruch's membrane, and drusen. Drusen are deposits of extracellular material thought to be accumulations or "garbage bags" of waste products from the retinal pigment epithelium. At least two types of drusen are recognized clinically on the basis of their appearance: small, hard drusen, which are a common feature of aging; and larger, soft drusen, which also are common with aging but are a likely risk factor for developing severe AMD. The presence of drusen in the fundus, thought to be the hallmark of early AMD, is being challenged as a marker by observations that drusen can appear and disappear over time (Bressler et al. 1995; Klein et al. 1997), that most people with large, soft drusen do not develop advanced AMD (Klein et al. 1997), and that epidemiologic patterns associated with advanced AMD are different from those for drusen-defined early AMD. This debate has relevance in evaluating the evidence for an association of smoking and early versus advanced AMD.

Biologic Basis

Of the postulated mechanisms underlying the retinal changes in AMD, three have bearing on the hypothesis that smoking is associated with AMD. The first can be characterized as oxidative stress leading to changes in the ability of the retinal pigment epithelium to phagocytize cellular products, which in turn leads to accumulations of debris that interfere with the nutrient exchange between the retinal pigment epithelium and the choriocapillaris. Oxidative stress can result from free-radical damage to proteins, lipids, and possibly, mitochondrial DNA. The stress is considered to contribute to malfunctions of the retinal pigment epithelium. The macula is a particularly likely target for oxidative stress because of the macula's high exposure to light, high metabolic rate, and high concentrations of fatty acids. But the macula also is very rich in antioxidative, protective mechanisms, including an array of antioxidant nutrients and enzymes, as well as melanin. Smoking, through its actions on reducing plasma levels of antioxidants in addition to reducing macular pigment, is hypothesized to increase the oxidative stress on the macula by robbing it of its defenses (Hammond et al. 1996).

The second hypothesis for the pathogenesis of AMD proposes that the degradation of Bruch's membrane, as manifested by thickening and changes in the composition, leads to interference with nutrient exchange between the retinal pigment epithelium and its blood supply. Vascular endothelial growth factor (VEGF) has been reported in the retinal pigment epithelium cells; these cells may liberate VEGF in response to the interference in nutrient exchange. Investigators are working on the role of VEGF, released in connection with hypoxia, in the pathogenesis of AMD, particularly for the neovascular type (Mousa et al. 1999). Smoking has been associated with an increase in plasma immunoreactive VEGF, at least acutely, operating likely through its ability to cause tissue hypoxia (Wasada et al. 1998).

The third hypothesis for the pathogenesis, or at least a possible contributing cause, of AMD is vascular insufficiency. Changes in the choroidal circulation may impair the ability of the retinal pigment epithelium to dispose of waste substances, leading to the accumulation of waste material. The rate and volume of blood flow through the choriocapillaris are high in response to the demands of the pigmented epithelium and the photoreceptors. Smoking has been shown to alter choroidal blood flow (Bettman et al. 1958). Smoking also affects the vasculature through platelet adhesions and hypoxia from elevated levels of carboxyhemoglobin, which might add to the stimulation of new vessel growth.

It is likely that multiple pathways are responsible for the degenerative changes in the macula with age, and a reasonable basis exists for presuming that smoking may operate through one or more of these pathways.

Table 6.27 Studies on the association between smoking and cataracts

Study	Population	Design
	Association found	
Clayton et al. 1982	931 cataract surgery patients; 325 controls	Case-control
Klein et al. 1985	1,370 persons with diabetes	Cross-sectional
Harding and Van Heyningen 1988	300 cataract surgery patients; 609 controls	Case-control
Flaye et al. 1989	983 volunteers with complete data	Cross-sectional
West et al. 1989a	838 male fishermen	Cross-sectional
Leske et al. 1991	945 clinic cases; 435 controls	Case-control
Christen et al. 1992	17,824 male physicians without self-reported cataracts at baseline	5-year prospective

*Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.
†OR = Odds ratio.
‡CI = Confidence interval.
§RR = Relative risk.

Cataract assessment	Results
No type specified; surgical cases	Heavy smoking was twice as common in cases; no data were reported; confounding was not addressed
Clinical exam for cataract type	Smoking was associated with cataracts (cataract type not stated, smoking not characterized)
No type specified; surgical cases	Heavy smoking (>75 pack-years*) was associated with cataracts, OR† = 1.97 (95% CI‡, 1.05–3.67); confounding was not addressed
Clinical exam for nuclear, cortical, and posterior subcapsular opacities	Nuclear opacity was associated with current smoking: OR = 2.5 for light smokers (95% CI, 1.6–4.0), 2.7 for moderate (95% CI, 1.6–4.3), and 2.9 for heavy (95% CI, 1.4–5.9); also related to past heavy smoking, OR = 2.6 (95% CI, 1.4–5.0); there were no associations with past light to moderate smoking or with other cataract types
Photographs for nuclear, cortical, and posterior subcapsular opacities; Wilmer grading system used	There was an association between cumulative pack-years and risk of nuclear opacities, $p < 0.004$ (too few posterior subcapsular opacities to analyze); risk declined if participants had stopped smoking for ≥10 years; adjusted for age and gender
Photographs for nuclear, cortical, and posterior subcapsular cataracts; Lens Opacities Classification System II used	Nuclear cataracts were associated with current smoking, OR = 1.68 (95% CI, 1.03–2.75); there were no associations with other cataract types or any analyses of former smokers; adjusted for confounders
Self-reported development of cataracts; medical records for date of diagnosis, date of extraction, type, and loss of vision	For current smokers of ≥20 cigarettes / day, RR§ = 2.24 for nuclear (95% CI, 1.47–3.41) and 3.17 (95% CI, 1.81–5.53) for posterior subcapsular cataracts; there was no association with <20 cigarettes / day; former smokers had no increased risk of nuclear or posterior subcapsular cataracts; adjusted for confounders

Table 6.27 Continued

Study	Population	Design
	Association found	
Hankinson et al. 1992	50,828 female nurses without self-reported cataracts at baseline	Approximately 8-year prospective
Klein et al. 1993b	Population-based sample of 4,926 adults	Cross-sectional
West et al. 1995	442 male fishermen with photographs 5 years apart	5-year prospective for incidence and progression
Cumming and Mitchell 1997	Population-based sample of 3,654 adults	Cross-sectional
Hiller et al. 1997	660 members of Framingham Eye Study with no lens opacities	12.5-year prospective
Leske et al. 1998	764 of 1,380 participants in a case-control study	4-year prospective of cases and controls
Christen et al. 2000	20,907 male physicians with no cataracts at baseline	13-year prospective

Cataract assessment	Results
Self-reported cataract extractions; medical records for type	Smokers of 65 pack-years had increased risks for nuclear cataracts, RR = 1.79 (95% CI, 0.83–3.88), and posterior subcapsular cataracts, RR = 2.59 (95% CI, 1.59–4.50) (few current smokers, few cases of nuclear cataracts); former smokers had no increased risk unless they had smoked ≥35 cigarettes / day; adjusted for confounders
Photographs for nuclear, cortical, and posterior subcapsular opacities; Wisconsin grading system used	Smoking was associated with nuclear opacity, OR = 1.09 for 10 pack-years (95% CI, 1.04–1.16), and with posterior subcapsular cataracts among men, OR = 1.05 (95% CI, 1.00–1.11), and women, OR = 1.06 (95% CI, 0.98–1.14); former smokers were not studied; adjusted for confounders
Photographs for nuclear, cortical, and posterior subcapsular opacities; Wilmer grading system used	OR for current smokers = 2.45 (95% CI, 1.00–6.04) for progression of nuclear opacity, which was associated with interim 5-year smoking, OR = 1.18 (95% CI, 1.06–1.32) for pack-years in 1 pack-year increments; adjusted for baseline severity and age; there was no association with incident nuclear opacity
Photographs of nuclear, cortical, and posterior subcapsular opacities; Wisconsin cataract system used	Ever smokers had increased ORs for nuclear opacity, OR = 1.3 (95% CI, 1.1–1.6), and posterior subcapsular opacity, OR = 1.5 (95% CI, 1.1–2.1); there was no risk for cortical opacity; former smokers (no time since quitting was specified) had similar risks
Clinical exam for nuclear, cortical, and posterior subcapsular opacities; Wilmer grading system used	Light smoking at baseline was associated with incident nuclear opacity, OR = 1.68 (95% CI, 1.14–2.49), as was heavy smoking, OR = 2.37 (95% CI, 1.43–3.93); former smokers (but could be interim smokers) had an increased risk of incident nuclear opacity, OR = 2.02 (95% CI, 1.14–3.57); there was no association with other cataract types
Photographs for nuclear, cortical, and posterior subcapsular opacities; Lens Opacities Classification System III used	There was an increase in nuclear opacity with smoking at baseline, RR = 1.58 (95% CI, 1.06–2.35); interim smoking, quitting smoking, and other opacities were not studied
Self-reported development of cataracts; medical records with dates of diagnosis and extraction, and loss of vision (type not specified)	Former smokers had a lower risk of cataracts (type not specified) compared with current smokers, and a lower risk of cataract surgery, adjusting for number of cigarettes smoked and other confounders, RR = 0.79 (95% CI, 0.67–0.92)

Table 6.27 Continued

Study	Population	Design
	No association found	
Bochow et al. 1989	Posterior subcapsular cataract cases and controls	Case-control
Italian-American Cataract Study Group 1991	1,008 clinic cases; 469 controls	Case-control
Mohan et al. 1989	1,441 patients in India with cataracts; 549 controls	Case-control

Epidemiologic Evidence

Two methodologic issues add to the complexity of assessing the relationship between AMD and smoking. The first issue is that advanced, or severe, AMD mostly occurs in the very old. About 7 percent of the white population aged 75 years and older will have advanced AMD (Klein et al. 1992). The second issue is that life expectancy of smokers is less than that of nonsmokers, so selective survival of smokers to even develop AMD is an issue. Together, the relatively low incidence of AMD and the low prevalence of smoking in very elderly populations diminish the power to detect associations in all but the largest studies, which is evident in the population-based studies of AMD that have low numbers of cases of severe AMD.

One way to circumvent the problem is to study the association of smoking in precursor lesions or early AMD; however, there is no uniform agreement on the clinical signs of early AMD. Many of the signs currently in use are common in the population and can be so unstable as to be almost uninformative about who will develop advanced AMD. Data are accumulating on predictors of advanced AMD, the presence of very large drusen, and the retinal area covered by drusen. In part, the difficulty of determining the relevant early signs may be due to the limitations of photographic systems to detect such changes in, for example, Bruch's membrane; for research purposes, however, no alternative detection systems are available for accurately detecting early changes.

With these caveats in mind, the research findings to date suggest a strong likelihood that smoking is related to advanced or severe AMD, particularly exudative AMD, but there is scant evidence that smoking is related to the apparent early signs of AMD (Table 6.28). One cross-sectional, population-based study (Smith et al. 1996) found increased odds of early AMD among smokers compared with nonsmokers (OR = 1.89 [95 percent CI, 1.25–2.84]). However, two others, using identical grading methods, found no increased odds (Klein et al. 1993c; Delcourt et al. 1998). In another cross-sectional survey of fishermen who were heavy smokers, a paradoxical protective effect was seen for smoking and the odds of early AMD, primarily cases of moderate drusen (West et al. 1989b). A prospective cohort study of the risk of developing early signs of AMD found an increased risk of developing large (>250 μm) drusen among smokers compared with lifetime nonsmokers; the RR was 3.21 (95 percent CI, 1.09–9.45) among men and 2.20 (95 percent CI, 1.04–4.66) among women. No other early sign was associated with smoking (Klein et al. 1998). The lack of association with presumed early AMD may be due to the imprecision of the signs chosen to represent early AMD, thus biasing the results toward the null. Further work on improving this classification is warranted. It is also possible that smoking is related to progression of AMD to the exudative form but not to the onset of early lesions.

Gender differences appear in the findings as well. In one case-control study of severe AMD, the relationship with smoking was observed in men only (Hyman et al. 1983). In one prospective cohort study in a population having primarily early AMD, progression of AMD among smokers was observed with a dose-response pattern only among men (Klein et al. 1998).

Cataract assessment	Results
Chart reviews for and absence of posterior subcapsular cataracts	Current and former smoking were not related to posterior subcapsular cataracts
Slit lamp exam for nuclear, cortical, and posterior subcapsular cataracts; Lens Opacities Classification System I used	Compared never, former, and current smokers among cases and controls; no differences were reported (data were not shown)
Nuclear, cortical, and posterior subcapsular cataracts on clinical exam; no grading scheme described	Compared never, former, and current smokers among cases and controls; no differences were reported (data were not shown)

A prospective cohort study of exudative AMD among men found a benefit of quitting smoking after 20 years of cessation (Christen et al. 1996), but a similar study among women found no benefit after 15 or more years of cessation (Seddon et al. 1996). There are not evident explanations for these differences, except that the significantly lower prevalences of smoking among women may reduce the power to detect associations with AMD, especially if heavy smoking is the risk-determining factor.

The strongest and most consistent association seen in the literature is the association of current smoking and risk of severe AMD, especially exudative AMD. Because several studies tended to combine atrophic and exudative AMD into "late" or "severe" AMD, it is difficult to know whether to attribute the association to either one or both, unless specified. Four case-control studies have been reported to date. A large case-control study of exudative disease (Eye Disease Case-Control Study Group 1992) found an increased OR with current and past smoking of 2.2 (95 percent CI, 1.4–3.5) and 1.5 (95 percent CI, 1.2–2.1), respectively. Three other case-control studies also found an increased risk for severe AMD in smokers, with estimated ORs between 2 and 3 (Hyman et al. 1983; Macular Photocoagulation Study Group 1986; Tamakoshi et al. 1997). Four cross-sectional, population studies found increased odds of exudative AMD among current smokers, with ORs between 1.5 and 3.6; two of the four studies found a dose-response relationship. Two of the four cross-sectional studies found increased odds of atrophic AMD with current smoking (Vinding et al. 1992; Smith et al. 1996), but the other two did not (Klein et al. 1993c; Vingerling et al. 1996). Two prospective studies found a significant association with either exudative disease or severe AMD in current heavy smokers (20 or more cigarettes per day) (Christen et al. 1996; Seddon et al. 1996). Former smokers also had an increased risk of AMD, although lower than that for current heavy smokers. Quitting more than 20 years previously appeared to decrease the risk in two cross-sectional studies (Vingerling et al. 1996; Delcourt et al. 1998), as well as in a prospective cohort study in men (Christen et al. 1996). In the prospective study in women (Seddon et al. 1996), however, quitting 15 or more years prior did not decrease the risk of severe AMD.

The data from cross-sectional studies suggest that passive smoking is not related to early or late AMD (Klein et al. 1993c; Smith et al. 1996). There are no corroborating data from animal models. Although animal models of induced retinal damage exist, no good animal models present the spectrum of features of AMD.

Evidence Synthesis

These data provide evidence that current smoking is associated with exudative AMD and possibly atrophic AMD. Dose-response relationships with the amount of smoking have been described. Maintaining smoking cessation at least 20 years decreased the risk of severe AMD and exudative AMD. The possibility that smoking is associated with the neovascular form of AMD is further bolstered by the findings from a study of ocular histoplasmosis (Ganley 1973), where

neovascularization can result from the infection. In that study, smokers were twice as likely as nonsmokers to develop disciform scars. Moreover, in a clinical trial of photocoagulation to halt progression of neovascularization, smokers were more likely than nonsmokers to have recurrent neovascularization over time (Macular Photocoagulation Study Group 1986). However, smoking did not predict development of neovascularization in the previously unaffected companion eyes of the eyes with neovascularization (Macular Photocoagulation Study Group 1997).

Conclusions

1. The evidence is suggestive but not sufficient to infer a causal relationship between current and past smoking, especially heavy smoking, with risk of exudative (neovascular) age-related macular degeneration.

2. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and atrophic age-related macular degeneration.

Implications

There is a need for more research into gender differences, dose-response relationships, and a possible threshold effect. Further research is also needed to determine the effect of smoking cessation on the risk of neovascular AMD.

Diabetic Retinopathy

Diabetic retinopathy is a serious ocular complication of diabetes associated primarily with long-term duration of diabetes and poor control in both type 1 and type 2 diseases. The retinopathy is likely the result of vascular changes occurring in the retinal circulation that feeds the inner layers of the retina. Diabetic retinopathy in the early stages (mild, nonproliferative retinopathy) is characterized by excessive permeability of the vasculature, with ballooning of the retinal capillaries to form microaneurysms, dot hemorrhages, and hard and soft exudates. Preproliferative retinopathy includes, in addition to the aforementioned features, vascular occlusion and dilation and/or venous beading. Proliferative diabetic retinopathy is characterized by new vessel growth or fibrous proliferation or both. Vitreous hemorrhage secondary to the neovascularization also may be seen. Clinically significant macular edema, the result of extensive vessel leakage, can be a feature of chronic diabetic eye disease that may occur at any stage of the process. The prevalence of diabetic retinopathy increases with duration of diabetes, and most persons with diabetes have signs after 10 years' duration. Moreover, diabetic retinopathy is an important cause of vision loss. Although photocoagulation is an effective means of treating proliferative diabetic retinopathy, too often the retinopathy is not diagnosed at an early stage when treatment can be maximally effective.

Biologic Basis

Several investigators have postulated that smoking may contribute to the onset of diabetic retinopathy and/or drive progression of existing retinopathy through its effect on the retinal circulation (Morgado et al. 1994). If such relationships exist, one mechanism of action is likely to be hypoxia from chronic exposure to carbon monoxide, which may be toxic to retinal vasculature. Carbon monoxide also is associated with separation of arterial endothelial cells, causing edema, which also is a feature of diabetic retinopathy. Nicotine exposure increases levels of plasma vasoconstrictors, such as angiotensin and vasopressin, which have binding sites on retinal blood vessels. In addition, nicotine exposure increases platelet adhesiveness, and persons with diabetic retinopathy are more likely to have increased platelet aggregation compared with persons with diabetes but without retinopathy. Although there is a reasonable biologic basis to the hypothesis that smoking is related to diabetic retinopathy, the data suggest otherwise.

Epidemiologic Evidence

Many studies have examined the association between smoking and diabetic retinopathy (Table 6.29), and the data from several studies do not support the proposed association. The well-controlled studies, including prospective cohort studies in large populations of persons with diabetes, found no association between smoking and the amount smoked and the prevalence, incidence, or progression of diabetic retinopathy (Klein et al. 1983; Moss et al. 1991, 1996). Studies that found an association in general did not adjust for level of control of diabetes, a major risk factor for diabetic retinopathy. One study did adjust for level of control and other risk factors and found an

association between smoking and a six-year progression of diabetic retinopathy (Mühlhauser et al. 1996). However, progression was defined as any progression, from onset of diabetic retinopathy to becoming blind, if proliferative diabetic retinopathy was present at baseline. There were no data shown on whether smokers tended to have worse retinopathy at baseline, but the analyses should have adjusted for baseline status of diabetic retinopathy as a risk factor for progression. When the progression was confined to the subgroup with no retinopathy at baseline, smoking was not significantly associated with either the incidence or progression of diabetic retinopathy.

Evidence Synthesis

Although smoking might plausibly worsen diabetic retinopathy, the evidence is inconsistent. The strongest studies, the prospective cohort studies, do not show an association. The level of diabetes control is a potential major confounder that has not been considered in a number of the studies.

Conclusion

1. The evidence is suggestive of no causal relationship between smoking and the onset or progression of retinopathy in persons with diabetes.

Implication

As research on diabetes continues, possible effects of smoking should be reassessed.

Glaucoma

Glaucoma is the third leading cause of blindness worldwide (Thylefors et al. 1995). In the United States, African Americans and Hispanics are more affected than other groups. Glaucoma is a disease characterized by loss of retinal ganglion cells, probably through a variety of mechanisms. The two main types of primary glaucoma are primary open-angle glaucoma and angle closure glaucoma. The angle refers to the angle between the iris and trabecular meshwork in the anterior chamber, which if shallow or closed impedes outflow of aqueous fluid and causes a rise in pressure. There are distinct differences between the two types of glaucoma, and their distribution differs in populations. In the United States, primary open-angle glaucoma is the more common type.

Biologic Basis

There is no evident basis for proposing that smoking might predispose a person to either developing glaucoma or having more severe glaucoma. Investigators have proposed that factors that diminish perfusion of the optic nerve head with blood may be associated with glaucoma. Because smoking affects the retinal circulation (although any direct effect of smoking on the optic nerve head is unknown), several investigators have examined the association of glaucoma with smoking. However, the effects of smoking on blood flow in ocular circulation are difficult to measure, in part because studies often do not consider separating acute effects in smokers and nonsmokers from the chronic effects that result from repeated exposures. The role of smoking in altering intraocular pressure also is variable. In one study (Shephard et al. 1978), smoking (including cumulative consumption) was not associated with intraocular pressure differences.

Evidence Synthesis

The few epidemiologic studies conducted (Table 6.30) do not indicate any relationship between smoking and glaucoma. Three cross-sectional studies found no association between smoking and glaucoma (Klein et al. 1993a; Ponte et al. 1994; Leske et al. 1995), and one prospective cohort study found no increased risk of glaucomatous field loss among persons with ocular hypertension who smoked compared with those who did not smoke (Quigley et al. 1994). The association has not been evaluated in angle closure glaucoma, but there is little biologic basis for proposing such a relationship.

Conclusion

1. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and glaucoma.

Implication

As further studies of glaucoma are undertaken, the role of smoking should remain under investigation.

Table 6.28 Studies on the association between smoking and age-related macular degeneration (AMD)

Study	Population	Design
Paetkau et al. 1978	114 cases of exudative AMD from 1 clinic	Cross-sectional
Maltzman et al. 1979	30 persons with AMD and 30 normal controls from 1 clinic matched for age, gender, and race	Case-control
Hyman et al. 1983	162 persons with AMD and 175 controls from 34 practices matched for age and gender	Case-control
Blumenkranz et al. 1986	26 persons with exudative AMD compared with 23 controls matched for age and gender (spouses or partners)	Case-control
Macular Photocoagulation Study Group 1986	119 eyes with neovascular AMD assigned to argon laser photocoagulation	3-year prospective
West et al. 1989b	838 male fishermen, 96 with early AMD (large drusen, confluence, and hyperpigmentation)	Cross-sectional
Eye Disease Case-Control Study Group 1992	421 persons with neovascular AMD from 5 centers; 615 controls (control group matched for age, gender, race, and center)	Case-control
Vinding et al. 1992	Population-based sample of 773 participants in Copenhagen aged ≥60 years; 88 cases of atrophic AMD and 24 of exudative AMD	Cross-sectional
Klein et al. 1993c	Population-based sample of 4,771 participants aged ≥43 years; 41 cases of exudative AMD and 29 of atrophic AMD	Cross-sectional

*OR = Odds ratio.
†CI = Confidence interval.
‡RR = Relative risk.

AMD assessment/type studied	Results
Fluorescein angiography	Current smokers had an earlier age of onset of vision loss (64 years) compared with nonsmokers (71 years), $p < 0.001$
Data were not reported	10 persons with AMD reported smoking at some point, compared with 7 controls; no association was concluded
Diagnosis of drusen and/or macular degeneration confirmed by fundus photographs	Male smokers (not defined) had an increased risk of AMD: OR* = 2.6 (95% CI†, 1.2–5.8); there was no dose-response pattern
Fundus photographs to determine cases and controls without AMD	Smokers were not significantly more likely to have exudative AMD, OR = 1.3 (95% CI, 0.3–4.4)
Angiograms showing choroidal neovascularization within 200–2,500 µm of the fovea; outcome: recurrence of choroidal neovascularization on photographs	Current smokers of ≥10 cigarettes/day had greater rates of choroidal neovascularization recurrences, RR‡ = 1.8 ($p < 0.02$); dose-response was not studied
Fundus photographs to diagnose AMD	Ever smokers had a lower risk than never smokers of AMD, OR = 0.54 (95% CI, 0.30–0.95); there was no dose-response relationship after adjusting for confounders
Physician-diagnosed AMD with visual loss, drusen, and 1 of several signs of choroidal neovascularization; verification by fundus photographs	Current smoking was associated with neovascular AMD, OR = 2.2 (95% CI, 1.4–3.5); former smokers also had an increased risk, OR = 1.5 (95% CI, 1.2–2.1); dose-response was not studied
Physician-diagnosed atrophic and exudative AMD, with visual loss	Both atrophic OR = 2.5 ($p < 0.01$) and exudative OR = 1.5 ($p > 0.05$, small sample size) AMD cases were more likely to be found in smokers than in nonsmokers
Fundus photographs; Wisconsin grading scheme used for early and late AMD	There was no relationship of early AMD (drusen characteristics, pigmentary disturbances) to smoking status, dose, or passive smoking; current smokers had a higher frequency of exudative AMD, OR = 2.50 (95% CI, 1.01–6.20) among women and 3.29 (95% CI, 1.03–10.5) among men; it was not associated with passive smoking; a dose-response pattern was reported only for women; there was no association with atrophic AMD

Table 6.28 Continued

Study	Population	Design
Christen et al. 1996	21,157 male physicians aged ≥40 years with no AMD at baseline, followed for ≥7 years; 268 had AMD with vision loss and 64 had exudative AMD	Prospective
Seddon et al. 1996	31,843 female nurses aged ≥50 years with no AMD at baseline, followed for 2–12 years; 215 had AMD with vision loss and 77 had exudative AMD	Prospective
Smith et al. 1996	Population-based study of 3,654 participants aged ≥49 years; 50 cases of exudative AMD and 22 of atrophic AMD	Cross-sectional
Vingerling et al. 1996	Population-based study of 6,251 participants aged ≥55 years; 65 cases of neovascular AMD and 36 of atrophic AMD	Cross-sectional
Tamakoshi et al. 1997	56 cases of exudative AMD among Japanese men aged 50–69 years in 5 hospitals; 82 male controls with no macular changes (coming for physical exam)	Case-control

[§]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

AMD assessment/type studied	Results
Self-reports with vision loss of 20/30 or worse; chart review by ophthalmologist/optometrist	Current smokers of ≥20 cigarettes/day had an increased risk of AMD with vision loss, RR = 2.57 (95% CI, 1.70–3.90); there was no increased risk with smoking <20 cigarettes/day, RR = 1.18 (95% CI, 0.57–2.42); former smokers had an increased risk, RR = 1.30 (95% CI, 1.01–1.69); dose-response relationship was present; quitting for ≥20 years decreased the risk; current smokers (no dose was given) had an increased risk of exudative AMD, RR = 1.95 (95% CI, 0.89–4.24); no increased risk with former smoking; cases of AMD without vision loss had no association with smoking
Self-reports with vision loss of 20/30 or worse; chart review by ophthalmologist/optometrist; subset validated by fundus photographs	Current smokers had an increased risk of AMD with vision loss, RR = 1.7 (95% CI, 1.2–2.5), greatest in those smoking ≥25 cigarettes/day, RR = 2.4 (95% CI, 1.4–4.0); former smokers had an increased risk, RR = 1.8 (95% CI, 1.3–2.5); dose-response relationship was present; former smokers had RRs similar to current smokers with no evidence of effects from quitting even after ≥15 years; a dose-response relationship was also seen with exudative AMD
Fundus photographs graded according to Wisconsin grading scheme for early and late AMD	Current smokers had a higher prevalence of neovascular AMD, OR = 3.26 (95% CI, 1.45–7.33); atrophic AMD, OR = 4.94 (95% CI, 1.29–18.82); and early AMD, OR = 1.89 (95% CI, 1.25–2.84); ORs were elevated for neovascular and atrophic AMD, but not significantly for men; passive smoking was not associated with any AMD; there were no associations between late or early AMD and pack-years[§]
Fundus photographs graded according to Wisconsin grading system	Current smokers aged <85 years had an increased prevalence of neovascular AMD, OR = 3.6 (95% CI, 1.8–7.4); no increase in atrophic AMD; there was a dose-response relationship with ≥10 pack-years, OR = 9.1 (95% CI, 3.2–25.9); stopping smoking for ≥20 years decreased the risk of neovascular AMD among nonsmokers
Fundus photographs and fluorescein angiography	Neovascular AMD was associated with current smoking, OR = 3.07 (95% CI, 1.09–8.63), and former smoking, OR = 2.09 (95% CI, 0.71–6.13); a dose-response relationship was present, with a high risk for those who started smoking before 20 years of age, OR = 3.41 (95% CI, 1.20–9.73)

Table 6.28 Continued

Study	Population	Design
Delcourt et al. 1998	2,196 participants aged ≥60 years in a population-based survey; 41 cases of late AMD (neovascularization or geographic atrophy)	Cross-sectional
Klein et al. 1998	3,583 participants aged ≥43 years in a longitudinal, population-based study (reported low incidence of atrophic and exudative AMD)	5-year prospective

AMD assessment/type studied	Results
Fundus photographs graded according to Wisconsin grading system	Current smoking, OR = 3.5 (95% CI, 1.0–12.2), and former smoking, OR = 2.8 (95% CI, 1.1–6.9), were associated with late AMD (not further separated into atrophic vs. neovascular AMD); dose-response relationship was present; those who stopped smoking within 20 years had the same risk as current smokers; there were no associations with early AMD
Fundus photographs graded according to Wisconsin grading system	Current smokers were more likely to develop large (>250 μm) drusen compared with never smokers, RR = 3.21 (95% CI, 1.09–9.45) among men and 2.20 (95% CI, 1.04–4.66) among women; dose-response relationship was present; no other sign was associated; male (not female) current smokers progressed to age-related maculopathy in a dose-response pattern

Table 6.29 Studies on the association between smoking and diabetic retinopathy (DR)

Study	Population	Design
Paetkau et al. 1977	150 cases of diabetes	Cross-sectional; compared PDR* cases with DR cases
Christiansen 1978	180 patients with insulin-dependent juvenile-onset diabetes of different durations	Cross-sectional
West et al. 1980	973 Native Americans with adult-onset diabetes	Cross-sectional
Gray et al. 1982	194 patients with type 1 diabetes with varying levels of DR	Cross-sectional
Klein et al. 1983	467 patients with younger-onset (diagnosed before 30 years of age and taking insulin) and 1,039 with adult-onset diabetes	Cross-sectional
Telmer et al. 1984	688 patients with insulin-dependent diabetes with a duration of 12–40 years	Cross-sectional
Rand et al. 1985	111 patients with insulin-dependent diabetes with PDR and 81 patients with diabetes with no or minimal DR	Case-control, matched for duration of diabetes
Sjolie 1985	577 insulin-treated patients with diabetes aged 10–70 years	Cross-sectional
Walker et al. 1985	193 diabetic patients	Cross-sectional
Ballard et al. 1986	Population-based group of 1,031 patients with adult-onset diabetes	Prospective, up to 20 years
Mühlhauser et al. 1986	192 smokers and 192 nonsmokers with type 1 diabetes	Matched case-control
Borch-Johnsen et al. 1987	184 survivors of long-term insulin-dependent diabetes participating in a prospective study	Cross-sectional
Kingsley et al. 1988	754 patients with insulin-dependent diabetes	Cross-sectional

*PDR = Proliferative diabetic retinopathy.
†NR = Data were not reported.
‡Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.
§OR = Odds ratio.

Diabetes/DR assessment	Results
NR[†]	Smoking was associated with PDR in patients with a long duration of diabetes; there was no adjustment for level of control of diabetes
Standard exam / clinical observer of DR	Smoking was not associated with DR or PDR
Standard exam / clinical exam for DR	Smoking was not associated with DR or PDR
Standard exam / not stated	Patients with DR were more likely to be smokers, likely explained by level of diabetes control; no dose-response pattern was noted
Fasting glucose / fundus photographs graded according to the modified Arlie House Classification	There were no associations between smoking, pack-years[‡], and DR or severity of DR
Clinic records / clinical exam and fluorescein angiogram for PDR	Smoking, smoking dose, and former smoking were not associated with PDR
Standard exam / PDR on stereo fundus photographs graded according to the modified Arlie House Classification	Smoking was not associated with PDR
Clinic reports / clinical exam for DR	There was an increased risk of any DR with smoking, OR[§] = 1.9; not adjusted for control of diabetes
Clinic records / clinical exam for DR	Smoking was related to DR in men, not in women; not adjusted for level of control of diabetes
Standard exam / DR by clinical exam	Smoking was not associated with incidence of DR or PDR
Clinic records / DR assessed by ophthalmologist	Smokers had more PDR compared with nonsmokers (12.5 vs. 6.8%); no increased risk of all DR; not adjusted for level of control of diabetes
Clinic records / clinical exam, DR graded in nonstandard fashion	Smoking was not associated with DR or PDR
Standard exam / 58 patients had angiography, otherwise self-reported	There were no differences in percentages for smokers with and without severe retinopathy; there were no adjustments for other factors

Table 6.29 Continued

Study	Population	Design
Moss et al. 1991	668 patients with early-onset and 1,379 with adult-onset diabetes	4-year prospective for incidence and progression of DR
Marshall et al. 1993	277 patients with type 1 diabetes with durations of ≥5 years	Prospective for ≥1 years (mean follow-up = 2.7 years)
Klein et al. 1995	765 patients with younger-onset (diagnosed under 30 years of age and taking insulin) and 533 with older-onset diabetes with a 10-year follow-up	10-year prospective
Moss et al. 1996	708 persons with early-onset and 987 with adult-onset diabetes	10-year prospective for progression of DR
Mühlhauser et al. 1996	636 patients with type 1 diabetes	6-year prospective for progression of DR
Sinha et al. 1997	100 patients with insulin-dependent diabetes (53 smokers)	Prospective for up to 6 years

*PDR = Proliferative diabetic retinopathy.

Diabetes/DR assessment	Results
Fasting glucose / fundus photographs graded according to modified Arlie system	Smoking was not associated with incidence or progression in either group with diabetes
Not stated / DR by fundus photographs graded according to modified Arlie classification	Smoking was not associated with a transition to DR in a consistent manner
Fasting glucose / fundus photographs graded according to modified Arlie system	10-year incidence of diabetic macular edema was not related to smoking history
Fasting glucose / fundus photographs graded according to modified Arlie system	Pack-years, pack-years while diabetic, and smoking status were not associated with incidence and progression of DR or progression to PDR*
Standard exam for diabetes / DR by clinical exam and photographs; grading system not described	Pack-years smoked while diabetic were associated with any progression; not adjusted for baseline status: OR = 1.44 / 10 pack-years (95% confidence interval, 1.10–1.88); there were no associations of smoking variables with incidence of or progression to PDR in the group with no DR at baseline; adjusted for level of control and duration of diabetes
NR	Smokers had more DR at baseline and follow-up; no adjustment for level of control of diabetes

Table 6.30 Studies on the association between smoking and glaucoma

Study	Population	Design	Glaucoma assessment	Results
Morgan and Drance 1975	Cases of glaucoma diagnosed by multiple ophthalmologists; neighborhood controls	Case-control	Data were not reported	Smoking was not related to glaucoma
Wilson et al. 1987	83 cases, 237 controls matched for age and gender	Case-control	Visual fields, cup and optic disc, and intraocular pressure on chart; controls without glaucoma	Smoking was related to glaucoma, odds ratio = 2.9 (95% confidence interval, 1.3–6.6)
Klein et al. 1993a	Population-based survey of 4,926 whites aged ≥43 years (104 cases of glaucoma)	Cross-sectional	Visual fields, intraocular pressure, and cup-to-disc ratio on photographs	Smoking was not related to glaucoma
Ponte et al. 1994	44 cases of glaucoma or elevated intraocular pressure (≥24 mm Hg); 220 controls with intraocular pressure <21 mm Hg	Cross-sectional	Visual fields and elevated intraocular pressure	Smoking was not related to glaucoma
Quigley et al. 1994	647 persons with ocular hypertension, followed for 1–12 years	Prospective	Intraocular pressure >21 mm Hg (ocular hypertension); visual field loss at follow-up	Smoking was not related to incident visual field loss
Leske et al. 1995	Population-based study of 4,314 Barbadian blacks (302 glaucoma cases)	Cross-sectional	Visual fields and optic disc	Smoking was not related to glaucoma

Other Eye Diseases: Graves' Ophthalmopathy

Several other eye diseases have been investigated for an association with smoking. Most were not reviewed for this report, however, because the data are insufficient to reach any conclusions. The one exception is an uncommon condition—Graves' ophthalmopathy, an ocular complication of Graves' disease.

Graves' disease is thought to be an autoimmune disease of the thyroid. It is likely that both genetic and environmental factors are related to the risk of the disease. Among its clinical manifestations, the ophthalmologic complications appear to be related to smoking. Graves' ophthalmopathy is characterized by proptosis (protrusion of the eyeball), diplopia (double vision), optic neuropathy, and conjunctival and periorbital inflammation. The pathogenesis of Graves' ophthalmopathy is not completely understood, but it appears to involve the orbital fibroblasts that are stimulated to release glycosaminoglycans, which in turn are related to the orbital edema seen with the ocular complications. Recent data suggest an autoimmune basis for Graves' ophthalmopathy as well (Bahn 2000).

Biologic Basis

The mechanism by which smoking may cause or aggravate Graves' ophthalmopathy is unknown. Orbital hypoxia and effects of thiocyanate have been postulated, and other research has investigated the effect of smoke constituents on orbital fibroblast activity. Researchers investigating the role of hypoxia in muscular inflammation have found stimulation of protein synthesis and proliferation of extra-ocular, muscle-derived fibroblasts under hypoxic conditions (Metcalfe and Weetman 1994). Smoking does not appear to affect serum concentrations of proinflammatory cytokines in Graves' disease, even among persons with ocular complications (Salvi et al. 2000).

Epidemiologic Evidence

Seven studies (Table 6.31) found an increased risk associated with smoking of developing the ophthalmologic complications of Graves' disease (Hägg and Asplund 1987; Shine et al. 1990; Tellez et al. 1992; Prummel and Wiersinga 1993; Winsa et al. 1993; Pfeilschifter and Ziegler 1996; Bartalena et al. 1998); three found a dose-response relationship with the number of cigarettes smoked (Shine et al. 1990; Tellez et al. 1992; Pfeilschifter and Ziegler 1996). The studies, while consistent, are limited in number and the sample sizes of some are small. The severity of the ophthalmopathy was associated with smoking in two studies (Prummel and Wiersinga 1993; Winsa et al. 1993). Estimates of the OR varied between 2 and 10, depending on the control population selected. The effect of quitting smoking on Graves' ophthalmopathy has not been well studied and would provide convincing evidence of a causal relationship. On the basis of the findings of the epidemiologic studies, several investigators are studying the effect of smoking on the thyroid gland and the extra-ocular, muscle-derived fibroblasts.

Evidence Synthesis

Although there are suggestive epidemiologic findings, the biologic basis for a role of smoking in Graves' ophthalmopathy is unclear. The epidemiologic data are still limited, although consistent in indicating an increased risk in smokers. Dose-response is not well documented.

Conclusion

1. The evidence is suggestive but not sufficient to infer a causal relationship between ophthalmopathy associated with Graves' disease and smoking.

Implication

Data on the role of smoking cessation in preventing or lessening the severity of the ophthalmopathy would be important to understanding the relationship between Graves' disease and smoking.

Table 6.31 Studies on the association between smoking and Graves' ophthalmopathy

Study	Population	Design	Diagnosis of ophthalmopathy	Results
Hägg and Asplund 1987	12 persons with Graves' ophthalmopathy, 24 controls with Graves' disease and no ophthalmopathy, 48 population controls	Case-control	Clinical exam	Smoking increased the OR* of ophthalmopathy compared with no ophthalmopathy among persons with Graves' disease, OR = 10.0 (95% CI†, 1.4–74.3), and with population controls, OR = 20.2 (95% CI, 2.8–144.8)
Shine et al. 1990	85 patients with ophthalmopathy, 62 with Graves' disease, 81 controls without Graves' disease	Case-control	Clinical exam	Cases of ophthalmopathy were more likely to be smokers than healthy controls or controls without ophthalmopathy; dose-response pattern was reported
Tellez et al. 1992	155 patients with newly diagnosed Graves' disease	Cross-sectional	Clinical exam, using American Thyroid Association Classification system	Ophthalmopathy prevalence was higher in smokers and in former smokers, OR = 2.4 (95% CI, 1.1–5.2); there was a dose-response pattern with cigarette-years‡
Prummel and Wiersinga 1993	100 cases of Graves' ophthalmopathy, 100 cases of Graves' disease without ophthalmopathy, 175 cases of goiter, 75 cases of hyperthyroidism, 400 controls	Case-control	Clinical exam	Graves' ophthalmopathy cases and severe cases (classified by total eye score) were adjusted for gender, age, and education, and were more likely to be smokers, OR = 6.5 (95% CI, 3.8–11.2), compared with controls; there was no dose-response pattern with an increasing severity of eye disease; smoking was not associated with other thyroid diseases
Winsa et al. 1993	208 patients with newly diagnosed Graves' disease and 72 cases of Graves' with ophthalmopathy	Cross-sectional	Clinical exam	Patients with ophthalmopathy were more likely to be current and former smokers compared with patients without ophthalmopathy, 63 vs. 45%; there was an increased prevalence of smoking with an increase in the severity of ophthalmopathy

*OR = Odds ratio.
†CI = Confidence interval.
‡Cigarette-years = The number of years of smoking multiplied by the number of cigarettes smoked per day.

Table 6.31 Continued

Study	Population	Design	Diagnosis of ophthalmopathy	Results
Pfeilschifter and Ziegler 1996	253 patients with recent onset of Graves' disease	≥1 year prospective	Clinical exam / patient report of double vision (diplopia) and exophthalmometer readings >20 mm (proptosis)	Current smoking was associated with incidence of symptomatic ophthalmopathy, OR = 1.3 (95% CI, 1.1–1.6), proptosis, OR = 2.6 (95% CI, 1.8–3.9), and diplopia, OR = 3.1 (95% CI, 1.7–6.0); there was a dose-response relationship; former smokers had no increased risk
Bartalena et al. 1998	300 patients with mild ophthalmopathy receiving 1 of 2 treatments, 150 patients with severe ophthalmopathy	Prospective, for risk of progression	Degree of ophthalmopathy assessed by clinical exam, masked to smoking status	Mild ophthalmopathy was more likely to progress among smokers and less likely to improve with treatment; severe ophthalmopathy was less likely to respond to treatment among smokers

Peptic Ulcer Disease

In the early 1990s, the central role played by the bacterium *Helicobacter pylori* (*H. pylori*) in both the incidence and recurrence of peptic ulcer disease was recognized (Kuipers et al. 1995). This section reviews the evidence of an association between smoking and peptic ulcer disease in light of this new understanding of the pathogenesis of ulcer disease. Relevant articles were identified through a MEDLINE search from 1985 through June 2000 using the following terms: "ulcer and smoking and pylori" and "smoking and pylori and eradication." A further search was performed for the years 1998 through June 2000, using the terms "ulcer and smoking" to identify any major studies that were not included in the previous Surgeon General's report (USDHHS 2001), even though the studies had not evaluated *H. pylori*.

Conclusions of Previous Surgeon General's Reports

Numerous studies have demonstrated an association between smoking and the occurrence of peptic ulcer disease. This evidence was reviewed in the 1964, 1971, and 1972 Surgeon General's reports on smoking and health (USDHEW 1964, 1971, 1972). The 1979 report concluded that cigarette smoking was significantly associated with both the incidence and an increased risk of dying from peptic ulcer disease: "the association between smoking and peptic ulcer disease is significant enough to suggest a causal relationship" (USDHEW 1979, p. 1-23). In addition, that report concluded that there was highly suggestive evidence that smoking also retards ulcer healing. The 1990 report concluded that smokers had an increased risk of developing both duodenal and gastric ulcers, and smoking cessation reduced that risk (USDHHS 1990). That report also found that among smokers ulcer disease was more severe, duodenal ulcers were less likely to heal, and both duodenal and gastric ulcers were more likely to recur. Ulcer patients who stopped smoking, however, were found to have an improved clinical course compared with continuing smokers. Although much of this previous evidence was based largely on studies of men, the more recent Surgeon General's report on women and smoking (USDHHS 2001) concluded that women who smoked also had an increased risk of peptic ulcer disease.

Biologic Basis

In the decades since the 1964 Surgeon General's report, explanations of the pathogenesis of peptic ulcer disease have changed dramatically with the identification of the gastric bacterium *H. pylori* in a high proportion of patients with peptic ulcers (Marshall and Warren 1984). Up to 100 percent of duodenal ulcers and 70 to 90 percent of gastric ulcers are now associated with *H. pylori* infection (Kuipers et al. 1995). Most ulcers in persons without *H. pylori* infection were linked to the use of nonsteroidal anti-inflammatory drugs (NSAIDs) (Borody et al. 1991, 1992a). Other causes of peptic ulcers, although rarer, include Crohn's disease and Zollinger-Ellison syndrome.

Normally, the gastrointestinal mucosa is protected from injury by, among other factors, a layer of mucus and the secretion of bicarbonate by gastric and duodenal epithelial cells to neutralize gastric acid. If these protective mechanisms are impaired, or if there is an increase in levels of damaging factors, then ulceration may occur.

Effects of Smoking on Gastrointestinal Physiology

The 1990 Surgeon General's report (USDHHS 1990) reviewed the effects of cigarette smoking on aspects of human gastrointestinal physiology relevant to peptic ulcer disease. Likely mechanisms whereby smoking could promote the development of peptic ulcer disease included the potential for tobacco smoke and/or nicotine to increase maximal gastric acid output and duodenogastric reflux and to decrease alkaline pancreatic secretion and prostaglandin synthesis.

Two subsequent reviews (Endoh and Leung 1994; Eastwood 1997) evaluating the potential effects of cigarette smoke and nicotine as injurious and protective factors that could play a role in peptic ulcer formation came to similar conclusions. Data on the effects of smoking on gastric acid secretion in humans have been highly inconsistent; multiple reports found that smoking and/or nicotine variously stimulated, inhibited, or had no effect on gastric acid secretion. However, there was more consistent evidence that smoking promotes reflux of duodenal contents into the stomach, and increases production of free radicals and the release of vasopressin, a potent vasoconstrictor. Protective mechanisms consistently affected by smoking were the chronic inhibition of gastric mucus secretion,

cytoprotective prostaglandin production, pancreatic and duodenal mucosal bicarbonate secretion, and a decrease in mucosal blood flow.

The mucosal protection mechanism most clearly affected by smoking is the pancreatic secretion of bicarbonate. A transient reduction in secretion is seen immediately after smoking, leading to a drop in pH in the duodenal bulb (Eastwood 1997). Acidity in the duodenal bulb appears to be the most important determinant for the development of gastric metaplasia in the duodenum, thus paving the way for duodenal colonization by *H. pylori* (Tytgat et al. 1993).

Results from studies evaluating mucosal blood flow among smokers and nonsmokers have been more varied, possibly because of a variation in the measurement methods. Taha and colleagues (1993) demonstrated that both gastric and duodenal mucosal blood flow were reduced in chronic NSAID users. However, after allowing for NSAID use, significantly reduced duodenal blood flow was seen only in *H. pylori*-positive smokers. There was no additional effect of either *H. pylori* infection or smoking on gastric mucosal blood flow.

Finally, some strains of *H. pylori* produce a vacuolating toxin that may be important in determining the virulence of the organism. This toxin induces vacuolation of HeLa cells in vitro, as does nicotine alone, but the addition of nicotine to *H. pylori* potentiates the vacuolating effect of the toxin (Cover et al. 1992).

In summary, studies document that smoking appears to have a multitude of effects on gastroduodenal physiology, and through a number of mechanisms it could promote peptic ulceration. These effects are, however, largely transient, and the affected physiologic measures return to normal within minutes or hours after smoking cessation (Eastwood 1997). These same studies also indicate that smoking could particularly increase the likelihood of ulceration in *H. pylori*-positive persons.

Smoking and *Helicobacter pylori* Infection

Both *H. pylori* infection (Malaty et al. 1992; EUROGAST Study Group 1993) and smoking (Bergen and Caporaso 1999) are more common among groups of lower SES. Cross-sectional studies that have evaluated the association between *H. pylori* infection and smoking in healthy volunteers consistently have reported higher infection rates in smokers (current or former) than in nonsmokers. In a study of 485 volunteers in the United States, current and former smokers were more likely to be seropositive for *H. pylori* than nonsmokers (among blacks, rates were 73 percent among current smokers, 85 percent among former smokers, and 61 percent among nonsmokers; and among whites, rates were 40 percent, 48 percent, and 25 percent, respectively) (Graham et al. 1991). Infection also was slightly more common among 3,496 adult smokers in Northern Ireland (65 percent among former smokers, 57 percent among smokers of fewer than 20 cigarettes, and 64 percent among smokers of 20 or more cigarettes per day compared with 53 percent among people who had never smoked) (Murray et al. 1997). Similar findings were seen in a group of 273 adults from Melbourne, Australia, among current and former smokers (45 percent and 44 percent, respectively, compared with 31 percent in people who had never smoked) (Lin et al. 1998) and among 1,064 adult heavy smokers in New Zealand (38 percent in smokers of more than 20 cigarettes per day compared with 23 percent in smokers of less than 20 cigarettes per day and nonsmokers) (Collett et al. 1999). Similar patterns have been reported in adults visiting general practitioners in Germany (Brenner et al. 1997) and in patients receiving an endoscopic examination in the United Kingdom (Bateson 1993) and Malaysia (Goh 1997).

In some of these studies, the association between *H. pylori* and smoking was attenuated after adjusting for other factors, including age and SES. In both developed and developing countries, *H. pylori* infection is believed to occur during childhood (Xia and Talley 1997), and thus it is unlikely that smoking influences the risk of initial *H. pylori* infection to any great extent. It is unclear whether smoking could be a risk factor for the acquisition or persistence of *H. pylori* infection in adulthood or if low SES is a common, more distal risk factor for both *H. pylori* and smoking. These variables do not, however, alter the fact that smokers are more likely than nonsmokers to be infected with *H. pylori*. The link between *H. pylori* and peptic ulcer disease is well established; thus, it is important to consider whether smoking also is a risk factor or if some or all of the observed associations between smoking and peptic ulcer disease could be due to confounding by *H. pylori* infection status.

Trends in Peptic Ulcer Disease

During the past several decades, rates of hospitalization for and mortality from peptic ulcer disease in the United States have declined dramatically. Using hospitalization rates from the computerized database of the U.S. Department of Veterans Affairs, El-Serag and Sonnenberg (1998) showed that although gastric ulcers accounted for 67.6 and duodenal ulcers

for 168.8 out of every 10,000 hospitalizations of veterans from 1970–1974, comparable figures for 1990–1995 were 49.6 per 10,000 and 52.5 per 10,000, respectively. Similarly, using vital statistics data from CDC's National Center for Health Statistics, these two authors showed that mortality from gastric ulcer disease had fallen from 17.4 per million per year in 1968–1972 to 7.7 per million per year in 1988–1992, with a comparable drop in mortality for duodenal ulcer disease from 19.6 to 8.4 per million per year (El-Serag and Sonnenberg 1998). However, peptic ulcer disease still is a leading cause of morbidity. In 1989, the National Health Interview Survey included a special questionnaire on digestive diseases. Among approximately 42,000 adult respondents, 10 percent reported that they had ever had a physician-diagnosed peptic ulcer, one-third of whom also reported having a new or recurring ulcer in the past 12 months (Sonnenberg and Everhart 1996). Among the 50 percent who reported the site of their ulcer, gastric and duodenal ulcers were equally common overall, although nonwhites reported gastric ulcers more frequently and duodenal ulcers less frequently than whites. When recurrent ulcers (defined as a relapse in the past 12 months of a previously diagnosed ulcer) were excluded, the incidence of new peptic ulcers in 1989 was an estimated 52.7 per 10,000 (Everhart et al. 1998). Among those respondents who specified the site of the ulcer, the incidence of gastric ulcers (17.0 per 10,000) was about three times that of duodenal ulcers (6.1 per 10,000). This finding suggests that the incidence of new duodenal ulcers may have fallen more rapidly over time than that of gastric ulcers.

A large part of the decrease in peptic ulcer rates over the last few decades in the United States has been attributed to lower smoking rates (Kurata et al. 1986), although the same pattern was not seen in the United Kingdom (Sonnenberg 1986). However, the prevalence of *H. pylori* infection in developed countries also is believed to have declined over a similar time period (Banatvala et al. 1993; Kosunen et al. 1997), and it is this decline, rather than falling smoking rates, that may explain some or all of the reductions in ulcer rates.

Epidemiologic Evidence

Smoking and Development of Peptic Ulcer

Studies that evaluated the relationship between tobacco smoking and the development of peptic ulcer disease repeatedly have shown an increased risk of both duodenal and gastric ulcers among smokers (USDHEW 1979; USDHHS 1990). In some studies, this risk also has been observed to increase with increasing levels of smoking. During a 149,291 person-years follow-up of a cohort of 7,624 Japanese men in Hawaii, the age-adjusted incidence of gastric and duodenal ulcers increased with increasing levels of smoking at baseline (RR among nonsmokers and smokers of less than 24, 24 through 40, and greater than 40 pack-years: 1.0, 1.5, 3.1, and 3.8 [P_{trend} <0.01], respectively, for gastric ulcers and 1.0, 1.8, 2.4, and 3.3 [P_{trend} <0.01], respectively, for duodenal ulcers [Kato et al. 1992]). In contrast, an analysis of self-reported ulcer history, using data from the 1989 National Health Interview Survey in the United States, suggested that smoking may be a stronger risk factor for chronic ulceration than for the development of new ulcers (Everhart et al. 1998). Although these data show a strong relation between smoking and age-standardized prevalence of chronic active ulcers (1.8 percent, 3.0 percent, 3.9 percent, and 5.3 percent among nonsmokers and smokers of <20, 20, and >20 cigarettes per day, respectively), there was no association between smoking and the incidence of new ulcers.

Helicobacter pylori, *Smoking, and Peptic Ulcer*

Only a few studies have considered both smoking and *H. pylori* infection in relation to the incidence of peptic ulcer disease (Table 6.32). These studies largely have been cross-sectional surveys of patients referred for upper gastrointestinal endoscopy using variable definitions of smoking, and rarely presenting results that distinguished between smokers with and without *H. pylori* infection. No studies have separately evaluated the risk of peptic ulcers in former smokers after allowing for *H. pylori* infection.

Four of these studies were conducted with groups receiving endoscopic examinations. Martin and colleagues (1989) found no duodenal ulcers in 47 *H. pylori*-negative persons although 4 of them, all of whom were taking NSAIDs, had a gastric ulcer. Among the 60 *H. pylori*-positive persons, peptic ulcers were significantly more common in smokers than in nonsmokers. Similarly, Talamini and colleagues (1997) reported a significant association between duodenal ulcers and smoking after adjusting for *H. pylori* infection. In a Swiss study, smoking also appeared to be associated with an increased risk of duodenal ulcers, particularly among *H. pylori*-positive persons (Halter and Brignoli 1998). The lack of a single reference group in this study, however, makes comparisons with other studies difficult. In contrast, Schubert and colleagues (1993) reported no significant differences between the

proportion of smokers in patients with and without ulcers and, as a consequence, did not include smoking status in their multivariable models adjusting for *H. pylori*. It is possible, however, that the very broad definition of smoking used in this last study may have led to very light or occasional smokers being inappropriately classified as smokers, thus masking differences between patients with and without ulcers.

Two other studies used groups of company employees. Wang and colleagues (1996) conducted a case-control study in a factory in Shanghai, China. To prevent confounding by SES and gender, data were analyzed separately for men and women, drivers and workers (lower SES), and staff (higher SES). Among male workers and drivers (304 cases and 263 controls), current smoking was associated with a significantly elevated risk of peptic ulcer disease that increased with the amount of cigarettes smoked. A similar pattern was seen for duodenal ulcer disease alone. There was only one female employee smoker, and too few former smokers to evaluate risks in those groups. Although smoking status was assessed after the development of ulcers, smoking rates were high and few workers reported having stopped smoking. It is therefore unlikely that many employees changed their smoking behavior following ulcer diagnosis.

Schlemper and colleagues (1996) conducted parallel studies in companies in Japan and the Netherlands. Men and women with verifiable ulcer disease who had not been treated with *H. pylori* eradication therapy were compared with those without ulcers or prior gastric surgery. After adjusting for potential confounders, researchers found that daily smoking was associated with a nonsignificant increased risk of peptic ulcer disease only in the Dutch population. In this study, the majority of ulcers had been diagnosed a median of six years before smoking data were collected, and it is possible that employees with peptic ulcer disease may have changed their smoking behaviors over time.

There is a potential for bias in any of these studies if participants altered their smoking behaviors because of ulcer symptoms or if they misreported their smoking patterns. If ulcer patients tend to stop or reduce their smoking because of symptoms, or if they systematically underreport the amount they smoke, then the true associations between smoking and ulcers could be greater than those reported. Conversely, if ulcer patients actually increase their smoking in response to ulcer symptoms or if they systematically overreport the amount they smoke, then the observed associations could exaggerate the true effect. This latter situation would seem less likely than the former.

Nonsteroidal Anti-Inflammatory Drugs, Smoking, and Peptic Ulcer

The main cause of ulcers in persons negative for *H. pylori* infection, at least in developed countries, is the use of NSAIDs (Borody et al. 1991, 1992a). In the 1990 Surgeon General's report (USDHHS 1990), smoking was associated with peptic ulcer disease and acute gastric erosions in three studies of NSAID users. Since then, three more studies have evaluated the relationship between smoking and peptic ulcers in NSAID users, with conflicting results.

Hansen and colleagues (1996) compared 94 NSAID users admitted to a hospital with complications of peptic ulcers (predominantly bleeding or perforated ulcers) with 324 controls selected at random from all assumed NSAID users. Overall, cases were no more likely than controls to be smokers (44 percent and 41 percent, respectively), but after adjusting for age, gender, ulcer history, and duration of NSAID use, current smoking was associated with an almost twofold increased risk of ulcer complications (OR = 1.9 [95 percent CI, 1.0–3.6]).

In contrast, Aalykke and colleagues (1999) compared 132 current NSAID users diagnosed with bleeding peptic ulcers with 136 ulcer-free NSAID users selected from a rheumatology clinic and geriatrics department. Smokers were not at an increased risk of developing bleeding ulcers compared with controls (OR, adjusted for age, gender, ulcer history, *H. pylori* infection status, and NSAID dose = 0.91 [95 percent CI, 0.48–1.71]). Similarly, in a large case-control study in the United Kingdom, Weil and colleagues (2000) compared 1,121 patients diagnosed with bleeding peptic ulcers with 989 community controls. Information on *H. pylori* infection status was not available, but among NSAID users the risk for bleeding peptic ulcers (compared with nonsmokers who did not use NSAIDs) did not differ appreciably between current smokers (OR = 4.0 [95 percent CI, 2.9–5.5]) and nonsmokers (OR = 3.6 [95 percent CI, 2.9–4.5]).

Mortality from Peptic Ulcer

Large-scale cohort studies consistently have shown that smokers are at a greater risk of dying from peptic ulcer disease than nonsmokers (USDHHS 1990). Follow-up of the U.S. Veterans Study now has been extended to 26 years, with a total of 5.4 million person-years. Smoking information was collected only at baseline. To allow for the fact that many current smokers at baseline subsequently would have stopped smoking, the analysis was restricted to people who never smoked (who were unlikely to have started

Table 6.32 Studies on the association between smoking and peptic ulcer disease, allowing for *Helicobacter pylori* (*H. pylori*) infection

Study/location	Population	Definition of smoking
Martin et al. 1989 United States	107 patients referred for endoscopy, including 14 with duodenal ulcers, 14 with gastric ulcers, and 19 healthy volunteers	>10 cigarettes / day
Schubert et al. 1993 United States	1,088 patients referred for endoscopy, including 107 with duodenal ulcer, 97 with gastric ulcer, and 5 with both duodenal and gastric ulcers	At least 1 cigarette 4 weeks before endoscopy
Schlemper et al. 1996 Japan and the Netherlands	215 Japanese and 493 Dutch employees in companies with periodic health screening, including 57 with past peptic ulcers (median 6 years since diagnosis) and 4 with current peptic ulcers	Daily smoking at time of interview
Wang et al. 1996 China	Factory employees: 500 (422 men) with any peptic ulcer within previous 2 years and 500 (396 men) ulcer-free employees	Current (≤15 and >15 cigarettes / day); former smokers excluded
Talamini et al. 1997 Italy	495 patients referred for endoscopy, including 69 with duodenal ulcers and 23 with gastric ulcers	1–10 or >10 cigarettes / day
Halter and Brignoli 1998 Switzerland	282 patients referred for endoscopy, including 24 with duodenal ulcers and 5 with gastric ulcers	Data were not reported

*OR = Odds ratio.
†CI = Confidence interval.

Results

Prevalence of peptic ulcers among *H. pylori*-positive patients:

Smokers	73%	
Nonsmokers	27%	(p <0.01)

No significant association was found between smoking and peptic ulcer: prevalence of smoking was 36.7% among ulcer-free group, 42.9% among duodenal ulcer group, and 34.0% among gastric ulcer group (no adjusted estimates provided)

OR (95% CI) adjusted for age, *H. pylori* infection, family history of peptic ulcers, and occupation, smokers vs. nonsmokers:

Netherlands (men only)	1.6 (0.5–4.9)
Japan (men and women)	0.8 (0.3–1.8)
	0.2 (0.1–0.9), duodenal ulcer only

OR* (95% CI†) adjusted for age, *H. pylori* infection, and family history of peptic ulcer among smokers vs. never smokers, by occupation group (men only):

	Workers / drivers	Staff
Any peptic ulcer		
≤15 cigarettes / day	3.85 (2.29–6.48)	1.24 (0.65–2.39)
>15 cigarettes / day	5.30 (3.10–9.05)	1.47 (0.66–3.27)
Duodenal ulcer		
≤15 cigarettes / day	3.38 (1.97–5.79)	1.36 (0.68–2.72)
>15 cigarettes / day	4.34 (2.49–7.57)	1.36 (0.57–3.22)

Percentage of those with duodenal ulcer: nonsmokers, 10.8%; smokers 1–10 cigarettes / day, 15.4%; and >10 cigarettes / day, 25.6%; p <0.001

OR (95% CI) adjusted for gender and *H. pylori* infection, smokers vs. nonsmokers:

Duodenal ulcer vs. rest (including gastric ulcer)	
1–10 cigarettes / day	1.35 (0.57–1.38)
>10 cigarettes / day	2.53 (1.35–4.74)

Crude OR (95% CI) vs. for each group vs. other 3 groups combined:

Duodenal ulcer vs. rest (including gastric ulcer)	
H. pylori-negative nonsmokers	0.13 (0.02–0.93)
H. pylori-negative smokers	0.37 (not reported)
H. pylori-positive nonsmokers	0.94 (not reported)
H. pylori-positive smokers	5.53 (1.97–15.53)

smoking) and to former smokers at baseline. Former smokers had elevated risks for mortality from both duodenal ulcer disease (OR = 1.8 [95 percent CI, 1.3–2.4]) and gastric ulcer disease (1.6 [1.1–2.2]) (NIH 1997). During follow-up of the British doctors cohort, information about smoking behaviors was collected at baseline in 1951 and again in 1957, 1966, 1972, 1978, and 1990. After 40 years, mortality from peptic ulcer disease was 8 per 100,000 per year among men who had never smoked cigarettes; 12 per 100,000 per year among former smokers; and 11, 33, and 34 per 100,000 per year among current smokers of 1 to 14, 15 to 24, and 25 or more cigarettes per day, respectively ($p < 0.001$) (Doll et al. 1994). None of these studies, however, could explore possible confounding of this association by *H. pylori* infection.

Effect of Smoking on Ulcer Severity

Ulcers may be more severe and complications may occur more frequently among continuing smokers (USDHHS 1990). Hasebe and colleagues (1998) compared 35 patients with deep gastric ulcers (ulceration beyond the muscularis propria) and 33 patients with shallow and intermediate depth ulcers (ulceration in submucosa and muscularis propria) in Japan. They found that patients with deep ulcers were more likely to be heavy smokers, defined as smoking 20 or more cigarettes per day, than patients with shallower ulcers (81 percent versus 55 percent, $p < 0.05$). However, patients with deep ulcers also were significantly more likely to drink alcohol on a daily basis (40 percent versus 27 percent, $p < 0.05$) and to have *H. pylori* infections (97 percent versus 79 percent, $p < 0.01$), so it is possible that these differences could explain some or all of the associations with smoking.

Smoking and Peptic Ulcer Complications

Svanes and colleagues (1997) compared patients diagnosed with perforated peptic ulcers with population controls (90 percent response rate) in Norway. Analyses of smoking were restricted to cases (36 gastric perforation and 73 duodenal perforation) and controls (n = 4,270) aged 15 through 74 years because smoking was rare in older patients. After adjusting for age and gender, the risk of perforated ulcers in current smokers increased significantly with the number of cigarettes smoked per day. The ORs were 7.3 (95 percent CI, 4.0–18.1) for smokers of 1 to 9 cigarettes per day, 8.7 (95 percent CI, 5.5–14.4) for smokers of 10 to 19 cigarettes per day, and 11.2 (95 percent CI, 6.3–27.5) for smokers of 20 or more cigarettes per day ($p < 0.001$) compared with people who had never smoked. The risk among former smokers was no greater than that among those who had never smoked (OR = 0.8 [95 percent CI, 0.2–2.2]). Smokers were less likely than nonsmokers to have used NSAIDs or other ulcerogenic drugs. Thus, variation in NSAID use could not explain the relationship with smoking. The high alcohol consumption, however, which was significantly more common among current smokers (25 percent versus 4 percent among nonsmokers), could possibly explain some of the strong associations between smoking and perforated ulcers. *H. pylori* infection was not assessed, but among the cases, 87 percent of smokers and 96 percent of nonsmokers reported previous "ulcer dyspepsia," suggesting that infection rates probably were high in both groups.

Lanas and colleagues (1997) conducted a similar study in Spain, comparing 76 patients with gastrointestinal perforation (including 31 with duodenal ulcers and 28 with gastric ulcers) with matched hospital and community controls. After adjusting for the use of NSAIDs and alcohol and histories of ulcers and arthritis, smoking was again associated with a significantly increased risk of perforated ulcers ($p = 0.003$). In Italy, Labenz and colleagues (1999) compared 72 patients admitted with bleeding peptic ulcers with matched hospital controls. After adjusting for *H. pylori* infection status, NSAID use, and alcohol intake, smoking was associated with a nonsignificant 40 percent increased risk of bleeding ulcers (OR = 1.4 [95 percent CI, 0.5–3.6]).

In the large case-control study conducted by Weil and colleagues (2000) in the United Kingdom, overall current smoking was associated with a 60 percent increased risk of bleeding peptic ulcers (OR = 1.6 [95 percent CI, 1.2–2.0]). This risk appeared to differ, however, between users and nonusers of NSAIDs. Among NSAID nonusers, smoking was associated with an almost twofold increased risk of bleeding ulcers (OR = 1.9 [95 percent CI, 1.4–2.4]). In contrast, the risk for peptic ulcers in NSAID users did not differ appreciably between current and nonsmokers as described above.

Effect of Smoking on Ulcer Healing and Recurrence

Ulcer Healing

Many studies have shown that smoking adversely affects healing of duodenal ulcers by acid-reducing agents (Lam 1990; USDHHS 1990). It does not appear, however, to have the same adverse effect

on healing by other agents, including sucralfate (Lam 1991) or colloidal bismuth subcitrate (Lam 1991; Lambert 1991). In a meta-analysis, data from six studies of sucralfate were combined, giving overall healing rates of 78 percent among 301 smokers and 78 percent among 272 nonsmokers (Lam 1991). In the same analysis, data also were pooled from three studies of colloidal bismuth subcitrate, giving healing rates of 82 percent among 55 smokers and 76 percent among 38 nonsmokers. Less consistent results were reported for the effects of smoking on gastric ulcer healing, although studies evaluating the benefits of smoking cessation have suggested that ulcer patients who stop smoking do better than patients who continue to smoke (USDHHS 1990).

Rates of ulcer healing are significantly higher (Hentschel et al. 1993; Labenz and Börsch 1994) and recurrence rates significantly lower (Rauws and Tytgat 1995) among patients with ulcers (gastric or duodenal) who received *H. pylori* eradication therapy, which now is the recommended treatment for patients with *H. pylori* infection (NIH 1997). The combined effects of smoking and *H. pylori* eradication on ulcer healing in the short term have not been directly evaluated; however, in three studies of ulcer patients treated with *H. pylori* eradication therapy, there were no significant differences in ulcer healing rates between smokers and nonsmokers (O'Connor et al. 1995; Bardhan et al. 1997; Kadayifçi and Simsek 1997). O'Connor and colleagues (1995) reported healing rates for gastric and duodenal ulcers of 83 percent for smokers compared with 92 percent for nonsmokers ($p = 0.3$); the *H. pylori* eradication rate also was slightly lower among smokers (83 percent versus 94 percent, $p = 0.2$), possibly explaining the slightly different healing rates. Bardhan and colleagues (1997) reported duodenal ulcer healing in 96 percent of smokers compared with 94 percent of nonsmokers ($p = 0.6$), whereas rates of *H. pylori* eradication were slightly higher for nonsmokers (77 percent versus 71 percent, $p = 0.5$). Kadayifçi and Simsek (1997) reported duodenal ulcer healing in 82 percent and 83 percent of heavy (more than 20 cigarettes per day) and mild (1 to 20 cigarettes per day) smokers, respectively, compared with 85 percent of nonsmokers ($p = 0.9$). In this study, *H. pylori* eradication rates were slightly higher for nonsmokers (68 percent versus 66 percent among mild and 59 percent among heavy smokers). These reports suggest that ulcer healing rates are high in patients treated with *H. pylori* eradication therapy, regardless of their smoking status.

Duodenal Ulcer Recurrence

In studies comparing duodenal ulcer recurrence rates for smokers and nonsmokers before the introduction of *H. pylori* eradication therapy, higher relapse rates consistently were reported for smokers (USDHHS 1990). However, ulcers rarely, if ever, recur in patients who remain free of *H. pylori*, regardless of their smoking status. George and colleagues (1990) observed no recurrence of duodenal ulcers among 71 patients (31 current and 12 former smokers, and 28 lifetime nonsmokers) whose ulcers had healed, whose *H. pylori* had been eradicated, and who remained free of *H. pylori* during the four years they were followed. In an Australian study, 197 patients successfully treated for *H. pylori*-positive duodenal ulcers had their infections eradicated and their ulcers cured. They then were followed for 12 to 73 months (Borody et al. 1992b). There was no recurrence of *H. pylori* or duodenal ulcers among the groups of 80 current smokers (smoking 5 to 40 cigarettes per day), 38 former smokers (who gave up smoking during follow-up or up to 20 years earlier), and 79 patients who had never smoked. In the Netherlands, Van Der Hulst and colleagues (1997) also found no recurrences in 141 duodenal ulcer patients whose ulcers had been cured and who had been treated successfully for *H. pylori* infection; they remained free of infection during nine years of follow-up. In Greece, there was no recurrence of duodenal ulcers during 12 to 72 months of follow-up in 141 patients who remained *H. pylori* negative, regardless of their smoking status; there were seven recurrences (six in smokers) among 24 patients (unknown number of smokers) who became reinfected with *H. pylori* (Archimandritis et al. 1999).

Although other authors have documented low ulcer recurrence rates in patients whose *H. pylori* infection was eradicated, ulcer recurrence commonly is associated with either reinfection with *H. pylori* (Bayerdörffer et al. 1993) or NSAID use (Chen et al. 1999). Furthermore, recurrence rates have not varied between smokers and nonsmokers. A study in Hong Kong followed patients for 10 to 18 months who had been successfully treated for *H. pylori* infection and whose duodenal ulcers had healed (Chan et al. 1997). The authors documented two recurrences (2.9 percent, both *H. pylori* negative) among 68 smokers (≥10 cigarettes per day) and four recurrences (2.1 percent, three *H. pylori* negative) among 188 persons who had never smoked or were former smokers. The study concluded that smoking did not influence ulcer recurrence after *H. pylori* eradication.

Patients treated for *H. pylori*-positive duodenal ulcers in a multicenter study (Canada, Ireland, United Kingdom, and United States) were followed for six months (Bardhan et al. 1997). All patients had healed ulcers, but *H. pylori* was eradicated in only 77 percent of nonsmokers and 71 percent of smokers. Ulcers recurred in 22 percent of 118 smokers and 16 percent of 117 nonsmokers ($p = 0.32$). The slightly higher rate seen in smokers could be a result of the slightly lower *H. pylori* eradication rate for this group. Recurrence rates in this study among patients who apparently remained free of *H. pylori* during follow-up were an unusually high 12 percent (<6 percent in three of the centers) for both smokers and nonsmokers.

In summary, smoking does not appear to affect duodenal ulcer recurrence rates in patients whose *H. pylori* infection has been eradicated. Among those who remain *H. pylori* positive, smoking may increase the risk of relapse, although no good data support or refute this possible association.

Gastric Ulcer Recurrence

A similar pattern is seen for *H. pylori*-positive gastric ulcers, which also rarely recur after successful *H. pylori* eradication therapy in the absence of NSAID use (Labenz and Börsch 1994). There were no relapses of gastric ulcers in 45 patients who remained *H. pylori* negative during 10 years of follow-up (Van Der Hulst et al. 1997). Chan and colleagues (1997) observed one recurrence of gastric ulcer accompanied by the reappearance of *H. pylori* in 15 smokers and no recurrences in 16 nonsmokers followed for up to 18 months after *H. pylori* eradication and successful ulcer healing.

These data suggest that for both gastric and duodenal ulcers, the main predictor of successful ulcer healing with no recurrence is *H. pylori* infection status. If smoking has any effect on the healing or recurrence of ulcers, it is therefore likely to be through an effect on the process of *H. pylori* eradication.

Smoking and Helicobacter pylori *Eradication*

A number of studies have evaluated the effects of smoking on *H. pylori* eradication. Results of studies that included more than 50 participants and presented separate eradication rates for smokers and nonsmokers are shown in Table 6.33. (Because three other studies [Fraser et al. 1996; Harris et al. 1996; Georgopoulos et al. 2000] simply reported that smoking was not significantly associated with eradication without presenting eradication rates, it is not possible to tell if there were nonsignificant differences between smokers and nonsmokers.) Although the definition of smoking in these studies often is unclear, and a range of different drug combinations was used to treat the infections, a fairly consistent pattern of lower eradication rates is seen in groups defined as smokers.

Other factors known to be strongly predictive of *H. pylori* eradication are compliance with therapy (Graham et al. 1992; Cutler and Schubert 1993; Labenz et al. 1994) and the prevalence of metronidazole resistance (O'Riordan et al. 1990). Although some studies have reported poorer compliance among smokers (Unge et al. 1993), others have found similarly high compliance rates between smokers and nonsmokers (O'Connor et al. 1995; Bardhan et al. 1997; Kamada et al. 1999). In a logistic regression model also adjusting for therapy duration and omeprazole pretreatment, Labenz and colleagues (1994) found both lack of compliance (OR = 74.72 [95% CI, 24.17–205.51]) and smoking (OR = 2.75 [95% CI, 1.56–4.86]) to be independent risk factors for treatment failure. Witteman and colleagues (1993) found that metronidazole resistance developed more readily in smokers following therapy with bismuth and metronidazole after allowing for variations in compliance ($p = 0.01$). However, poorer eradication rates in smokers also are seen with regimens that do not contain this class of drug. Therefore, it seems unlikely that the lower eradication rates for smokers can be attributed to either poorer compliance or an increase in metronidazole resistance. It has been suggested that smoking may adversely affect eradication by increasing acid output or by decreasing gastric blood flow, thereby reducing drug delivery to the gastric mucosa, but little evidence supports either of these hypotheses.

Evidence Synthesis

Incidence of Peptic Ulcer

Many studies have reported strong and significant associations between smoking and peptic ulcer disease. Only six studies, however, have allowed for the effects of *H. pylori* infection when evaluating this association. Three of those studies reported significantly increased risks of ulcer disease in smokers after adjusting for *H. pylori* infection; in each study, the majority (80 to 90 percent) of ulcer patients were *H. pylori* positive (Wang et al. 1996; Talamini et al. 1997; Halter and Brignoli 1998). A fourth study reported a significant association between smoking and ulcers

only among *H. pylori*-positive persons (Martin et al. 1989). The remaining two studies (Schubert et al. 1993; Schlemper et al. 1996) reported little or no association, but the classification of smoking status in these studies is potentially unreliable.

Cigarette smoking has a number of effects on gastroduodenal physiology that could lead to the development of peptic ulceration, and evidence suggests that some of these effects may be potentiated in *H. pylori*-positive persons. Taken together, these data strongly suggest a causal relationship between smoking and the development of peptic ulcers, at least in *H. pylori*-positive persons. There is insufficient evidence to evaluate the relation between smoking and peptic ulcers in those who are *H. pylori* negative. Conflicting and inadequate data link smoking to ulcer occurrence in NSAID users and it is not possible to evaluate an independent effect for smoking in the development of NSAID-induced peptic ulcers.

There is evidence to suggest that after adjusting for NSAID use, smoking may be associated with an increased risk of peptic ulcer complications, including perforation and bleeding. Data from the most recent study (Weil et al. 2000), however, suggest that this effect may be restricted to nonusers of NSAIDs.

The effects of smoking cessation on ulcer risk have not been evaluated in the context of *H. pylori* infection. However, the transient nature of many of the physiologic effects of smoking suggests that an excess risk may be restricted to current smokers.

Ulcer Healing and Recurrence

Healing and recurring *H. pylori*-positive ulcers are closely associated with eradication and recurrence of the infection. The evidence strongly suggests that if *H. pylori* is eradicated, smoking has no effect on either the healing or recurrence of ulcers. There is, however, evidence to suggest that *H. pylori* eradication therapy is somewhat less successful for current smokers. There are no good data to evaluate the effects of smoking on the recurrence of ulcers associated with *H. pylori* infection when long-term *H. pylori* eradication fails, or on the treatment and recurrence of ulcers in persons negative for *H. pylori* infection.

Conclusions

1. The evidence is sufficient to infer a causal relationship between smoking and peptic ulcer disease in persons who are *Helicobacter pylori* positive.

2. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and peptic ulcer disease in nonsteroidal anti-inflammatory drug users or in those who are *Helicobacter pylori* negative.

3. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and risk of peptic ulcer complications, although this effect might be restricted to nonusers of nonsteroidal anti-inflammatory drugs.

4. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and the treatment and recurrence of *Helicobacter pylori*-negative ulcers.

Implications

The prevalence of *H. pylori* has declined in developed countries (Banatvala et al. 1993; Kosunen et al. 1997) and, as a result, the proportion of patients with *H. pylori*-negative ulcers will increase, making them an important group to study. Also, an increasing number of *H. pylori*-negative ulcers may not be attributable to NSAID use or other established causes of ulcers (Jyotheeswaran et al. 1998). The rarity of ulcer recurrence when *H. pylori* is eradicated, regardless of smoking status, suggests that smoking is not an important factor in the initial development or recurrence of ulcers among persons who are *H. pylori* negative. However, this topic has not been well investigated, largely because of the paucity of such ulcers, and is likely to be an important area for future research.

Because the main effects of smoking on gastrointestinal physiology appear to be short-lived, it is likely that smoking cessation will both reduce ulcer occurrence in those persons who are *H. pylori* positive and improve the chances of eradication in patients (with or without ulcers) treated for *H. pylori* infection. Even if eradication is successful, it seems unlikely that a continuation of smoking will influence the course of peptic ulcer disease.

Table 6.33 Studies on *Helicobacter pylori* (*H. pylori*) eradication rates among smokers and nonsmokers

Study/location	Population	Therapy
Cutler and Schubert 1993 United States	96 patients with gastric ulcers, duodenal ulcers, or nonulcer dyspepsia	Bismuth, tetracycline, and metronidazole
Labenz et al. 1994 Germany	405 patients with *H. pylori*-related diseases of the gastroduodenum (231 with duodenal ulcer disease, 138 with gastric ulcer disease, 14 with gastroduodenal double ulcers, and 22 with *H. pylori* gastritis-associated dyspepsia)	Omeprazole and amoxicillin
O'Connor et al. 1995 Ireland	85 patients with gastric or duodenal ulcers and confirmed *H. pylori* infection	Bismuth, metronidazole, tetracycline
Goddard and Spiller 1996 United Kingdom	200 patients with endoscopically proven *H. pylori*	Bismuth, tetracycline, and metronidazole (BTT); omeprazole, clarithromycin, and metronidazole (OCM); omeprazole, clarithromycin, and tinidazole (OCT); omeprazole, clarithromycin, metronidazole, and tinidazole (OCN)
Bardhan et al. 1997 Canada, Ireland, United Kingdom, United States	284 duodenal ulcer patients with *H. pylori* infection	Clarithromycin, omeprazole
Breuer et al. 1997a Korea	72 patients with *H. pylori* infection and endoscopically confirmed gastric or duodenal ulcers	Amoxicillin, clarithromycin, and nizatidine
Breuer et al. 1997b Korea	79 patients with *H. pylori* infection and endoscopically confirmed gastric or duodenal ulcers	Metronidazole, amoxicillin, omeprazole
Kadayifçi and Simsek 1997 Turkey	232 patients with endoscopically verified *H. pylori*-positive active duodenal ulcer disease	Amoxicillin, clarithromycin, metranidazole, roxitromycin, and nitrimidazine (alone or in different combinations)

*NR = Data were not reported.
†NS = Not significant.

Definition of smoking	Eradication rate (%)		Absolute percent difference (%)
	Smokers	Nonsmokers	
NR*	73.7	89.7	16.0 (p = 0.040)
NR	65	83	18 (p <0.001)
NR	82.6	94.4	11.8 (NS†)
NR	BTT: 76.3 OCM: 85.7 OCT: 68.7 OCN: 79.5	84.2 88.8 87.5 88.2	7.9 (NS) 3.1 (NS) 18.8 (NS) 8.7 (p <0.05)
NR	71	77	6 (NS)
NR	93.7	100	6.3 (p = 0.55)
≥5 cigarettes / day	65	88	23 (p = 0.035)
Eradication rates were stratified by cigarettes / day categories, but it is unclear how the analysis defined "nonsmokers"	5–20 cigarettes / day: 66 >20 cigarettes / day: 59	68	2 (NS) 9 (NS)

Table 6.33 Continued

Study/location	Population	Therapy
Moayyedi et al. 1997 United Kingdom	273 *H. pylori*-positive patients, diagnosed by ^{13}C-UBT (127 with normal endoscopy, 68 with duodenitis, 28 with duodenal ulcers, 8 with gastric ulcers, 18 with esophagitis, and 24 miscellaneous)	Omeprazole, clarithromycin, and tinidazole
Kamada et al. 1999 Japan	137 *H. pylori*-positive patients (60 with duodenal ulcers, 19 with gastric ulcers, and 58 with nonulcer dyspepsia)	Omeprazole, amoxicillin, clarithromycin

Definition of smoking	Eradication rate (%)		Absolute percent difference (%)
	Smokers	Nonsmokers	
NR	87	95	8
NR	57.7	80.0	22.3 ($p < 0.01$)

Conclusions

Diminished Health Status

1. The evidence is sufficient to infer a causal relationship between smoking and diminished health status that may manifest as increased absenteeism from work and increased use of medical care services.

2. The evidence is sufficient to infer a causal relationship between smoking and increased risks for adverse surgical outcomes related to wound healing and respiratory complications.

Loss of Bone Mass and the Risk of Fractures

3. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and reduced bone density before menopause in women and in younger men.

4. In postmenopausal women, the evidence is sufficient to infer a causal relationship between smoking and low bone density.

5. In older men, the evidence is suggestive but not sufficient to infer a causal relationship between smoking and low bone density.

6. The evidence is sufficient to infer a causal relationship between smoking and hip fractures.

7. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and fractures at sites other than the hip.

Dental Diseases

8. The evidence is sufficient to infer a causal relationship between smoking and periodontitis.

9. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and coronal dental caries.

10. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and root-surface caries.

Erectile Dysfunction

11. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and erectile dysfunction.

Eye Diseases

12. The evidence is sufficient to infer a causal relationship between smoking and nuclear cataract.

13. The evidence is suggestive but not sufficient to infer that smoking cessation reduces the risk of nuclear opacity.

14. The evidence is suggestive but not sufficient to infer a causal relationship between current and past smoking, especially heavy smoking, with risk of exudative (neovascular) age-related macular degeneration.

15. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and atrophic age-related macular degeneration.

16. The evidence is suggestive of no causal relationship between smoking and the onset or progression of retinopathy in persons with diabetes.

17. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and glaucoma.

18. The evidence is suggestive but not sufficient to infer a causal relationship between ophthalmopathy associated with Graves' disease and smoking.

Peptic Ulcer Disease

19. The evidence is sufficient to infer a causal relationship between smoking and peptic ulcer disease in persons who are *Helicobacter pylori* positive.

20. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and peptic ulcer disease in nonsteroidal anti-inflammatory drug users or in those who are *Helicobacter pylori* negative.

21. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and risk of peptic ulcer complications, although this effect might be restricted to nonusers of non-steroidal anti-inflammatory drugs.

22. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and the treatment and recurrence of *Helicobacter pylori*-negative ulcers.

References

Aalykke C, Lauritsen JM, Hallas J, Reinholdt S, Krogfelt K, Lauritsen K. *Helicobacter pylori* and risk of ulcer bleeding among users of nonsteroidal anti-inflammatory drugs: a case-control study. *Gastroenterology* 1999;116(6):1305–9.

Abber JC, Lue TF, Orvis BR, McClure RD, Williams RD. Diagnostic tests for impotence: a comparison of papaverine injection with the penile-brachial index and nocturnal penile tumescence monitoring. *Journal of Urology* 1986;135(5):923–5.

Abidi NA, Dhawan S, Gruen GS, Vogt MT, Conti SF. Wound-healing risk factors after open reduction and internal fixation of calcaneal fractures. *Foot and Ankle International* 1998;19(12):856–61.

Adaikan PG, Ratnam SS. Pharmacology of penile erection in humans. *Cardiovascular and Interventional Radiology* 1988;11(4):191–4.

Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Archives of Ophthalmology* 2001;119(10):1417–36.

Ah MKB, Johnson GK, Kaldahl WB, Patil KD, Kalkwarf KL. The effect of smoking on the response to periodontal therapy. *Journal of Clinical Periodontology* 1994;21(2):91–7.

Ahlberg J, Tuominen R, Murtomaa H. Periodontal status among male industrial workers in southern Finland with or without access to subsidized dental care. *Acta Odontologica Scandinavica* 1996;54(3): 166–70.

Ainamo J. The seeming effect of tobacco consumption on the occurrence of periodontal disease and dental caries. *Suomen Hammaslaakariseuran Toimituksia* 1971;67(2):87–94.

Ainamo J, Barmes D, Beagrie G, Cutress T, Martin J, Sardo-Infirri J. Development of the World Health Organization (WHO) community periodontal index of treatment needs (CPITN). *International Dental Journal* 1982;32(3):281–91.

Alberg AJ, Chen JC, Zhao H, Hoffman SC, Comstock GW, Helzlsouer KJ. Household exposure to passive cigarette smoking and serum micronutrient concentrations. *American Journal of Clinical Nutrition* 2000;72(6):1576–82.

Alexander AG. The relationship between tobacco smoking calculus and plaque accumulation and gingivitis. *Dental Health (London)* 1970;9(1):6–9.

Allen RA, Kluft C, Brommer EJP. Effect of chronic smoking on fibrinolysis. *Arteriosclerosis* 1985;5(5): 443–50.

Allen RP, Brendler CB. Nocturnal penile tumescence with polysomnography (NPT-PSG) remains the only objectively validated procedure for differential diagnosis of organic versus psychogenic erectile impotence. In: Lue TF, editor. *World Book of Impotence*. London: Smith-Gordon, 1992:75–80.

Aloia JF, Cohn SH, Vaswani A, Yeh JK, Yuen K, Ellis K. Risk factors for postmenopausal osteoporosis. *American Journal of Medicine* 1985;78(1):95–100.

Alpagot T, Wolff LF, Smith QT, Tran SD. Risk indicators for periodontal disease in a racially diverse urban population. *Journal of Clinical Periodontology* 1996;23(11):982–8.

American Academy of Periodontology. Position paper: epidemiology of periodontal diseases. *Journal of Periodontology* 1996;67(9):935–45. [See also comments in *Journal of Periodontology* 1997;68(8):804; *Journal of Periodontology* 1997;68(10):1022–3.]

American Academy of Periodontology. The pathogenesis of periodontal diseases. *Journal of Periodontology* 1999;70(4):457–70.

Ames BN, Gold LS, Willett WC. The causes and prevention of cancer. *Proceedings of the National Academy of Sciences of the United States of America* 1995; 92(12):5258–65.

Amin S, LaValley MP, Zhang Y, Evans SR, Sawin C, Wilson PWF, Hannan MT, Kiel DP, Felson DT. Is the effect of smoking on bone mineral density (BMD) in elderly men mediated through estradiol (E2)? The Framingham Osteoporosis Study. *Journal of Bone and Mineral Research* 1999;14(Suppl 1):S147.

Andersson G, Malmgren S. Risk factors and reported sick leave among employees of Saab-Scania, Linköping, Sweden, between the ages of 50 and 59. *Scandinavian Journal of Social Medicine* 1986;14(1): 25–30.

Andrews JA, Severson HH, Lichtenstein E, Gordon JS. Relationship between tobacco use and self-reported oral hygiene habits. *Journal of the American Dental Association* 1998;129(3):313–20.

Aoki K, Ito Y, Sasaki R, Ohtani M, Hamajima N, Asano A. Smoking, alcohol drinking and serum carotenoids levels. *Japanese Journal of Cancer Research* 1987;78(10):1049–56.

Apple DF Jr, Hayes WC, editors. *Prevention of Falls and Hip Fractures in the Elderly*. Rosemont (IL): American Academy of Orthopaedic Surgeons, 1994.

Archimandritis A, Balatsos V, Delis V, Manika Z, Skandalis N. "Reappearance" of *Helicobacter pylori* after eradication: implications on duodenal ulcer recurrence. A prospective 6 year study. *Journal of Clinical Gastroenterology* 1999;28(4):345–7.

Arend SM, Mallat MJ, Westendorp RJ, van der Woude FJ, van Es LA. Patient survival after renal transplantation; more than 25 years follow-up. *Nephrology, Dialysis, Transplantation* 1997;12(8):1672–9.

Armitage GC. Development of a classification system for periodontal diseases and conditions. *Annals of Periodontology* 1999;4(1):1–6.

Arno A, Schei O, Lovdal A, Wæhaug J. Alveolar bone loss as a function of tobacco consumption. *Acta Odontologica Scandinavica* 1959;17:3–10.

Asami S, Manabe H, Miyake J, Tsurdome Y, Hirano T, Yamaguchi R, Itoh H, Kasai H. Cigarette smoking induces an increase in oxidative DNA damage, 8-hydroxydeoxyguanosine, in a central site of the human lung. *Carcinogenesis* 1997;18(9):1763–6.

Ascherio A, Rimm EB, Giovannucci EL, Spiegelman D, Stampfer M, Willett WC. Dietary fat and risk of coronary heart disease in men: cohort follow up study in the United States. *British Medical Journal* 1996;13(7049):84–90.

Ashford JR. Smoking and the use of the health services. *British Journal of Preventive and Social Medicine* 1973;27(1):8–17.

Ashraf SS, Shaukat N, Kamaly ID, Durrani A, Doran B, Grotte GJ, Keenan DJ. Determinants of early and late mortality in patients with end-stage renal disease undergoing cardiac surgery. *Scandinavian Journal of Thoracic and Cardiovascular Surgery* 1995;29(4): 187–93.

Athanasou JA. Smoking and absenteeism. *The Medical Journal of Australia* 1979;1(6):234–6.

Athanasou JA, Reid CC, Ferguson DA. Sickness absence and smoking. *The Medical Journal of Australia* 1981;1(5):211–2.

Ault RW, Ekelund RB Jr, Jackson JD, Saba RS, Saurman DS. Smoking and absenteeism. *Applied Economics* 1991;23(4B):743–54.

Axelsson P, Paulander J, Lindhe J. Relationship between smoking and dental status in 35-, 50-, 65-, and 75-year-old individuals. *Journal of Clinical Periodontology* 1998;25(4):297–305.

Baab DA, Öberg PÅ. The effect of cigarette smoking on gingival blood flow in humans. *Journal of Clinical Periodontology* 1987;14(7):418–24.

Bacon C, Mittleman M, Glasser D, Rimm E. Can lifestyle factors help prevent erectile dysfunction? *European Urology* 2001;39(Suppl 5):17.

Bahn RS. Understanding the immunology of Graves' ophthalmopathy: is it an autoimmune disease? *Endocrinology and Metabolism Clinics of North America* 2000;29(2):287–96.

Bähren W, Gall H, Scherb W, Stief C, Thon W. Arterial anatomy and arteriographic diagnosis of arteriogenic impotence. *Cardiovascular and Interventional Radiology* 1988;11(4):195–210.

Balarajan R, Yuen P, Bewley BR. Smoking and state of health. *British Medical Journal (Clinical Research Edition)* 1985;291(6510):1682.

Ballard DJ, Melton LJ III, Dwyer MS, Trautmann JC, Chu C-P, O'Fallon WM, Palumbo PJ. Risk factors for diabetic retinopathy: a population-based study in Rochester, Minnesota. *Diabetes Care* 1986;9(4): 334–42.

Banatvala N, Mayo K, Megraud F, Jennings R, Deeks JJ, Feldman RA. The cohort effect and *Helicobacter pylori*. *Journal of Infectious Diseases* 1993;168(1): 219–21.

Barbour SE, Nakashima K, Zhang J-B, Tandaga S, Hahn C-L, Schenkein HA, Tew JG. Tobacco and smoking: environmental factors that modify the host response (immune system) and have an impact on periodontal health. *Critical Reviews in Oral Biology and Medicine* 1997;8(4):437–60.

Bardhan KD, Graham DY, Hunt RH, O'Morain CA. Effects of smoking on cure of *Helicobacter pylori* infection and duodenal ulcer recurrence in patients treated with clarithromycin and omeprazole. *Helicobacter* 1997;2(1):27–31.

Barker GJ, Williams KB. Tobacco use cessation activities in U.S. dental and dental hygiene student clinics. *Journal of Dental Education* 1999;63(11):828–33.

Baron JA, Comi RJ, Cryns V, Brinck-Johnsen T, Mercer NG. The effect of cigarette smoking on adrenal cortical hormones. *Journal of Pharmacology and Experimental Therapeutics* 1995;272(1):151–5.

Baron JA, Farahmand BY, Weiderpass E, Michaëlsson K, Alberts A, Persson I, Ljunghall S. Cigarette smoking, alcohol consumption, and risk of hip fracture in women. *Archives of Internal Medicine* 2001;161(7): 983–8.

Baron JA, Karagas M, Barrett J, Kniffin W, Malenka D, Mayor M, Keller RB. Basic epidemiology of fractures of the upper and lower limb among Americans over 65 years of age. *Epidemiology* 1996;7(6):612–8.

Bartalena L, Marcocci C, Tanda ML, Manetti L, Dell'Unto E, Bartolomei MP, Nardi M, Martino E, Pinchera A. Cigarette smoking and treatment outcomes in Graves ophthalmopathy. *Annals of Internal Medicine* 1998;129(8):632–5.

Bastiaan RJ, Waite IM. Effects of tobacco smoking on plaque development and gingivitis. *Journal of Periodontology* 1978;49(8):480–2.

Batenburg M, Reinken JA. The relationship between sickness absence from work and pattern of cigarette smoking. *New Zealand Medical Journal* 1990;103(882): 11–3.

Bateson MC. Cigarette smoking and *Helicobacter pylori* infection. *Postgraduate Medical Journal* 1993; 69(807):41–4.

Bauer DC, Browner WS, Cauley JA, Orwoll ES, Scott JC, Black DM, Tao JL, Cummings SR. Factors associated with appendicular bone mass in older women. The Study of Osteoporotic Fractures Research Group. *Annals of Internal Medicine* 1993;118(9): 657–65.

Bayerdörffer E, Mannes GA, Sommer A, Höchter W, Weingart J, Hatz R, Lehn N, Ruckdeschel G, Dirschedl P, Stolte M. Long-term follow-up after eradication of *Helicobacter pylori* with a combination of omeprazole and amoxycillin. *Scandinavian Journal of Gastroenterology Supplement* 1993;28:19–25.

Beaulieu M-D, Beland F, Roy D, Falardeau M, Hebert G. Factors determining compliance with screening mammography. *Canadian Medical Association Journal* 1996;154(9):1335–43.

Beck JD, Cusmano L, Green-Helms W, Koch GG, Offenbacher S. A 5-year study of attachment loss in community-dwelling older adults: incidence density. *Journal of Periodontal Research* 1997;32(6):506–15.

Beck JD, Koch GG, Rozier RG, Tudor GE. Prevalence and risk indicators for periodontal attachment loss in a population of older community-dwelling blacks and whites. *Journal of Periodontology* 1990;61(8): 521–8.

Belloc NB, Breslow L. Relationship of physical health status and health practices. *Preventive Medicine* 1972;1(3):409–21.

Benedetto MC, Kerns RD, Rosenberg R, Burg MM, Westgate K. Health risk behaviors and their relationships to health care utilization among veterans receiving primary medical care. *Journal of Clinical Psychology in Medical Settings* 1998;5(4):441–7.

Bergen AW, Caporaso N. Cigarette smoking. *Journal of the National Cancer Institute* 1999;91(16):1365–75.

Bergström J. Short-term investigation on the influence of cigarette smoking upon plaque accumulation. *Scandinavian Journal of Dental Research* 1981;89(3): 235–8.

Bergström J. Oral hygiene compliance and gingivitis expression in cigarette smokers. *Scandinavian Journal of Dental Research* 1990;98(6):497–503.

Bergström J, Eliasson S. Cigarette smoking and alveolar bone height in subjects with a high standard of oral hygiene. *Journal of Clinical Periodontology* 1987a;14(8):466–9.

Bergström J, Eliasson S. Noxious effect of cigarette smoking on periodontal health. *Journal of Periodontal Research* 1987b;22(6):513–7.

Bergström J, Eliasson S, Preber H. Cigarette smoking and periodontal bone loss. *Journal of Periodontology* 1991;62(4):242–6. [See also erratum in *Journal of Periodontology* 1991;62(12):809.]

Bergström J, Floderus-Myrhed B. Co-twin control study of the relationship between smoking and some periodontal disease factors. *Community Dentistry and Oral Epidemiology* 1983;11(2):113–6.

Bergström J, Preber H. The influence of cigarette smoking on the development of experimental gingivitis. *Journal of Periodontal Research* 1986;21(6):668–76.

Berkman LF, Seeman TE, Albert M, Blazer D, Kahn R, Mohs R, Finch C, Schneider E, Cotman C, McClearn G. High, usual and impaired functioning in community-dwelling older men and women: findings from the MacArthur Foundation Research Network on Successful Aging. *Journal of Clinical Epidemiology* 1993;46(10):1129–40.

Berr C, Coudray C, Bonithon-Kopp C, Roussci AN, Mainard F, Alperovitch A, Eva Study Group. Demographic and cardiovascular rise factors in relation to antioxidant status: the EVA Study. *International Journal of Vitamin and Nutrition Research* 1998;68(1):26–35.

Bertera RL. The effects of behavioral risks on absenteeism and health-care costs in the workplace. *Journal of Occupational Medicine* 1991;33(11):1119–24.

Best D, Rawaf S, Rowley J, Floyd K, Manning V, Strang J. Drinking and smoking as concurrent predictors of illicit drug use and positive drug attitudes in adolescents. *Drug and Alcohol Dependence* 2000;60(3): 319–21.

Bettman JW, Fellows V, Chao P. The effect of cigarette smoking on the intraocular circulation. *Archives of Ophthalmology* 1958;59:481–8.

Bhattacharyya MH, Whelton BD, Stern PH, Peterson DP. Cadmium accelerates bone loss in ovariectomized mice and fetal rat limb bones in culture. *Proceedings of the National Academy of Sciences of the United States of America* 1988;85(22):8761–5.

Billimoria JD, Pozner H, Metselaar B, Best FW, Janus DC. Effect of cigarette smoking on lipids, lipoproteins, blood coagulation, fibrinolysis and cellular components of human blood. *Atherosclerosis* 1975;21(1):61–76.

Bjarnason NH, Christiansen C. The influence of thinness and smoking on bone loss and response to hormone replacement therapy in early postmenopausal women. *Journal of Clinical Endocrinology and Metabolism* 2000;85(2):590–6.

Blair A, Blair SN, Howe HG, Pate RR, Rosenberg M, Parker GM, Pickle LW. Physical, psychological, and sociodemographic differences among smokers, exsmokers, and nonsmokers in a working population. *Preventive Medicine* 1980;9(6):747–59.

Blake GH, Abell TD, Stanley WG. Cigarette smoking and upper respiratory infection among recruits in basic combat training. *Annals of Internal Medicine* 1988;109(3):198–202.

Blanker MH, Bohnen AM, Groeneveld FPMJ, Bernsen RMD, Prins A, Thomas S, Bosch JLHR. Correlates for erectile and ejaculatory dysfunction in older Dutch men: a community-based study. *Journal of the American Geriatrics Society* 2001;49(4):436–42.

Bluman LG, Mosca L, Newman N, Simon D. Preoperative smoking habits and postoperative pulmonary complications. *Chest* 1998;113(4):883–9.

Blumenkranz MS, Russell SR, Robey MG, Kott-Blumenkranz R, Penneys N. Risk factors in age-related maculopathy complicated by choroidal neovascularization. *Ophthalmology* 1986;93(5): 552–8.

Bobak M, Pikhart H, Hertzman C, Rose R, Marmot M. Socioeconomic factors, perceived control and self-reported health in Russia: a cross-sectional survey. *Social Science Medicine* 1998;47(2):269–79.

Bochow TW, West SK, Azar A, Munoz B, Sommer A, Taylor HR. Ultraviolet light exposure and risk of posterior subcapsular cataracts. *Archives of Ophthalmology* 1989;107(3):369–72.

Bolin A, Eklund G, Frithiof L, Lavstedt S. The effect of changed smoking habits on marginal alveolar bone loss: a longitudinal study. *Swedish Dental Journal* 1993;17(5):211–6.

Bolin A, Lavstedt S, Frithiof L, Henrikson CO. Proximal alveolar bone loss in a longitudinal radiographic investigation. IV: smoking and some other factors influencing the progress in individuals with at least 20 remaining teeth. *Acta Odontologica Scandinavica* 1986;44(5):263–9.

Bolton-Smith C, Casey CE, Gey KF, Smith WCS, Tunstall-Pedoe H. Antioxidant vitamin intakes assessed using a food-frequency questionnaire: correlation with biochemical status in smokers and non-smokers. *British Journal of Nutrition* 1991;65(3): 337–46.

Bonithon-Kopp C, Coudray C, Berr C, Touboul P-J, Fève JM, Favier A, Ducimetière P. Combined effects of lipid peroxidation and antioxidant status on carotid atherosclerosis in a population aged 59-71 y: the EVA Study. *American Journal of Clinical Nutrition* 1997;65(1):121–7.

Boot AM, de Ridder MAJ, Pols HAP, Krenning EP, de Muinck Keizer-Schrama SMPF. Bone mineral density in children and adolescents: relation to puberty, calcium intake, and physical activity. *Journal of Clinical Endocrinology and Metabolism* 1997;82(1):57–62.

Borch-Johnsen K, Nissen H, Henriksen E, Kreiner S, Salling N, Deckert T, Nerup J. The natural history of insulin-dependent diabetes mellitus in Denmark: 1. Long-term survival with and without late diabetic complications. *Diabetic Medicine* 1987;4(3): 201–10.

Bornman MS, Du Plessis DJ. Smoking and vascular impotence: a reason for concern. *South African Medical Journal* 1986;70(6):329–30.

Borody TJ, Brandl S, Andrews P, Jankiewicz E, Ostapowicz N. *Helicobacter pylori*-negative gastric ulcer. *American Journal of Gastroenterology* 1992a; 87(10):1403–6.

Borody TJ, George LL, Brandl S, Andrews P, Jankiewicz E, Ostapowicz N. Smoking does not contribute to duodenal ulcer relapse after *Helicobacter pylori* eradication. *American Journal of Gastroenterology* 1992b; 87(10):1390–3.

Borody TJ, George LL, Brandl S, Andrews P, Ostapowicz N, Hyland L, Devine M. *Helicobacter pylori*-negative duodenal ulcer. *American Journal of Gastroenterology* 1991;86(9):1154–7.

Boström L, Linder LE, Bergström J. Clinical expression of TNF-α in smoking-associated periodontal disease. *Journal of Clinical Periodontology* 1998a;25(10): 767–73.

Boström L, Linder LE, Bergström J. Influence of smoking on the outcome of periodontal surgery: a 5-year follow-up. *Journal of Clinical Periodontology* 1998b;25(3):194–201.

Boucher JM, Dupras A, Jutras N, Page V, LeLorier J, Gagnon RM. Long-term survival and functional status in the elderly after cardiac surgery. *Canadian Journal of Cardiology* 1997;13(7):646–52.

Bovill EG, Bild DE, Heiss G, Kuller LH, Lee MH, Rock R, Wahl PW. White blood cell counts in persons aged 65 years or more from the Cardiovascular Health

Study: correlations with baseline clinical and demographic characteristics. *American Journal of Epidemiology* 1996;143(11):1107–15.

Brady WE, Mares-Perlman JA, Bowen P, Stacewicz-Sapuntzakis M. Human serum carotenoid concentrations are related to physiologic and lifestyle factors. *Journal of Nutrition* 1996;126(1):129–37.

Brain K, Parker H, Carnwath T. Drinking with design: young drinkers as psychoactive consumers. *Drugs: Education, Prevention and Policy* 2000;7(1):5–20.

Brandtzaeg P, Jamison HC. A study of periodontal health and oral hygiene in Norwegian army recruits. *Journal of Periodontology* 1964;35:22–7.

Brenner H, Rothenbacher D, Bode G, Adler G. Relation of smoking and alcohol and coffee consumption to active *Helicobacter pylori* infection: cross sectional study. *British Medical Journal* 1997;315(7121): 1489–92.

Bressler NM, Munoz B, Maguire MG, Vitale SE, Schein OD, Taylor HR, West SK. Five-year incidence and disappearance of drusen and retinal pigment epithelial abnormalities: waterman study. *Archives of Ophthalmology* 1995;113(3):301–8.

Breuer T, Kim JG, el-Zimaity HM, Nakajima S, Ota H, Osato M, Graham DY. Clarithromycin, amoxycillin, and H_2-receptor antagonist therapy for *Helicobacter pylori* peptic ulcer disease in Korea. *Alimentary Pharmacology and Therapeutics* 1997a;11(5):939–42.

Breuer T, Kim JG, Gurer IE, Graham DP, Osato M, Genta RM, Graham DY. Successful low-dose amoxycillin, metronidazole and omeprazole combination therapy in a population with a high frequency of metronidazole-resistant *Helicobacter pylori*. *Alimentary Pharmacology and Therapeutics* 1997b;11(3):523–7.

Bridges RB, Anderson JW, Saxe SR, Gregory K, Bridges SR. Periodontal status of diabetic and non-diabetic men: effects of smoking, glycemic control, and socioeconomic factors. *Journal of Periodontology* 1996;67(11):1185–92.

Brook M, Grimshaw JJ. Vitamin C concentration of plasma and leukocytes as related to smoking habit, age, and sex of humans. *American Journal of Clinical Nutrition* 1968;21(11):1254–8.

Brooks-Brunn JA. Predictors of postoperative pulmonary complications following abdominal surgery. *Chest* 1997;111(3):564–71.

Brot C, Jensen LB, Sørensen OH. Bone mass and risk factors for bone loss in perimenopausal Danish women. *Journal of Internal Medicine* 1997;242(6): 505–11.

Brot C, Jørgensen NR, Sørensen OH. The influence of smoking on vitamin D status and calcium metabolism. *European Journal of Clinical Nutrition* 1999;53(12):920–6.

Brown AJ. Acute effects of smoking cessation on antioxidant status. *Journal of Nutritional Biochemistry* 1996;7(1):29–39.

Brown CW, Orme TJ, Richardson HD. The rate of pseudarthrosis (surgical nonunion) in patients who are smokers and patients who are non-smokers: a comparison study. *Spine* 1986;11(9):942–3.

Brown LF, Beck JD, Rozier RG. Incidence of attachment loss in community-dwelling older adults. *Journal of Periodontology* 1994;65(4):316–23.

Buiatti E, Muñoz N, Kato I, Vivas J, Muggli R, Plummer M, Benz M, Franceschi S, Oliver W. Determinants of plasma anti-oxidant vitamin levels in a population at high risk for stomach cancer. *International Journal of Cancer* 1996;65(3):317–22.

Burger H, de Laet CEDH, van Daele PLA, Weel AEAM, Witteman JCM, Hofman A, Pols HAP. Risk factors for increased bone loss in an elderly population: the Rotterdam Study. *American Journal of Epidemiology* 1998;147(9):871–9.

Burger H, de Laet CEDH, Weel AEAM, Hofman A, Pols HAP. Added value of bone mineral density in hip fracture risk scores. *Bone* 1999;25(3):369–74.

Burnett AL. Nitric oxide in the penis: physiology and pathology. *Journal of Urology* 1997;157(1):320–4.

Burt BA, Eklund SA. *Dentistry, Dental Practice, and the Community*. 5th ed. Philadelphia: WB Saunders Company, 1999.

Burt BA, Ismail AI, Eklund SA. Root caries in an optimally fluoridated and a high-fluoride community. *Journal of Dental Research* 1986;65(9):1154–8.

Bush R, Wooden M. Smoking and absence from work: Australian evidence. *Social Science and Medicine* 1995;41(3):437–46.

Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, Rubin HR. Why don't physicians follow clinical practice guidelines? A framework for improvement. *Journal of the American Medical Association* 1999;282(15):1458–65.

Callahan CM, Stump TE, Stroupe KT, Tierney WM. Cost of health care for a community of older adults in an urban academic healthcare system. *Journal of the American Geriatric Society* 1998;46(11):1371–7.

Calori G, D'Angelo A, Della Valle P, Ruotolo G, Ferini-Strambi L, Giusti C, Errera A, Gallus G. The effect of cigarette-smoking on cardiovascular risk factors: a study of monozygotic twins discordant for smoking. *Thrombosis and Hemostatis* 1996;75(1):14–8.

Camilleri IG, Malata CM, Stavrianos S, Mclean NR. A review of 120 Becker permanent tissue expanders in reconstruction of the breast. *British Journal of Plastic Surgery* 1996;49(6):346–51.

Carel RS, Eviatar J. Factors affecting leukocyte count in healthy adults. *Preventive Medicine* 1985;14(5): 607–19.

Casasnovas JA, Lapetra A, Puzo J, Pelegrin J, Hermosilla T, De Vicente J, Garza F, Del Rio A, Giner A, Ferreira IJ. Tobacco, physical exercise and lipid profile. *European Heart Journal* 1992;13(4):440–5.

Cekic O. Effect of cigarette smoking on copper, lead, and cadmium accumulation in human lens. *British Journal of Ophthalmology* 1998;82(2):186–8.

Centers for Disease Control and Prevention. Incidence and costs to Medicare of fractures among Medicare beneficiaries aged ≥65 years—United States, July 1991–June 1992. *Morbidity and Mortality Weekly Report* 1996;45(41):877–83.

Chan FK, Sung JJ, Lee YT, Leung WK, Chan LY, Yung MY, Chung SC. Does smoking predispose to peptic ulcer relapse after eradication of *Helicobacter pylori*? *American Journal of Gastroenterology* 1997;92(3): 442–5.

Chan WH, Wong WK, Chan HS, Soo KC. Results of surgical resection of oesophageal carcinoma in Singapore. *Annals of Academic Medicine in Singapore* 2000;29(1):57–61.

Chan-Yeung M, Abboud R, Buncio AD, Vedal S. Peripheral leukocyte count and longitudinal decline in lung function. *Thorax* 1988;43(6):462–6.

Chan-Yeung M, Vedal S, Kus J, MacLean L, Enarson D, Tse KS. Symptoms, pulmonary function, and bronchial hyperreactivity in western red cedar workers compared with those in office workers. *American Review of Respiratory Diseases* 1984;130(6): 1038–41.

Chen T-S, Chang F-Y, Lee S-D, Lee S-C. Recurrence of *H. pylori* infection and dyspeptic symptoms after successful eradication in patients cured of duodenal ulcer disease. *Hepato-Gastroenterology* 1999; 46(25):252–6.

Cheng S, Fan B, Wang L, Fuerst T, Lian M, Njeh C, He Y, Kern M, Lappin M, Tylavsky F, Casal D, Harris S, Genant HK. Factors affecting broadband ultrasound attenuation results of the calcaneus using a gel-coupled quantitative ultrasound scanning system. *Osteoporosis International* 1999;10(6):495–504.

Cheng S, Suominen H, Heikkinen E. Bone mineral density in relation to anthropometric properties, physical activity and smoking in 75-year-old men and women. *Aging: Clinical and Experimental Research* 1993;5(1):55–62.

Cheng S, Suominen H, Rantanen T, Parkatti T, Heikkinen E. Bone mineral density and physical activity in 50–60-year-old women. *Bone and Mineral* 1991;12(2):123–32.

Chetwynd J, Rayner T. Impact of smoking on health care resource use. *New Zealand Medical Journal* 1986; 99(799):230–2.

Chimbira W, Sweeney BP. The effect of smoking on postoperative nausea and vomiting. *Anaesthesia* 2000;55(6):540–4.

Christen AG, McDonald JL Jr, Christen JA. *The Impact of Tobacco Use and Cessation on Nonmalignant and Precancerous Oral and Dental Diseases and Conditions*. Indianapolis (IN): Indiana University School of Dentistry, 1991.

Christen WG, Glynn RJ, Ajani UA, Schaumberg DA, Buring JE, Hennekens CH, Manson JE. Smoking cessation and risk of age-related cataract in men. *Journal of the American Medical Association* 2000;284(6):713–6.

Christen WG, Glynn RJ, Manson JE, Ajani UA, Buring JE. A prospective study of cigarette smoking and risk of age-related macular degeneration in men. *Journal of the American Medical Association* 1996; 276(14):1147–51.

Christen WG, Manson JE, Seddon JM, Glynn RJ, Buring JE, Rosner B, Hennekens CH. A prospective study of cigarette smoking and risk of cataract in men. *Journal of the American Medical Association* 1992; 268(8):989–93.

Christiansen JS. Cigarette smoking and prevalence of microangiopathy in juvenile-onset insulin-dependent diabetes mellitus. *Diabetes Care* 1978;1(3): 146–9.

Clark P, de la Peña F, Gomez Garcia F, Orozco JA, Tugwell P. Risk factors for osteoporotic hip fractures in Mexicans. *Archives of Medical Research* 1998;29(3): 253–7.

Clarke NG, Shephard BC. The effects of epinephrine and nicotine on gingival blood flow in the rabbit. *Archives of Oral Biology* 1984;29(10):789–93.

Clarke NG, Shephard BC, Hirsch RS. The effects of intra-arterial epinephrine and nicotine on gingival circulation. *Oral Surgery, Oral Medicine, Oral Pathology* 1981;52(6):577–82.

Clayton RM, Cuthbert J, Duffy J, Seth J, Phillips CI, Bartholomew RS, Reid JM. Some risk factors associated with cataract in S.E. Scotland: a pilot study. *Transactions of the Ophthalmological Societies of the United Kingdom* 1982;102(Pt 3):331–6.

Collett JA, Burt MJ, Frampton CMA, Yeo KHJ, Chapman TM, Buttimore RC, Cook HB, Chapman BA. Seroprevalence of *Helicobacter pylori* in the adult

population of Christchurch: risk factors and relationship to dyspeptic symptoms and iron studies. *New Zealand Medical Journal* 1999;112(1093):292–5.

Colsher PL, Wallace RB, Pomrehn PR, La Croix AZ, Cornoni-Huntley J, Blazer D, Scherr PA, Berkman L, Hennekens CH. Demographic and health characteristics of elderly smokers: results from established populations for epidemiologic studies of the elderly. *American Journal of Preventive Medicine* 1990;6(2):61–70.

Comstock GW, Menkes MS, Schober SE, Vuilleumier J-P, Helsing KJ. Serum levels of retinol, beta-carotene, and alpha-tocopherol in older adults. *American Journal of Epidemiology* 1988;127(1):114–23.

Condra M, Morales A, Owen JA, Surridge DH, Fenemore J. Prevalence and significance of tobacco smoking in impotence. *Urology* 1986;27(6):495–8.

Cooper C, Barker DJP, Wickham C. Physical activity, muscle strength, and calcium intake in fracture of the proximal femur in Britain. *British Medical Journal* 1988;297(6661):1443–6.

Cooper C, Shah S, Hand DJ, Adams J, Compston J, Davie M, Woolf A. Screening for vertebral osteoporosis using individual risk factors: the Multicentre Vertebral Fracture Study Group. *Osteoporosis International* 1991;2(1):48–53.

Cornuz J, Feskanich D, Willett WC, Colditz GA. Smoking, smoking cessation, and risk of hip fracture in women. *American Journal of Medicine* 1999;106(3): 311–4.

Coronary Drug Project Research Group. Aspirin in coronary heart disease. *Journal of Chronic Diseases* 1976;29(10):625–42.

Corre F, Lellouch J, Schwartz D. Smoking and leucocyte-counts: results of an epidemiological survey. *Lancet* 1971;2(7725):632–4.

Cover TL, Vaughan SG, Cao P, Blaser MJ. Potentiation of *Helicobacter pylori* vacuolating toxin activity by nicotine and other weak bases. *Journal of Infectious Diseases* 1992;166(5):1073–8.

Cross CE, Traber M, Eiserich J, van der Vliet A. Micronutrient antioxidants and smoking. *British Medical Bulletin* 1999;55(3):691–704.

Cumming RG, Klineberg RJ. Case-control study of risk factors for hip fractures in the elderly. *American Journal of Epidemiology* 1994;139(5):493–503.

Cumming RG, Mitchell P. Alcohol, smoking, and cataracts: the Blue Mountains Eye Study. *Archives of Ophthalmology* 1997;115(10):1296–303.

Cummings SR, Black DM, Nevitt MC, Browner W, Cauley J, Ensrud K, Genant HK, Palermo L, Scott J, Vogt TM. Bone density at various sites for prediction of hip fractures. *Lancet* 1993;341(8837):72–5.

Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, Cauley J, Black D, Vogt TM. Risk factors for hip fracture in white women: the Study of Osteoporotic Fractures Research Group. *New England Journal of Medicine* 1995;332(12):767–73.

Cutler AF, Schubert TT. Patient factors affecting *Helicobacter pylori* eradication with triple therapy. *American Journal of Gastroenterology* 1993;88(4): 505–9.

D'Agostino RS, Svensson LG, Neumann DJ, Balkhy H, Williamson WA, Shahian D. Screening carotid ultrasonography and risk factors for stroke in coronary artery surgery patients. *Annals of Thoracic Surgery* 1996;62(6):1714–23.

Danesh J, Muir J, Wong Y-k, Ward M, Gallimore JR, Pepys MB. Risk factors for coronary heart disease and acute-phase proteins. *European Heart Journal* 1999;20(13):954–9.

Daniel M, Martin AD, Drinkwater DT. Cigarette smoking, steroid hormones, and bone mineral density in young women. *Calcified Tissue International* 1992; 50(4):300–5.

Danielsen B, Manji F, Nagelkerke N, Fejerskov O, Baelum V. Effect of cigarette smoking on the transition dynamics in experimental gingivitis. *Journal of Clinical Periodontology* 1990;17(3):159–64.

Das I. Raised C-reactive protein levels in serum from smokers. *Clinica Chemica Acta* 1985;153(1):9–13.

Dawson DA. Drinking as a risk factor for sustained smoking. *Drug and Alcohol Dependence* 2000;59(3): 235–49.

de Maat MPM, Pietersma A, Kofflard M, Sluiter W, Kluft C. Association of plasma fibrinogen levels with coronary artery disease, smoking and inflammatory markers. *Atherosclerosis* 1996;121(2):185–91.

Degan P, Bonassi S, De Caterina M, Korkina LG, Pinto L, Scopacasa F, Zatterale A, Calzone R, Pagano G. *In vivo* accumulation of 8-hydroxy-2'-deoxyguano-sine in DNA correlates with release of reactive oxygen species in Fanconi's anaemia families. *Carcinogenesis* 1995;16(4):735–41.

Delcourt C, Diaz J-L, Ponton-Sanchez A, Papoz L. Smoking and age-related macular degeneration: the POLA study. *Archives of Ophthalmology* 1998;116(8): 1031–5.

Dennerstein L, Smith AMA, Morse C. Psychological well-being, mid-life and the menopause. *Maturitas* 1994;20(1):1–11.

DePalma RG, Emsellem HA, Edwards CM, Druy EM, Shultz SW, Miller HC, Bergsrud D. A screening sequence for vasculogenic impotence. *Journal of Vascular Surgery* 1987;5(2):228–36.

Derby CA, Araujo AB, Johannes CB, Feldman HA, McKinlay JB. Measurement of erectile dysfunction in population-based studies: the use of a single question self-assessment in the Massachusetts Male Aging Study. *International Journal of Impotence Research* 2000a;12(4):197–204.

Derby CA, Mohr BA, Goldstein I, Feldman HA, Johannes CB, McKinlay JB. Modifiable risk factors and erectile dysfunction: can life-style changes modify risk? *Urology* 2000b:56(2):302–6.

Dimberg L, Olafsson A, Stefansson E, Aagaard H, Odén A, Andersson GBJ, Hagert C-G, Hansson T. Sickness absenteeism in an engineering industry—an analysis with special reference to absence for neck and upper extremity symptoms. *Scandinavian Journal of Social Medicine* 1989;17(1):77–84.

Dodsworth H, Dean A, Boom G. Effects of smoking and the pill on blood count. *British Journal of Haematology* 1981;49(3):484–8.

Dolan TA, Gilbert GH, Ringelberg ML, Legler DW, Antonson DE, Foerster U, Heft MW. Behavioral risk indicators of attachment loss in adult Floridians. *Journal of Clinical Periodontology* 1997a;24(4):223–32.

Dolan TA, McGorray SP, Grinstead-Skigen CL, Mecklenburg R. Tobacco control activities in U.S. dental practices. *Journal of the American Dental Association* 1997b;128(12):1669–79.

Doll R, Peto R, Wheatley K, Gray R, Sutherland I. Mortality in relation to smoking: 40 years' observations on male British doctors. *British Medical Journal* 1994;309(6959):901–11.

Donaldson SI, Sussman S, Dent CW, Severson HH, Stoddard JL. Health behavior, quality of work life, and organizational effectiveness in the lumber industry. *Health Education and Behavior* 1999;26(4): 579–91.

Drake CW, Beck JD, Lawrence HP, Koch GG. Three-year coronal caries incidence and risk factors in North Carolina elderly. *Caries Research* 1997;31(1): 1–7.

Durak I, Yalein S, Burak Cimen MY, Buyukkocak S, Kacmaz M, Ozturk HS. Effects of smoking on plasma and erythrocyte antioxidant defense systems. *Journal of Toxicology and Environmental Health Part A* 1999;56(6):373–8.

Duthie GG, Arthur JR, Beattie JA, Brown KM, Morrice PC, Robertson JD, Shortt CT, Walker KA, James WP. Cigarette smoking antioxidants, lipid peroxidation, and coronary heart disease. *Annals of the New York Academy of Sciences* 1993;686:120–9.

Eastwood GL. Is smoking still important in the pathogenesis of peptic ulcer disease? *Journal of Clinical Gastroenterology* 1997;25(Suppl 1):S1–S7.

Edgar W, Higham SM. Saliva and the control of plaque pH. In: Edgar WM, O'Mullane DM, editors. *Saliva and Oral Health*. 2nd ed. London: British Dental Association, 1996:81–94.

Edwards N, Boulet J. Implementing breast cancer screening guidelines: results of the Ontario Health Status Survey. *American Journal of Preventive Medicine* 1997;13(2):143–9.

Egger P, Duggleby S, Hobbs R, Fall C, Cooper C. Cigarette smoking and bone mineral density in the elderly. *Journal of Epidemiology and Community Health* 1996;50(1):47–50.

Eichel B, Shahrik HA. Tobacco smoke toxicity: loss of human oral leukocyte function and fluid-cell metabolism. *Science* 1969;166(911):1424–8.

Eickholz P, Hausmann E. Accuracy of radiographic assessment of interproximal bone loss in intrabony defects using linear measurements. *European Journal of Oral Sciences* 2000;108(1):70–3.

Eiserich JP, van der Vliet A, Handelman GJ, Halliwell B, Cross CE. Dietary antioxidants and cigarette smoke–induced bimolecular damage: a complex interaction. *American Journal of Clinical Nutrition* 1995;62(6 Suppl):1490S–1500S.

Eisman JA. Genetics of osteoporosis. *Endocrine Reviews* 1999;20(6):788–804.

Elist J, Jarman WD, Edson M. Evaluating medical treatment of impotence. *Urology* 1984;23(4):374–5.

El-Serag HB, Sonnenberg A. Opposing time trends of peptic ulcer and reflux disease. *Gut* 1998;43(3): 327–33.

Elter JR, Beck JD, Slade GD, Offenbacher S. Etiologic models for incident periodontal attachment loss in older adults. *Journal of Clinical Periodontology* 1999; 26(2):113–23.

Endoh K, Leung FW. Effect of smoking and nicotine on the gastric mucosa: a review of clinical and experimental evidence. *Gastroenterology* 1994;107(3): 864–78.

Ensrud KE, Palermo L, Black DM, Cauley J, Jergas M, Orwoll ES, Nevitt MC, Fox KM, Cummings SR. Hip and calcaneal bone loss increase with advancing age: longitudinal results from the study of osteoporotic fractures. *Journal of Bone and Mineral Research* 1995;10(11):1778–87.

Erdmann MW, Court-Brown CM, Quaba AA. A five year review of islanded distally based fasciocutaneous flaps on the lower limb. *British Journal of Plastic Surgery* 1997;50(6):421–7.

Erickson P. Evaluation of a population-based measure of quality of life: the Health and Activity Limitation Index (HALex). *Quality of Life Research* 1998; 7(2):101–14.

Espehaug B, Havelin LI, Engesaeter LB, Langeland N, Vollset SE. Patient-related risk factors for early revision of total hip replacements: a population register-based case-control study of 674 revised hips. *Acta Orthopaedica Scandinavica* 1997;68(3):207–15.

EUROGAST Study Group. Epidemiology of, and risk factors for, *Helicobacter pylori* infection among 3194 asymptomatic subjects in 17 populations. *Gut* 1993;34(12):1672–6.

Everhart JE, Byrd-Holt D, Sonnenberg A. Incidence and risk factors for self-reported peptic ulcer disease in the United States. *American Journal of Epidemiology* 1998;147(6):529–36.

Eye Disease Case-Control Study Group. Risk factors for neovascular age-related macular degeneration. *Archives of Ophthalmology* 1992;110(12):1701–8.

Faddy MJ, Cullinan MP, Palmer JE, Westerman B, Seymour GJ. Ante-dependence modeling in a longitudinal study of periodontal disease: the effect of age, gender, and smoking status. *Journal of Periodontology* 2000;71(3):454–9.

Fang MA, Frost PJ, Iida-Klein A, Hahn TJ. Effects of nicotine on cellular function in UMR 106-01 osteoblast-like cells. *Bone* 1991;12(4):283–6.

Featherstone JDB. Prevention and reversal of dental caries: role of low level fluoride. *Community Dentistry and Oral Epidemiology* 1999;27(1):31–40.

Fehily AM, Coles RJ, Evans WD, Elwood PC. Factors affecting bone density in young adults. *American Journal of Clinical Nutrition* 1992;56(3):579–86.

Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *Journal of Urology* 1994;151(1): 54–61.

Feldman HA, Johannes CB, Derby CA, Kleinman KP, Mohr BA, Araujo AB, McKinlay JB. Erectile dysfunction and coronary risk factors: prospective results from the Massachusetts Male Aging Study. *Preventive Medicine* 2000;30(4):328–38.

Feldman RS, Alman JE, Chauncey HH. Periodontal disease indexes and tobacco smoking in healthy aging men. *Gerodontics* 1987;3(1):43–6.

Feldman RS, Bravacos JS, Rose CL. Association between smoking different tobacco products and periodontal disease indexes. *Journal of Periodontology* 1983;54(8):481–7.

Ferguson D. Sickness absence: an analysis of the problem. *The Medical Journal of Australia* 1973;1(7): 334–40.

Fisch IR, Freedman SH. Smoking, oral contraceptives, and obesity: effects on white blood cell count. *Journal of the American Medical Association* 1975; 234(5):500–6.

Flaye DE, Sullivan KN, Cullinan TR, Silver JH, Whitlocke RAF. Cataracts and cigarette smoking: the City Eye Study. *Eye* 1989;3(Pt 4):379–84.

Flemmig TF. Periodontitis. *Annals of Periodontology* 1999;4(1):32–8.

Forrester BG, Weaver MT, Brown KC, Phillips JA, Hilyer JC. Personal health-risk predictors of occupational injury among 3415 municipal employees. *Journal of Occupational and Environmental Medicine* 1996;38(5):515–21.

Forsberg L, Gustavii B, Höjerback T, Olsson AM. Impotence, smoking and β-blocking drugs. *Fertility and Sterility* 1979;31(5):589–91.

Forsberg L, Hederström E, Olsson AM. Severe arterial insufficiency in impotence confirmed with an improved angiographic technique: the impact of smoking and some other etiologic factors. *European Urology* 1989;16(5):357–60.

Forsén L, Bjartveit K, Bjørndal A, Edna T-H, Meyer HE, Schei B. Ex-smokers and risk of hip fracture. *American Journal of Public Health* 1998;88(10):1481–3.

Forsén L, Bjørndal A, Bjartveit K, Edna T-H, Holmen J, Jessen V, Westberg G. Interaction between current smoking, leanness, and physical inactivity in the prediction of hip fracture. *Journal of Bone and Mineral Research* 1994;9(11):1671–8.

Fraser AG, Moore L, Ali MR, Chua LE, Hollis B, Little SV. An audit of low dose triple therapy for eradication of *Helicobacter pylori*. *New Zealand Medical Journal* 1996;109(1027):290–2.

Freeborn DK, Mullooly JP, Pope CR, McFarland BH. Smoking and consistently high use of medical care among older HMO members. *American Journal of Public Health* 1990;80(5):603–5.

Fried LP, Moore RD, Pearson TA. Long-term effects of cigarette smoking and moderate alcohol consumption on coronary artery diameter: mechanisms of coronary artery disease independent of atherosclerosis or thrombosis. *American Journal of Medicine* 1986;80(1):37–44.

Friedman GD, Siegelaub AB. Changes after quitting cigarette smoking. *Circulation* 1980;61(4):716–23.

Friedman GD, Siegelaub AB, Seltzer CC, Feldman R, Collen MF. Smoking habits and the leukocyte count. *Archives of Environmental Health* 1973;26(3):137–43.

Fujisawa T, Iizasa T, Saitoh Y, Sekine Y, Motohashi S, Yasukawa T, Shibuya K, Hiroshima K, Ohwada H. Smoking before surgery predicts poor long-term survival in patients with stage I non-small-cell lung carcinomas. *Journal of Clinical Oncology* 1999;17(7): 2086–91.

Fujiwara S, Kasagi F, Yamada M, Kodama K. Risk factors for hip fracture in a Japanese cohort. *Journal of Bone and Mineral Research* 1997;12(7):998–1004.

Fylkesnes K, Førde O. The Tromsø study: predictors of self-evaluated health—has society adopted the expanded health concept? *Social Science and Medicine* 1991;32(2):141–6.

Gallop B. Sickness absenteeism and smoking. *New Zealand Medical Journal* 1989;102(863):112.

Ganley JP. Epidemiologic characteristics of presumed ocular histoplasmosis. *Acta Ophthalmologica Supplement* 1973;119:1–63.

Gärdsell P, Johnell O, Nilsson BE. Predicting fractures in women by using forearm bone densitometry. *Calcified Tissue International* 1989;44(4):235–42.

Gelskey SC, Young TK, Singer DL. Factors associated with adult periodontitis in a dental teaching clinic population. *Community Dentistry and Oral Epidemiology* 1998;26(4):226–32.

Genco RJ. Classification and clinical and radiographic features of periodontal disease. In: Genco RJ, Goldman HM, Cohen DW, editors. *Contemporary Periodontics*. St. Louis: CV Mosby Company, 1990a: 63–81.

Genco RJ. Periodontal diagnosis, prognosis, and treatment planning. In: Genco RJ, Goldman HM, Cohen DW, editors. *Contemporary Periodontics*. St. Louis: CV Mosby Company, 1990b:348–59.

Genco RJ. Current view of risk factors for periodontal diseases. *Journal of Periodontology* 1996;67(10 Suppl):1041–9.

Genco RJ. Risk factors for periodontal disease. In: Rose LF, Genco RJ, Cohen DW, Mealey BL, editors. *Periodontal Medicine*. St. Louis: BC Decker, 2000:11–33.

Gentile AT, Mills JL, Gooden MA, Westerband A, Cui H, Berman SS, Hunter GC, Hughes JD. Identification of predictors for lower extremity vein graft stenosis. *American Journal of Surgery* 1997;174(2): 218–21.

George LL, Borody TJ, Andrews P, Devine M, Moore-Jones D, Walton M, Brandl S. Cure of duodenal ulcer after eradication of *Helicobacter pylori*. *Medical Journal of Australia* 1990;153(3):145–9.

Georgopoulos SD, Ladas SD, Karatapanis S, Mentis A, Spiliadi C, Artikis V, Raptis SA. Factors that may affect treatment outcome of triple *Helicobacter pylori* eradication therapy with omeprazole, amoxicillin, and clarithromycin. *Digestive Diseases and Sciences* 2000;45(1):63–7.

Gilbert DG, Hagen RL, D'Agostino JA. The effects of cigarette smoking on human sexual potency. *Addictive Behaviors* 1986;11(4):431–4.

Giovino GA, Henningfield JE, Tomar SL, Escobedo LG, Slade J. Epidemiology of tobacco use and dependence. *Epidemiologic Reviews* 1995;17(1):48–65.

Glina S, Reichelt AC, Leão PP, dos Reis JMSM. Impact of cigarette smoking on papaverine-induced erection. *Journal of Urology* 1988;140(3):523–4.

Goddard AF, Spiller RC. *Helicobacter pylori* eradication in clinical practice: one-week low-dose triple therapy is preferable to classical bismuth based triple therapy. *Alimentary Pharmacology and Therapeutics* 1996;10(6):1009–13.

Goh KL. Prevalence of and risk factors for *Helicobacter pylori* infection in a multi-racial dyspeptic Malaysian population undergoing endoscopy. *Journal of Gastroenterology and Hepatology* 1997;12(Suppl): S29–S35.

Goldberg MS, Scott SC, Mayo NE. A review of the association between cigarette smoking and the development of nonspecific back pain and related outcomes. *Spine* 2000;25(8):995–1014.

Golding J. Unnatural constituents of breast milk—medication, lifestyle, pollutants, viruses. *Early Human Development* 1997;49(Suppl):S29–S43.

Goldstein I, Feldman MI, Deckers PJ, Babayan RK, Krane RJ. Radiation-associated impotence: a clinical study of its mechanism. *Journal of the American Medical Association* 1984;251(7):903–10.

Goldstein I, Hatzichristou D. Epidemiology of impotence. In: Bennett AH, editor. *Impotence: Diagnosis and Management of Erectile Dysfunction*. Philadelphia: W.B. Saunders Company, 1994:1–17.

Golosow LM, Wagner JD, Feeley M, Sharp T, Havlik R, Sood R, Coleman JJ. Risk factors for predicting surgical salvage of sternal wound-healing complications. *Annals of Plastic Surgery* 1999;43(1):30–5.

González YM, De Nardin A, Grossi SG, Machtei EE, Genco RJ, De Nardin E. Serum cotinine levels, smoking, and periodontal attachment loss. *Journal of Dental Research* 1996;75(2):796–802.

Goodman CM, Cohen V, Armenta A, Thornby J, Netscher DT. Evaluation of results and treatment variables for pressure ulcers in 48 veteran spinal cord-injured patients. *Annals of Plastic Surgery* 1999;42(6):665–72.

Goodson JM. Selection of suitable indicators of periodontitis. In: Bader JD, editor. *Risk Assessment in Dentistry: Proceedings of a Conference, June 2–3, 1989*. Chapel Hill (NC): University of North Carolina Dental Ecology, 1990:69–74.

Goultschin J, Cohen HDS, Donchin M, Brayer L, Soskolne WA. Association of smoking with periodontal treatment needs. *Journal of Periodontology* 1990;61(6):364–7.

Graham DY, Lew GM, Malaty HM, Evans DG, Evans DJ Jr, Klein PD, Alpert LC, Genta RM. Factors influencing the eradication of *Helicobacter pylori* with triple therapy. *Gastroenterology* 1992;102(2):493–6.

Graham DY, Malaty HM, Evans DG, Evans DJ Jr, Klein PD, Adam E. Epidemiology of *Helicobacter pylori* in an asymptomatic population in the United States: effect of age, race, and socioeconomic status. *Gastroenterology* 1991;100(6):1495–501.

Grainge MJ, Coupland CAC, Cliffe SJ, Chilvers CED, Hosking DJ. Cigarette smoking, alcohol and caffeine consumption, and bone mineral density in postmenopausal women: the Nottingham EPIC Study Group. *Osteoporosis International* 1998;8(4):355–63.

Gray RS, Starkey IR, Rainbow S, Kurtz AB, Abdel-Khalik A, Urbaniak S, Elton RA, Duncan LJP, Clarke BF. HLA antigens and other risk factors in the development of retinopathy in type 1 diabetes. *British Journal of Ophthalmology* 1982;66(5):280–5.

Green MS, Luz J, Gofer D. Absence from work among smokers and nonsmokers in Israeli industries—the Cordis Study. *Israel Journal of Medical Sciences* 1992;28(8–9):645–9.

Gregg EW, Cauley JA, Seeley DG, Ensrud KE, Bauer DC. Physical activity and osteoporotic fracture risk in older women: Study of Osteoporotic Fractures Research Group. *Annals of Internal Medicine* 1998; 129(2):81–8.

Gregg EW, Kriska AM, Salamone LM, Wolf RL, Roberts MM, Ferrell RE, Anderson SJ, Kuller LH, Cauley JA. Correlates of quantitative ultrasound in the Women's Healthy Lifestyle Project. *Osteoporosis International* 1999;10(5):416–24.

Grembowski D, Patrick D, Diehr P, Durham M, Beresford S, Kay E, Hecht J. Self-efficacy and health behavior among older adults. *Journal of Health and Social Behavior* 1993;34(2):89–104.

Grisso JA, Kelsey JL, O'Brien LA, Miles CG, Sidney S, Maislin G, La Pann K, Moritz D, Peters B. Risk factors for hip fracture in men: Hip Fracture Study Group. *American Journal of Epidemiology* 1997;145(9): 786–93.

Grisso JA, Kelsey JL, Strom BL, O'Brien LA, Maislin G, LaPann K, Samelson L, Hoffman S. Risk factors for hip fracture in black women: the Northeast Hip Fracture Study Group. *New England Journal of Medicine* 1994;330(22):1555–9.

Grossi SG, Genco RJ, Machtei EE, Ho AW, Koch G, Dunford R, Zambon JJ, Hausmann E. Assessment of risk for periodontal disease. II: risk indicators for alveolar bone loss. *Journal of Periodontology* 1995; 66(1):23–9.

Grossi SG, Skrepcinski FB, DeCaro T, Zambon JJ, Cummins D, Genco RJ. Response to periodontal therapy in diabetics and smokers. *Journal of Periodontology* 1996;67(10 Suppl):1094–102.

Grossi SG, Zambon J, Machtei EE, Schifferle R, Andreana S, Genco RJ, Cummins D, Harrap G. Effects of smoking and smoking cessation on healing after mechanical periodontal therapy. *Journal of the American Dental Association* 1997;128(5):599–607.

Grossi SG, Zambon JJ, Ho AW, Koch G, Dunford RG, Machtei EE, Norderyd OM, Genco RJ. Assessment of risk for periodontal disease. I: risk indicators for attachment loss. *Journal of Periodontology* 1994; 65(3):260–7.

Guay AT, Perez JB, Heatley GJ. Cessation of smoking rapidly decreases erectile dysfunction. *Endocrine Practice* 1998;4(1):23–6.

Gunsolley JC, Quinn SM, Tew J, Gooss CM, Brooks CN, Schenkein HA. The effect of smoking on individuals with minimal periodontal destruction. *Journal of Periodontology* 1998;69(2):165–70.

Guralnik JM, Kaplan GA. Predictors of healthy aging: prospective evidence from the Alameda County Study. *American Journal of Public Health* 1989;79(6): 703–8.

Guthrie JR, Ebeling PR, Hopper JL, Barrett-Connor E, Dennerstein L, Dudley EC, Burger HG, Wark JD. A prospective study of bone loss in menopausal Australian-born women. *Osteoporosis International* 1998;8(3):282–90.

Guthrie JR, Ebeling PR, Hopper JL, Dennerstein L, Wark JD, Burger HG. Bone mineral density and hormone levels in menopausal Australian women. *Gynecological Endocrinology* 1996;10(3):199–205.

Haber J, Kent RL. Cigarette smoking in a periodontal practice. *Journal of Periodontology* 1992;63(2):100–6.

Haber J, Wattles J, Crowley M, Mandell R, Joshipura K, Kent RL. Evidence for cigarette smoking as a major risk factor for periodontitis. *Journal of Periodontology* 1993;64(1):16–23.

Hägg E, Asplund K. Is endocrine ophthalmopathy related to smoking? *British Medical Journal (Clinical Research Edition)* 1987;295(6599):634–5.

Hagiwara S, Tsumura K. Smoking as a risk factor for bone mineral density in the heel of Japanese men. *Journal of Clinical Densitometry* 1999;2(3):219–22.

Halpern MT, Warner KE. Differences in former smokers' beliefs and health status following smoking cessation. *American Journal of Preventive Medicine* 1994;10(1):31–7.

Halter F, Brignoli R. *Helicobacter pylori* and smoking: two additive risk factors for organic dyspepsia. *Yale Journal of Biology and Medicine* 1998;71(2):91–9.

Hammond EC. Evidence on the effects of giving up cigarette smoking. *American Journal of Public Health* 1965;55(5):682–91.

Hammond BR Jr, Wooten BR, Snodderly DM. Cigarette smoking and retinal carotenoids: implications for age-related macular degeneration. *Vision Research* 1996;36(18):3003–9.

Handelman GJ, van Kuijk FJGM, Chatterjee A, Krinsky NI. Characterization of products formed during the autoxidation of β-carotene. *Free Radical Biology and Medicine* 1991;10(6):427–37.

Hanes PJ, Schuster GS, Lubas S. Binding, uptake, and release of nicotine by human gingival fibroblasts. *Journal of Periodontology* 1991;62(2):147–52.

Hankinson SE, Willett WC, Colditz GA, Seddon JM, Rosner B, Speizer FE, Stampfer MJ. A prospective study of cigarette smoking and risk of cataract surgery in women. *Journal of the American Medical Association* 1992;268(8):994–8.

Hannan MT, Felson DT, Dawson-Hughes B, Tucker KL, Cupples LA, Wilson PWF, Kiel DP. Risk factors for longitudinal bone loss in elderly men and women: the Framingham Osteoporosis Study. *Journal of Bone and Mineral Research* 2000;15(4):710–20.

Hansen BF, Bjertness E, Gjermo P. Changes in periodontal disease indicators in 35-year-old Oslo citizens from 1973 to 1984. *Journal of Clinical Periodontology* 1990a;17(4):249–54.

Hansen JM, Hallas J, Lauritsen JM, Bytzer P. Nonsteroidal anti-inflammatory drugs and ulcer complications: a risk factor analysis for clinical decision-making. *Scandinavian Journal of Gastroenterology* 1996;31(2):126–30.

Hansen LK, Grimm RH Jr, Neaton JD. The relationship of white blood cell count to other cardiovascular risk factors. *International Journal of Epidemiology* 1990b;19(4):881–8.

Hansen MA, Overgaard K, Riis BJ, Christiansen C. Potential risk factors for development of postmenopausal osteoporosis—examined over a 12-year period. *Osteoporosis International* 1991;1(2):95–102.

Harats D, Ben-Naim M, Dabach Y, Hollander G, Havivi E, Stein O, Stein Y. Effect of Vitamin C and E supplementation on susceptibility of plasma lipoproteins to peroxidation induced by acute smoking. *Atherosclerosis* 1990;85(1):47–54.

Harats D, Ben-Naim M, Dabach Y, Hollander G, Stein O, Stein Y. Cigarette smoking renders LDL susceptible to peroxidative modification and enhanced metabolism by macrophages. *Atherosclerosis* 1989; 79(2-3):245–52.

Harding J. *Cataract: Biochemistry, Epidemiology, and Pharmacology*. London: Chapman and Hall, 1991.

Harding JJ. Cigarettes and cataract: cadmium or a lack of vitamin C? *British Journal of Ophthalmology* 1995;79(3):199–200.

Harding JJ, Van Heyningen R. Drugs, including alcohol, that act as risk factors for cataract, and possible protection against cataract by aspirin-like analgesics and cyclopenthiazide. *British Journal of Ophthalmology* 1988;72(11):809–14.

Harris AW, Pryce DI, Gabe SM, Karim QN, Walker MM, Langworthy H, Baron JH, Misiewicz JJ. Lansoprazole, clarithromycin and metronidazole for seven days in *Helicobacter pylori* infection. *Alimentary Pharmacology and Therapeutics* 1996;10(6): 1005–8.

Hart GT, Brown DM, Mincer HH. Tobacco use and dental disease. *Journal of the Tennessee Dental Association* 1995;75(2):25–7.

Hasebe T, Harasawa S, Miwa T. Factors affecting depth of gastric ulcers. *Tokai Journal of Experimental Clinical Medicine* 1998;23(4):177–82.

Haverstock BD, Mandracchia VJ. Cigarette smoking and bone healing: implications in foot and ankle surgery. *Journal of Foot and Ankle Surgery* 1998;37(1): 69–74.

Hawker R, Holtby I. Smoking and absence from work in a population of student nurses. *Public Health* 1988;102(2):161–7.

Hecht SS. Tobacco smoke carcinogens and lung cancer. *Journal of the National Cancer Institute* 1999; 91(14):1194–210.

Heinemann G, Schievelbein H, Eber S. Effect of cigarette smoking on white blood cells and erythrocyte enzymes. *Archives of Environmental Health* 1982;37(5): 261–5.

Heintze U. Secretion rate, buffer effect and number of lactobacilli and Streptococcus mutans of whole saliva of cigarette smokers and nonsmokers. *Scandinavian Journal of Dental Research* 1984;92(4):294–301.

Helman N, Rubenstein LS. The effects of age, sex, and smoking on erythrocytes and leukocytes. *American Journal of Clinical Pathology* 1975;63(1):35–44.

Hemenway D, Colditz GA, Willett WC, Stampfer MJ, Speizer FE. Fractures and lifestyle: effect of cigarette smoking, alcohol intake, and relative weight on the risk of hip and forearm fractures in middle-aged women. *American Journal of Public Health* 1988;78(12): 1554–8.

Hendrix WH, Taylor GS. A multivariate analysis of the relationship between cigarette smoking and absence from work. *American Journal of Health Promotion* 1987;2(2):5–11.

Hentschel E, Brandstätter G, Dragosics B, Hirschl AM, Nemec H, Schütze K, Taufer M, Wurzer H. Effect of

ranitidine and amoxicillin plus metronidazole on the eradication of *Helicobacter pylori* and the recurrence of duodenal ulcer. *New England Journal of Medicine* 1993;328(5):308–12.

Hermann AP, Brot C, Gram J, Kolthoff N, Mosekilde L. Premenopausal smoking and bone density in 2015 perimenopausal women. *Journal of Bone and Mineral Reseach* 2000;15(4):780–7.

Hildebolt CF, Pilgram TK, Dotson M, Yokoyama-Crothers N, Muckerman J, Hauser J, Cohen S, Kardaris E, Vannier MW, Hanes P, Shrout MK, Civitelli R. Attachment loss with postmenopausal age and smoking. *Journal of Periodontal Research* 1997;32(7):619–25.

Hiller R, Sperduto RD, Podgor MJ, Wilson PWF, Ferris FL III, Colton T, D'Agostino RB, Roseman MJ, Stockman ME, Milton RC. Cigarette smoking and the risk of development of lens opacities: the Framingham studies. *Archives of Ophthalmology* 1997;115(9): 1113–8.

Hirsch JM, Livian G, Edward S, Noren JG. Tobacco habits among teenagers in the city of Göteborg, Sweden, and possible association with dental caries. *Swedish Dental Journal* 1991;15(3):117–23.

Hirshkowitz M, Karacan I, Howell JW, Arcasoy MO, Williams RL. Nocturnal penile tumescence in cigarette smokers with erectile dysfunction. *Urology* 1992;39(2):101–7.

Hodgson TA. Cigarette smoking and lifetime medical expenditures. *Milbank Quarterly* 1992;70(1):81–125.

Hogarty V, May H, Khaw KT. White blood cell count, blood pressure, and cigarette smoking in older adults. *Journal of American Geriatric Society* 1995; 43(7):837–8.

Høidrup S, Grønbæk M, Pedersen AT, Lauritzen JB, Gottschau A, Schroll M. Hormone replacement therapy and hip fracture risk: effect modification by tobacco smoking, alcohol intake, physical activity, and body mass index. *American Journal of Epidemiology* 1999;150(10):1085–93.

Høidrup S, Prescott E, Sørensen TIA, Gottschau A, Lauritzen JB, Schroll M, Grønbaek M. Tobacco smoking and risk of hip fracture in men and women. *International Journal of Epidemiology* 2000;29(2): 253–9.

Holbrook TL, Barrett-Connor E, Wingard DL. Dietary calcium and risk of hip fracture: 14-year prospective population study. *Lancet* 1988;2(8619):1046–9.

Holcomb HS III, Meigs JW. Medical absenteeism among cigarette, and cigar and pipe smokers. *Archives of Environmental Health* 1972;25(4):295–300.

Hollenbach KA, Barrett-Connor E, Edelstein SL, Holbrook T. Cigarette smoking and bone mineral density in older men and women. *American Journal of Public Health* 1993;83(9):1265–70.

Hollinger JO, Schmitt JM, Hwang K, Soleymani P, Buck D. Impact of nicotine on bone healing. *Journal of Biomedical Materials Research* 1999;45(4):294–301.

Holló I, Gergely I, Boross M. Influence of heavy smoking upon the bone mineral content of the radius of the aged and effect of tobacco smoke on the sensitivity to calcitonin of rats. *Aktuelle Gerontologie* 1979;9(8):365–8.

Honkanen R, Tuppurainen M, Kröger H, Alhava E, Saarikoski S. Relationships between risk factors and fractures differ by type of fracture: a population-based study of 12,192 perimenopausal women. *Osteoporosis International* 1998;8(1):25–31.

Hopper JL, Seeman E. The bone density of female twins discordant for tobacco use. *New England Journal of Medicine* 1994;330(6):387–92.

Horning GM, Hatch CL, Cohen ME. Risk indicators for periodontitis in a military treatment population. *Journal of Periodontology* 1992;63(4):297–302.

Hovell MF, Slymen DJ, Jones JA, Hofstetter CR, Burkham-Kreitner S, Conway TL, Rubin B, Noel D. An adolescent tobacco-use prevention trial in orthodontic offices. *American Journal of Public Health* 1996;86(12):1760–6.

Howell RW. Smoking habits and laboratory tests. *Lancet* 1970;2(7664):152.

Hui SL, Slemenda CW, Johnston CC Jr. Baseline measurement of bone mass predicts fracture in white women. *Annals of Internal Medicine* 1989;111(5): 355–61.

Huopio J, Kröger H, Honkanen R, Saarikoski S, Alhava E. Risk factors for perimenopausal fractures: a prospective study. *Osteoporosis International* 2000;11(3): 219–27.

Husgafvel-Pursiainen K. Sister-chromatid exchange and cell proliferation in cultured lymphocytes of passively and actively smoking restaurant personnel. *Mutation Research* 1987;190(3):211–5.

Huuskonen J, Väisänen SB, Kröger H, Jurvelin C, Bouchard C, Alhava E, Rauramaa R. Determinants of bone mineral density in middle-aged men: a population-based study. *Osteoporosis International* 2000;11(8):702–8.

Hyman LG, Lilienfeld AM, Ferris FL III, Fine SL. Senile macular degeneration: a case-control study. *American Journal of Epidemiology* 1983;118(2):213–27.

Imaki M, Yoshida Y, Tanada S. Relation between smoking and periodontal disease by oral hygiene status in Japanese factory workers. *Applied Human Science* 1997;16(2):77–81.

Ismail AI, Burt BA, Eklund SA. Epidemiologic patterns of smoking and periodontal disease in the United States. *Journal of the American Dental Association* 1983;106(5):617–21.

Ismail AI, Morrison EC, Burt BA, Caffesse RG, Kavanagh MT. Natural history of periodontal disease in adults: findings from the Tecumseh Periodontal Disease Study, 1959–87. *Journal of Dental Research* 1990;69(2):430–5.

Italian-American Cataract Study Group. Risk factors for age-related cortical, nuclear, and posterior subcapsular cataracts. *American Journal of Epidemiology* 1991;133(6):541–53.

Jackson SE, Chenoweth D, Glover ED, Holbert D, White D. Study indicates smoking cessation improves workplace absenteeism rate. *Occupational Health and Safety* 1989;58(13):13, 15–6, 18.

Jacqmin-Gadda H, Fourrier A, Commenges D, Dartigues J-F. Risk factors for fractures in the elderly. *Epidemiology* 1998;9(4):417–23.

Jaglal SB, Kreiger N, Darlington G. Past and recent physical activity and risk of hip fracture. *American Journal of Epidemiology* 1993;138(2):107–18.

James JA, Sayers NM, Drucker DB, Hull PS. Effects of tobacco products on the attachment and growth of periodontal ligament fibroblasts. *Journal of Periodontology* 1999;70(5):518–25.

Janzon L, Lindell SE, Trell E, Larme P. Smoking habits and carboxyhaemoglobin: a cross-sectional study of an urban population of middle-aged men. *Journal of Epidemiology and Community Health* 1981;35(4):271–3.

Jeffrey RW, Forster JL, Baxter JE, French SA, Kelder SH. An empirical evaluation of the effectiveness of tangible incentives in increasing participation and behavior change in a worksite health promotion program. *American Journal of Health Promotion* 1993;8(2):98–100.

Jensen GF. Osteoporosis of the slender smoker revisited by epidemiologic approach. *European Journal of Clinical Investigation* 1986;16(3):239–42.

Jensen JS. Determining factors for the mortality following hip fractures. *Injury* 1984;15(6):411–4.

Jensen EJ, Pedersen B, Fredericksen R, Dahl R. Prospective study on the effect of smoking and nicotine substitution on leucocyte blood counts and relation between blood leucocytes and lung function. *Thorax* 1998;53(9):784–9.

Jensen J, Christiansen C. Effects of smoking on serum lipoproteins and bone mineral content during postmenopausal hormone replacement therapy. *American Journal of Obstetrics and Gynecology* 1988;159(4):820–5.

Jensen J, Christiansen C, Rødbro P. Cigarette smoking, serum estrogens, and bone loss during hormone-replacement therapy early after menopause. *New England Journal of Medicine* 1985;313(16):973–5.

Jensen JS, Tondevold E. Mortality after hip fractures. *Acta Orthopaedica Scandinavica* 1979;50(2):161–7.

Jette AM, Feldman HA, Tennstedt SL. Tobacco use: a modifiable risk factor for dental disease among the elderly. *American Journal of Public Health* 1993;83(9):1271–6.

Johannes CB, Araujo AB, Feldman HA, Derby CA, Kleinman KP, McKinlay JB. Incidence of erectile dysfunction in men 40 to 69 years old: longitudinal results from the Massachusetts Male Aging Study. *Journal of Urology* 2000;163(2):460–3.

Johansson C, Mellström D, Lerner U, Österberg T. Coffee drinking: a minor risk factor for bone loss and fractures. *Age and Ageing* 1992;21(1):20–6.

Johnell O, Nilsson BE. Life-style and bone mineral mass in perimenopausal women. *Calcified Tissue International* 1984;36(4):354–6.

Johnson GK, Fung YK, Squier CA. Effects of systemic administration of nicotine on capillaries in rat oral mucosa. *Journal of Oral Pathology and Medicine* 1989;18(4):230–2.

Johnson GK, Todd GL, Johnson WT, Fung YK, Dubois LM. Effects of topical and systemic nicotine on gingival blood flow in dogs. *Journal of Dental Research* 1991;70(5):906–9.

Jones G, Nguyen T, Sambrook P, Kelly PJ, Eisman JA. Progressive loss of bone in the femoral neck in elderly people: longitudinal findings from the Dubbo osteoporosis epidemiology study. *British Medical Journal* 1994;309(6956):691–5.

Jones G, Scott FS. A cross-sectional study of smoking and bone mineral density in premenopausal parous women: effect of body mass index, breastfeeding, and sports participation. *Journal of Bone and Mineral Research* 1999;14(9):1628–33.

Jones RC, Bly JL, Richardson JE. A study of a work site health promotion program and absenteeism. *Journal of Occupational Medicine* 1990;32(2):95–9.

Jorgensen LN, Kallehave F, Christensen E, Siana JE, Gottrup F. Less collagen production in smokers. *Surgery* 1998;123(4):450–5.

Joung IMA, Stronks K, van de Mheen H, Mackenbach JP. Health behaviors explain part of the differences in self-reported health associated with partner/marital status in The Netherlands. *Journal of Epidemiology and Community Health* 1995;49(5):482–8.

Juenemann K-P, Lue TF, Luo J-A, Benowitz NL, Abozeid M, Tanagho EA. The effect of cigarette

smoking on penile erection. *Journal of Urology* 1987;138(2):438–41.

Jyotheeswaran S, Shah AN, Jin HO, Potter GD, Ona FV, Chey WY. Prevalence of *Helicobacter pylori* in peptic ulcer patients in Greater Rochester, NY: is empirical triple therapy justified? *American Journal of Gastroenterology* 1998;93(4):574–8.

Kadayifçi A, Simsek H. Does smoking influence the eradication of *Helicobacter pylori* and duodenal ulcer healing with different regimens? *International Journal of Clinical Practice* 1997;51(8):516–7.

Kadioğlu A, Erdoğru T, Karşida K, Dinççağ N, Satman I, Yilmaz M, Tellaloğlu S. Evaluation of penile arterial system with color Doppler ultrasonography in nondiabetic and diabetic males. *European Urology* 1995; 27(4):311–4.

Kaldahl WB, Johnson GK, Patil KD, Kalkwarf KL. Levels of cigarette consumption and response to periodontal therapy. *Journal of Periodontology* 1996;67(7): 675–81.

Källestål C. Dental caries in 16- and 18-year-old adolescents in northern Sweden. *Scandinavian Journal of Dental Research* 1991;99(2):100–5.

Kallner AB, Hartmann D, Hornig DH. On the requirements of ascorbic acid in man: steady-state turnover and body pool in smokers. *American Journal of Clinical Nutrition* 1981;34(7):1347–55.

Kamada T, Haruma K, Komoto K, Mihara M, Chen X, Yoshihara M, Sumii K, Kajiyama G, Tahara K, Kawamura Y. Effect of smoking and histological gastritis severity on the rate of *Helicobacter pylori* eradication with omeprazole, amoxicillin, and clarithromycin. *Helicobacter* 1999;4(3):204–10.

Kamma JJ, Nakou M, Baehni PC. Clinical and microbiological characteristics of smokers with early onset periodontitis. *Journal of Periodontal Research* 1999; 34(1):25–33.

Kanis J, Johnell O, Gullberg B, Allander E, Elffors L, Ranstam JP, Dequeker J, Dilsen G, Gennari C, Vaz AL, Lyritis G, Mazzuoli G, Miravet L, Passeri M, Cano RP, Rapado A, Ribot C. Risk factors for hip fracture in men from southern Europe: the MEDOS Study. Mediterranean Osteoporosis Study. *Osteoporosis International* 1999;9(1):45–54.

Kaplan RM, Wingard DL, McPhillips JB, Williams-Jones D, Barrett-Connor E. Cigarette smoking, mortality, institutional and community-based care utilization in an adult community. *Journal of Community Health* 1992;17(1):53–60.

Kaprio J, Koskenvuo M. A prospective study of psychological and socioeconomic characteristics, health behavior and morbidity in cigarette smokers prior to quitting compared to persistent smokers and non-smokers. *Journal of Clinical Epidemiology* 1988; 41(2):139–50.

Karacan I, Hirshkowitz M, Howell JW, Arcasoy MO, Acik G, Aydin F, Thornby JI, Williams RL. Smoking more than a pack-per-day has a worsening effect on impotence. *Sleep Research* 1988;17:287.

Karacan I, Salis PJ, Williams RL. The role of the sleep laboratory in diagnosis and treatment of impotence. In: Williams RL, Karacan I, editors. *Sleep Disorders: Diagnosis and Treatment.* New York: John Wiley and Sons, 1978:353–82.

Kassirer B. Smoking as a risk factor for gingival problems, periodontal problems and caries. *University of Toronto Dental Journal* 1994;7(1):6–10.

Kato I, Nomura AMY, Stemmermann GN, Chyou P-H. A prospective study of gastric and duodenal ulcer and its relation to smoking, alcohol, and diet. *American Journal of Epidemiology* 1992;135(5):521–30.

Kato J, Toniolo P, Zeleniuch-Jacquotte A, Shore RE, Koenig KL, Akhmedkhanov A, Riboli E. Diet, smoking and anthropometric indices and postmenopausal bone fractures: a prospective study. *International Journal of Epidemiology* 2000;29(1):85–92.

Katz RV. Assessing root caries in populations: the evolution of the root caries index. *Journal of Public Health Dentistry* 1980;40(1):7–16.

Kazor C, Taylor GW, Loesche WJ. The prevalence of BANA-hydrolyzing periodontopathic bacteria in smokers. *Journal of Clinical Periodontology* 1999; 26(12):814–21.

Kelsey JL, Browner WS, Seeley DG, Nevitt MC, Cummings SR. Risk factors for fractures of the distal forearm and proximal humerus. *American Journal of Epidemiology* 1992;135(5):477–89. [See also erratum in *American Journal of Epidemiology* 1992; 135(10):1183.]

Kelsey JL, Hoffman S. Risk factors for hip fracture. *New England Journal of Medicine* 1987;316(7):404–6.

Kempczinski RF. Role of the vascular diagnostic laboratory in the evaluation of male impotence. *American Journal of Surgery* 1979;138(2):278–82.

Kenney EB, Kraal JH, Saxe SR, Jones J. The effect of cigarette smoke on human oral polymorphonuclear leukocytes. *Journal of Periodontal Research* 1977;12(4): 227–34.

Kenzora JE, McCarthy RE, Lowell JD, Sledge CB. Hip fracture mortality: relation to age, treatment, preoperative illness, time of surgery, and complications. *Clinical Orthopaedics and Related Research* 1984;186: 45–56.

Kerdvongbundit V, Wikesjö UME. Effect of smoking on periodontal health in molar teeth. *Journal of Periodontology* 2000;71(3):433–7.

Khaw K-T, Tazuke S, Barrett-Connor E. Cigarette smoking and levels of adrenal androgens in postmenopausal women. *New England Journal of Medicine* 1988; 318(26):1705–9.

Khosla S, Melton LJ III, Atkinson EJ, O'Fallon WM, Klee GG, Riggs BL. Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men and women: a key role for bioavailable estrogen. *Journal of Clinical Endocrinology and Metabolism* 1998;83(7):2266–74.

Kiel DP, Baron JA, Anderson JJ, Hannan MT, Felson DT. Smoking eliminates the protective effect of oral estrogens on the risk for hip fracture among women. *Annals of Internal Medicine* 1992;116(9):716–21.

Kiel DP, Felson DT, Anderson JJ, Wilson PWF, Moskowitz MA. Hip fracture and the use of estrogens in postmenopausal women: the Framingham Study. *New England Journal of Medicine* 1987;317(19): 1169–74.

Kiel DP, Zhang Y, Hannan MT, Anderson JJ, Baron JA, Felson DT. The effect of smoking at different life stages on bone mineral density in elderly men and women. *Osteoporosis International* 1996;6(3):240–8.

Kim C-H, Kim YI, Choi CS, Park JY, Lee MS, Lee S-I, Kim GS. Prevalence and risk factors of low quantitative ultrasound values of calcaneus in Korean elderly women. *Ultrasound in Medicine and Biology* 2000;26(1):35–40.

Kinane DF, Radvar M. The effect of smoking on mechanical and antimicrobial periodontal therapy. *Journal of Periodontology* 1997;68(5):467–72.

Kingsley LA, Dorman JS, Doft BH, Orchard TJ, LaPorte RE, Kuller LH, Drash AL. An epidemiologic approach to the study of retinopathy: the Pittsburgh diabetic morbidity and retinopathy studies. *Diabetes Research and Clinical Practice* 1988;4(2):99–109.

Kinsella JB, Rassekh CH, Wassmuth ZD, Hokanson JA, Calhoun KH. Smoking increases facial skin flap complications. *Annals of Otology, Rhinology and Laryngology* 1999;108(2):139–42.

Kiyosawa H, Suko M, Okudaira H, Murata K, Miyamoto T, Chung M-H, Kasai H, Nishimura S. Cigarette smoking induces formation of 8-hydroxydeoxyguanosine, one of the oxidative DNA damages in human peripheral leukocytes. *Free Radical Research Communications* 1990;11(1-3):23–7.

Kleerekoper M, Peterson E, Nelson D, Tilley B, Phillips E, Schork MA, Kuder J. Identification of women at risk for developing postmenopausal osteoporosis with vertebral fractures: role of history and single photon absorptiometry. *Bone and Mineral* 1989;7(2): 171–86.

Klein BE, Klein R, Moss SE. Prevalence of cataracts in a population-based study of persons with diabetes mellitus. *Ophthalmology* 1985;92(9):1191–6.

Klein BE, Klein R, Ritter LL. Relationship of drinking alcohol and smoking to prevalence of open-angle glaucoma: the Beaver Dam Eye Study. *Ophthalmology* 1993a;100(11);1609–13.

Klein BEK, Klein R, Linton KLP, Franke T. Cigarette smoking and lens opacities: the Beaver Dam Eye Study. *American Journal of Preventive Medicine* 1993b;9(1):27–30.

Klein H, Palmer CE, Knutson JW. Studies on dental caries. I: dental status and dental needs of elementary school children. *Public Health Reports* 1938; 53:751–65.

Klein R, Klein BE, Jensen SC, Meuer SM. The five-year incidence and progression of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology* 1997;104(1):7–21.

Klein R, Klein BE, Linton KL. Prevalence of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology* 1992;99(6):933–43.

Klein R, Klein BE, Moss SE. Relation of smoking to the incidence of age-related maculopathy: the Beaver Dam Eye Study. *American Journal of Epidemiology* 1998;147(2):103–10.

Klein R, Klein BEK, Davis MD. Is cigarette smoking associated with diabetic retinopathy? *American Journal of Epidemiology* 1983;118(2):228–38.

Klein R, Klein BEK, Linton KLP, DeMets DL. The Beaver Dam Eye Study: the relation of age-related maculopathy to smoking. *American Journal of Epidemiology* 1993c;137(2):190–200.

Klein R, Klein BEK, Moss SE, Cruickshanks KJ. The Wisconsin Epidemiologic Study of Diabetic Retinopathy XV: the long-term incidence of macular edema. *Ophthalmology* 1995;102(1):7–16.

Kleinman KP, Feldman HA, Johannes CB, Derby CA, McKinlay JB. A new surrogate variable for erectile dysfunction status in the Massachusetts male aging study. *Journal of Clinical Epidemiology* 2000;53(1): 71–8.

Knoke JD, Hunninghake DB, Heiss G. Physiological markers of smoking and their relation to coronary heart disease: the Lipid Research Clinics Coronary Primary Prevention Trial. *Atherosclerosis* 1987;7(5): 477–82.

Komulainen M, Kröger H, Tuppurainen MT, Heikkinen A-M, Honkanen R, Saarikoski S. Identification of early postmenopausal women with no bone response to HRT: results of a five-year clinical trial. *Osteoporosis International* 2000;11(3):211–8.

Kornman KS, di Giovine FS. Genetic variations in cytokine expression: a risk factor for severity of adult periodontitis. *Annals of Periodontology* 1998; 3(1):327–38.

Kosunen TU, Aromaa A, Knekt P, Salomaa A, Rautelin H, Lohi P, Heinonen OP. *Helicobacter* antibodies in 1973 and 1994 in the adult population of Vammala, Finland. *Epidemiology and Infection* 1997;119(1): 29–34.

Kotani N, Hashimoto H, Sessler DI, Yoshida H, Kimura N, Okawa H, Muraoka M, Matsuki A. Smoking decreases alveolar macrophage function during anesthesia and surgery. *Anesthesiology* 2000;92(5): 1268–77.

Krall EA, Dawson-Hughes B. Smoking and bone loss among postmenopausal women. *Journal of Bone and Mineral Research* 1991;6(4):331–8.

Krall EA, Dawson-Hughes B. Smoking increases bone loss and decreases intestinal calcium absorption. *Journal of Bone and Mineral Research* 1999;14(2): 215–20.

Kreiger N, Gross A, Hunter G. Dietary factors and fracture in postmenopausal women: a case-control study. *International Journal of Epidemiology* 1992;21(5): 953–8.

Kreiger N, Kelsey JL, Holford TR, O'Connor T. An epidemiologic study of hip fracture in postmenopausal women. *American Journal of Epidemiology* 1982;116(1):141–8.

Kreutzfeldt J, Haim M, Bach E. Hip fracture among the elderly in a mixed urban and rural population. *Age and Ageing* 1984;13(2):111–9.

Kristein MM. How much can business expect to profit from smoking cessation? *Preventive Medicine* 1983;12(2):358–81.

Kroger H, Kotaniemi A, Vainio P, Alhava E. Bone densitometry of the spine and femur in children by dual-energy x-ray absorptiometry. *Bone and Mineral* 1992;17(1):75–85. [See also erratum in *Bone and Mineral* 1992;17(3):429.]

Kroll SS, Schusterman MA, Reece GP, Miller MJ, Evans GR, Robb GL, Baldwin B. Choice of flap and incidence of free flap success. *Plastic Reconstruction and Surgery* 1996;98(3):459–63.

Kuipers EJ, Thijs JC, Festen HPM. The prevalence of *Helicobacter pylori* in peptic ulcer disease. *Alimentary Pharmacology and Therapeutics* 1995;9(Suppl 2):59–69.

Kurata JH, Elashoff JD, Nogawa AN, Haile BM. Sex and smoking differences in duodenal mortality. *American Journal of Public Health* 1986;76(6):700–2.

La Vecchia C, Negri E, Levi F, Baron JA. Cigarette smoking, body mass and other risk factors for fractures of the hip in women. *International Journal of Epidemiology* 1991;20(3):671–7.

Labenz J, Börsch G. Evidence for the essential role of *Helicobacter pylori* in gastric ulcer disease. *Gut* 1994; 35(1):19–22.

Labenz J, Leverkus F, Börsch G. Omeprazole plus amoxicillin for cure of *Helicobacter pylori* infection: factors influencing the treatment success. *Scandinavian Journal of Gastroenterology* 1994;29(12):1070–5.

Labenz K, Peitz U, Köhl H, Kaiser J, Malfertheiner P, Hackelsberger A, Börsch G. *Helicobacter pylori* increases the risk of peptic ulcer bleeding: a case-control study. *Italian Journal of Gastroenterology and Hepatology* 1999;31(2):110–5.

Lagorio S, Tagesson C, Forastiere F, Iavarone I, Axelson O, Carere A. Exposure to benzene and urinary concentrations of 8-hydroxydeoxyguanosine, a biological marker of oxidative damage to DNA. *Occupational and Environmental Medicine* 1994;51(11): 739–43.

Lam SK. Treatment of duodenal ulcer with sucralfate. *Scandinavian Journal of Gastroenterology* 1991; 26(Suppl 185):22–8.

Lam SK. Why do ulcers heal with sucralfate? *Scandinavian Journal of Gastroenterology* 1990;25(Suppl 173):6–16.

Lambert JR. Clinical indications and efficacy of colloidal bismuth subcitrate. *Scandinavian Journal of Gastroenterology* 1991;26(Suppl 185):13–21.

Lanas A, Serrano P, Bajador E, Esteva F, Benito R, Sáinz R. Evidence of aspirin use in both upper and lower gastrointestinal perforation. *Gastroenterology* 1997;112(3):683–9.

Lau E, Donnan S, Barker DJP, Cooper C. Physical activity and calcium intake in fracture of the proximal femur in Hong Kong. *British Medical Journal* 1988;297(6661):1441–3.

Lau EMC, Chan YH, Chan M, Woo J, Griffith J, Chan HHL, Leung PC. Vertebral deformity in Chinese men: prevalence, risk factors, bone mineral density, and body composition measurements. *Calcified Tissue International* 2000;66(1):47–52.

Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. *Journal of the American Medical Association* 1999;281(6): 537–44.

Lavernia CJ, Sierra RJ, Gomez-Marin O. Smoking and joint replacement: resource consumption and short-term outcome. *Clinical Orthopaedics* 1999;367:172–80.

Lavstedt S, Modéer T, Welander E. Plaque and gingivitis in a group of Swedish schoolchildren with special reference to toothbrushing habits. *Acta Odontologica Scandinavica* 1982;40(5):307–11.

Law MR, Cheng R, Hackshaw AK, Allaway S, Hale AK. Cigarette smoking, sex hormones and bone density in women. *European Journal of Epidemiology* 1997;13(5):553–8.

Law MR, Hackshaw AK. A meta-analysis of cigarette smoking, bone mineral density and risk of hip fracture: recognition of a major effect. *British Medical Journal* 1997;315(7112):841–6.

Leanderson P, Tagesson C. Cigarette smoke-induced DNA-damage: role of hydroquinone and catechol in the formation of oxidative DNA-adduct, 8-hydroxydeoxyguanosine. *Chemico-Biological Interactions* 1990;75(1):71–81.

Leanderson P, Tagesson C. Cigarette smoke-induced DNA damage in cultured human lung cells: role of hydroxyl radicals and endonuclease activation. *Chemico-Biological Interactions* 1992;81(1-2):197–208.

Lee BM, Lee SK, Kim HS. Inhibition of oxidative DNA damage, 8-OHdG, and carbonyl contents in smokers treated with antioxidants (vitamin E, vitamin C, ß-carotene and red ginseng). *Cancer Letters* 1998; 132(1-2):219–27.

Leigh JP. Sex differences in absenteeism. *Industrial Relations* 1983;22(3):349–61.

Leigh JP, Fries JF. Health habits, health care use and costs in a sample of retirees. *Inquiry* 1992;29(1): 44–54.

Leijon M, Mikaelsson B. Repeated short-term sick-leave as a possible symptom of psycho-social problems. *Scandinavian Journal of Social Medicine* 1984;12(4):165–9.

Leske MC, Chylack LT Jr, He Q, Wu S-Y, Schoenfeld E, Friend J, Wolfe J, the LSC Group. Risk factors for nuclear opalescence in a longitudinal study. *American Journal of Epidemiology* 1998;147(1):36–41.

Leske MC, Chylack LT Jr, Wu S-Y, the Lens Opacities Case-Control Study Group. The Lens Opacities Case-Control Study: risk factors for cataract. *Archives of Ophthalmology* 1991;109(2):244–51.

Leske MC, Connell AMS, Wu S-Y, Hyman LG, Schachat AP, the Barbados Eye Study Group. Risk factors for open-angle glaucoma: the Barbados Eye Study. *Archives of Ophthalmology* 1995;113(7):918–24.

Levine L, Gerber G. Acute vasospasm of penile arteries in response to cigarette smoking [letter]. *Urology* 1990;36(1):99–100.

Levy SM, Heckert DA, Beck JD, Kohout FJ. Multivariate correlates of periodontally healthy teeth in an elderly population. *Gerodontics* 1987;3(2):85–8.

Lie MA, van der Weijden GA, Timmerman MF, Loos BG, van Steenbergen TJM, van der Velden U. Oral microbiota in smokers and non-smokers in natural and experimentally-induced gingivitis. *Journal of Clinical Periodontology* 1998;25(8):677–86.

Liede KE, Haukka JK, Hietanen JHP, Mattila MH, Rönka H, Sorsa T. The association between smoking cessation and periodontal status and salivary proteinase levels. *Journal of Periodontology* 1999; 70(11):1361–8.

Lilienfeld AM. Emotional and other selected characteristics of cigarette smokers and nonsmokers as related to epidemiological studies of lung cancer and other diseases. *Journal of the National Cancer Institute* 1959;22(2):259–82.

Lin SK, Lambert JR, Nicholson L, Lukito W, Wahlqvist M. Prevalence of *Helicobacter pylori* in a representative Anglo-Celtic population of urban Melbourne. *Journal of Gastroenterology and Hepatology* 1998;13(5): 505–10.

Linden GJ, Mullally BH. Cigarette smoking and periodontal destruction in young adults. *Journal of Periodontology* 1994;65(7):718–23.

Lindenthal JK, Myers JK, Pepper M. Smoking, psychological status and stress. *Social Science and Medicine* 1972;6(5):583–91.

Lindquist LW, Carlsson GE, Jemt T. Association between marginal bone loss around osseointegrated mandibular implants and smoking habits: a 10-year follow-up study. *Journal of Dental Research* 1997; 76(10):1667–74.

Locker D. Smoking and oral health in older adults. *Canadian Journal of Public Health* 1992;83(6):429–32.

Locker D. Incidence of root caries in an older Canadian population. *Community Dentistry and Oral Epidemiology* 1996;24(6):403–7.

Locker D, Leake JL. Risk indicators and risk markers for periodontal disease experience in older adults living independently in Ontario, Canada. *Journal of Dental Research* 1993;72(1):9–17.

Lodovici M, Casalini C, Cariaggi R, Michelucci L, Dolara P. Levels of 8-hydroxydeoxyguanosine as a marker of DNA in human damage in human leukocytes. *Free Radical Biology and Medicine* 2000;28(1): 13–7.

Loft S, Vistisen K, Ewertz M, Tjønneland A, Overvad K, Poulsen HE. Oxidative DNA damage estimated by 8-hydroxydeoxyguanosine excretion in humans: influence of smoking, gender and body mass index. *Carcinogenesis* 1992;13(12):2241–7.

Lötborn M, Bratteby L-E, Samuelson G, Ljunghall S, Sjöström L. Whole-body bone mineral measurements in 15-year-old Swedish adolescents. *Osteoporosis International* 1999;9(2):106–14.

Low I, Mitchell C. Absence and labour turnover in a foundry attributable to respiratory disease. *Journal of Social and Occupational Medicine* 1991;41(4):185–7.

Lowe CR. Smoking habits related to injury and absenteeism in industry. *British Journal of Preventive and Social Medicine* 1960;14:57–63.

Lu PW, Cowell CT, Lloyd-Jones SA, Briody JN, Howman-Giles R. Volumetric bone mineral density in normal subjects, aged 5–27 years. *Journal of Clinical Endocrinology and Metabolism* 1996;81(4):1586–90.

Ludwick W, Massler M. Relation of dental caries experience and gingivitis to cigarette smoking in males 17 to 21 years old (at the Great Lakes Naval Training Center). *Journal of Dental Research* 1952;31(3): 319–22.

Lue TF, Tanagho EA. Physiology of erection and pharmacologic management of impotence. *Journal of Urology* 1987;137(5):829–36.

Lykkesfeldt J, Loft S, Nielsen JB, Poulsen HE. Ascorbic acid and dehydroascorbic acid as biomarkers of oxidative stress caused by smoking. *American Journal of Clinical Nutrition* 1997;65(4):959–63.

Lyons RA, Lo SV, Littlepage NC. Perception of health amongst ever-smokers and never-smokers: a comparison using the SF-36 Health Survey Questionnaire. *Tobacco Control* 1994;3(3):213–5.

MacFarlane GD, Herzberg MC, Wolff LF, Hardie NA. Refractory periodontitis associated with abnormal polymorphonuclear leukocyte phagocytosis and cigarette smoking. *Journal of Periodontology* 1992;63(11):908–13.

Macgregor IDM. Effects of smoking on oral ecology: a review of the literature. *Clinical Preventive Dentistry* 1989;11(1):3–7.

Macgregor ID, Rugg-Gunn AJ. Toothbrushing sequence in smokers and nonsmokers. *Clinical Preventive Dentistry* 1986;8(2):17–20.

Macgregor IDM, Edgar WM, Greenwood AR. Effects of cigarette smoking on the rate of plaque formation. *Journal of Clinical Periodontology* 1985;12(1): 35–41.

Machtei EE, Dunford R, Hausmann E, Grossi SG, Powell J, Cummins D, Zambon JJ, Genco RJ. Longitudinal study of prognostic factors in established periodontitis patients. *Journal of Clinical Periodontology* 1997;24(2):102–9.

Machtei EE, Hausmann E, Dunford R, Grossi S, Ho A, Davis G, Chandler J, Zambon JJ, Genco RJ. Longitudinal study of predictive factors for periodontal disease and tooth loss. *Journal of Clinical Periodontology* 1999;26(6):374–80.

Machtei EE, Hausmann E, Schmidt M, Grossi SG, Dunford R, Schifferle R, Munoz K, Davies G, Chandler J, Genco RJ. Radiographic and clinical responses to periodontal therapy. *Journal of Periodontology* 1998;69(5):590–5.

Machuca G, Rosales I, Lacalle JR, Machuca C, Bullón P. Effect of cigarette smoking on periodontal status of healthy young adults. *Journal of Periodontology* 2000;71(1):73–8.

Macnee CL. Perceived well-being of persons quitting smoking. *Nursing Research* 1991;40(4):200–3.

Macular Photocoagulation Study Group. Recurrent choroidal neovascularization after argon laser photocoagulation for neovascular maculopathy. *Archives of Ophthalmology* 1986;104(4):503–12.

Macular Photocoagulation Study Group. Risk factors for choroidal neovascularization in the second eye of patients with juxtafoveal or subfoveal choroidal neovascularization secondary to age-related macular degeneration. *Archives of Ophthalmology* 1997; 115(6):741–7.

Malaty HM, Evans DG, Evans DJ Jr, Graham DY. *Helicobacter pylori* in Hispanics: comparison with blacks and whites of similar age and socioeconomic class. *Gastroenterology* 1992;103(3):813–6.

Mallmin H, Ljunghall S, Persson I, Bergström R. Risk factors for fractures of the distal forearm: a population-based case-control study. *Osteoporosis International* 1994;4(6):298–304.

Maltzman BA, Mulvihill MN, Greenbaum A. Senile macular degeneration and risk factors: a case-control study. *Annals of Ophthalmology* 1979;11(8): 1197–201.

Manderbacka K, Lunberg O, Martikainen P. Do risk factors and health behaviours contribute to self-ratings of health. *Social Science and Medicine* 1999;48(12):1713–20.

Manning MR, Osland JS, Osland A. Work-related consequences of smoking cessation. *Academy of Management Journal* 1989;32(3):606–21.

Mannino DM, Klevens RM, Flanders WD. Cigarette smoking: an independent risk factor for impotence? *American Journal of Epidemiology* 1994;140(11): 1003–8.

Marangon K, Herbeth B, Lecomte E, Paul-Dauphin A, Grolier P, Chancerelle Y, Artur Y, Siest G. Diet, antioxidant status, and smoking habits in French men. *American Journal of Clinical Nutrition* 1998;67(2): 231–9.

Markkanen H, Paunio I, Tuominen R, Rajala M. Smoking and periodontal disease in the Finnish population aged 30 years and over. *Journal of Dental Research* 1985;64(6):932–5.

Marmot MG, North F, Feeney A, Head J. Alcohol consumption and sickness absence: from the Whitehall II study. *Addiction* 1993;88(3):369–82.

Marsden ME, Bray RM, Herbold JR. Substance use and health among U.S. military personnel: findings from the 1985 Worldwide Survey. *Preventive Medicine* 1988;17(3):366–76.

Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* 1984;1(8390):1311–5.

Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *British Medical Journal* 1996;312(7041):1254–9.

Marshall G, Garg SK, Jackson WE, Holmes DL, Chase HP. Factors influencing the onset and progression of diabetic retinopathy in subjects with insulin-dependent diabetes mellitus. *Ophthalmology* 1993; 100(8):1133–9.

Martin DF, Montgomery E, Dobek AS, Patrissi GA, Peura DA. *Campylobacter pylori*, NSAIDS, and smoking: risk factors for peptic ulcer disease. *American Journal of Gastroenterology* 1989;84(10):1268–72.

Martin-Morales A, Sanchez-Cruz JJ, Saenz de Tejada I, Rodriguez-Vela L, Jimenez-Cruz JF, Burgos-Rodriguez R. Prevalence and independent risk factors for erectile dysfunction in Spain: results of the Epidemiologia de la Disfuncion Erectil Masculina Study. *Journal of Urology* 2001;166(2):569–75.

Martinez-Canut P, Lorca A, Magán R. Smoking and periodontal disease severity. *Journal of Clinical Periodontology* 1995;22(10):743–9.

Matarazzo JD, Saslow G. Psychological and related characteristics of smokers and nonsmokers. *Psychological Bulletin* 1960;57(6):493–513.

Mazess RB. On aging bone loss. *Clinical Orthopaedics and Related Research* 1982;165:239–52.

Mazess RB, Barden HS. Bone density in premenopausal women: effects of age, dietary intake, physical activity, smoking, and birth-control pills. *American Journal of Clinical Nutrition* 1991;53(1):132–42.

McClean HE, Dodds PM, Abernethy MH, Stewart AW, Beaven DW. Vitamin C concentration in plasma and leucocytes of men related to age and smoking habit. *New Zealand Medical Journal* 1976;83(561):226–9.

McCulloch RG, Bailey DA, Houston CS, Dodd BL. Effects of physical activity, dietary calcium intake and selected lifestyle factors on bone density in young women. *Canadian Medical Association Journal* 1990;142(3):221–7.

McDermott MT, Witte MC. Bone mineral content in smokers. *Southern Medical Journal* 1988;81(4):477–80.

McGuire MK, Nunn ME. Prognosis versus actual outcome. II: the effectiveness of clinical parameters in developing an accurate prognosis. *Journal of Periodontology* 1996;67(7):658–65.

Medina C, Vergara M, Casellas F, Lara F, Naval J, Malagelada JR. Influence of the smoking habit in the surgery of inflammatory bowel disease. *Revista Espanola de Enfermedades Digestivas* 1998;90(11): 771–8.

Melhus H, Michaëlsson K, Holmberg L, Wolk A, Ljunghall S. Smoking, antioxidant vitamins, and the risk of hip fracture. *Journal of Bone and Mineral Research* 1999;14(1):129–35.

Mellstrom D, Rundgren A, Jagenburg R, Steen B, Svanborg A. Tobacco smoking, ageing and health among the elderly: a longitudinal population study of 70-year-old men and an age cohort comparison. *Age and Ageing* 1982;11(1):45–58.

Melman A, Gingell JC. The epidemiology and pathophysiology of erectile dysfunction. *Journal of Urology* 1999;161(1):5–11.

Melton LJ III, O'Fallon WM, Riggs BL. Secular trends in the incidence of hip fractures. *Calcified Tissue International* 1987;41(2):57–64.

Melton LJ III, Riggs BL. Epidemiology of age-related fractures. In: Avioli LV, editor. *The Osteoporotic Syndrome: Detection, Prevention, and Treatment.* Orlando (FL): Grune & Stratton, 1987:1–30.

Mercelina-Roumans PE, Ubachs JM, van Wersch JW. Leucocyte count and leucocyte differential in smoking and non-smoking females during pregnancy. *European Journal of Obstetrics and Gynecology and Reproductive Biology* 1994;55(3):169–73.

Merrill JC, Kleber HD, Shwartz M, Liu H, Lewis SR. Cigarettes, alcohol, marijuana, other risk behaviors, and American youth. *Drug and Alcohol Dependence* 1999;56(3):205–12.

Mersdorf A, Goldsmith PC, Diederichs W, Padula CA, Lue TF, Fishman IJ, Tanagho EA. Ultrastructural changes in impotent penile tissue: a comparison of 65 patients. *Journal of Urology* 1991;145(4):749–58.

Metcalfe RA, Weetman AP. Stimulation of extraocular muscle fibroblasts by cytokines and hypoxia: possible role in thyroid-associated ophthalmopathy. *Clinical Endocrinology* 1994;40(1):67–72.

Meyer HE, Tverdal A, Falch JA. Risk factors for hip fracture in middle-aged Norwegian women and men. *American Journal of Epidemiology* 1993;137(11): 1203–11.

Michaelsson K, Holmberg L, Mallmin H, Sorensen S, Wolk A, Bergstrom R, Ljunghall S. Diet and hip fracture risk: a case-control study. Study Group of the

Multiple Risk Survey on Swedish Women for Eating Assessment. *International Journal of Epidemiology* 1995;24(4):771–82.

Michnovicz JJ, Hershcopf RJ, Naganuma H, Bradlow HL, Fishman J. Increased 2-hydroxylation of estradiol as a possible mechanism for the anti-estrogenic effect of cigarette smoking. *New England Journal of Medicine* 1986;315(21):1305–9.

Miller CW. Survival and ambulation following hip fracture. *Journal of Bone and Joint Surgery* 1978;60(7): 930–4.

Miller ER 3rd, Apper LJ, Jiang L, Risby TH. Association between cigarette smoking and lipid peroxidation in a controlled feeding study. *Circulation* 1997;96(4):1097–101.

Miller VP, Ernst C, Collin F. Smoking-attributable medical care costs in the USA. *Social Science and Medicine* 1999;48(3):375–91.

Moayyedi P, Chalmers DM, Axon ATR. Patient factors that predict failure of omeprazole, clarithromycin, and tinidazole to eradicate *Helicobacter pylori*. *Journal of Gastroenterology* 1997;32(1):24–7.

Modéer T, Lavstedt S, Åhlund C. Relation between tobacco consumption and oral health in Swedish schoolchildren. *Acta Odontologica Scandinavica* 1980;38(4):223–7.

Mohan M, Sperduto RD, Angra SK, Milton RC, Mathur RL, Underwood BA, Jaffery N, Pandya CB, Chhabra VK, Vajpayee RB, Kalra VK, Sharma YR. India-US case-control study of age-related cataracts: the India-US Case-Control Study Group. *Archives of Ophthalmology* 1989;107(5):670–6.

Morgado PB, Chen HC, Patel V, Herbert L, Kohner EM. The acute effect of smoking on retinal blood flow in subjects with and without diabetes. *Ophthalmology* 1994;101(7):1220–6.

Morgan RW, Drance SM. Chronic open-angle glaucoma and ocular hypertension: an epidemiological study. *British Journal of Ophthalmology* 1975;59(4): 211–5.

Morrow JD, Frei B, Longmire AW, Gaziano JM, Lynch SM, Shyr Y, Strauss WE, Oates JA, Roberts LJ II. Increase in circulating products of lipid peroxidation (F_2-isoprostanes) in smokers: smoking as a cause of oxidative damage. *New England Journal of Medicine* 1995;332(18):1198–203.

Morrow JD, Roberts LJ II. The isoprostanes: current knowledge and directions for future research. *Biochemical Pharmacology* 1996;51(5):1–9.

Mosca L, Rubenfine M, Tarshis T, Tsai A, Pearson T. Clinical predictors of oxidized low-density lipoprotein in patients with coronary artery disease. *American Journal of Cardiology* 1997;80(1):825–30.

Moss SE, Klein R, Klein BEK. Association of cigarette smoking with diabetic retinopathy. *Diabetes Care* 1991;14(2):119–26.

Moss SE, Klein R, Klein BEK. Cigarette smoking and ten-year progression of diabetic retinopathy. *Ophthalmology* 1996;103(9):1438–42.

Motoyama T, Kawano H, Kugiyama K, Hirashima O, Ohgushi M, Yoshimora M, Ogawa H, Yasue H. Endothelium-dependent vasodilation in the brachial artery is impaired in smokers: effect of vitamin C. *American Journal of Physiology* 1997;273 (4 Pt 2):H1644–H1650.

Mousa SA, Lorelli W, Campochiaro PA. Role of hypoxia and extracellular matrix-integrin binding in the modulation of angiogenic growth factors secretion by retinal pigmented epithelial cells. *Journal of Cellular Biochemistry* 1999;74(1):135–43.

Mühlhauser I, Bender R, Bott U, Jörgens V, Grüsser M, Wagener W, Overmann H, Berger M. Cigarette smoking and progression of retinopathy and nephropathy in type 1 diabetes. *Diabetic Medicine* 1996; 13(6):536–43.

Mühlhauser I, Sawicki P, Berger M. Cigarette-smoking as a risk factor for macroproteinuria and proliferative retinopathy in type 1 (insulin-dependent) diabetes. *Diabetologia* 1986;29(8):500–2.

Mühlhauser I, Verhasselt R, Sawicki PT, Berger M. Leucocyte count, proteinuina and smoking in type 1 diabetes mellitus. *Acta Diabetologica* 1993;30(2): 105–7.

Mullally BH, Breen B, Linden GJ. Smoking and patterns of bone loss in early-onset periodontitis. *Journal of Periodontology* 1999;70(4):394–401.

Mullally BH, Linden GJ. Molar furcation involvement associated with cigarette smoking in periodontal referrals. *Journal of Clinical Periodontology* 1996;23(7): 658–61.

Muñoz B, West SK, Rubin GS, Schein OD, Quigley HA, Bressler SB, Bandeen-Roche K, SEE Study Team. Causes of blindness and visual impairment in a population of older Americans: the Salisbury Eye Evaluation Study. *Archives of Ophthalmology* 2000; 118(6):819–25.

Murray JF. *The Normal Lung: The Basis for Diagnosis and Treatment of Pulmonary Disease.* Philadelphia: W.B. Saunders, 1986.

Murray LJ, McCrum EE, Evans AE, Bamford KB. Epidemiology of *Helicobacter pylori* infection among 4742 randomly selected subjects from Northern Ireland. *International Journal of Epidemiology* 1997; 26(4):880–7.

Mussolino ME, Looker AC, Madans JH, Langlois JA, Orwoll ES. Risk factors for hip fracture in white men:

the NHANES I Epidemiologic Follow-up Study. *Journal of Bone and Mineral Research* 1998;13(6): 918–24.

Nagler R, Lischinsky S, Diamond E, Drigues N, Klein I, Reznick AZ. Effect of cigarette smoke on salivary proteins and enzyme activities. *Archives of Biochemistry and Biophysics* 2000;379(2):229–36.

Nancy NR, Subramanian N, Rai UC. Effect of cigarette smoking on leucocytes in South Indians. *Indian Journal of Physiology and Pharmacology* 1982;26(3): 196–200.

National Advisory Eye Council. *Vision Research—A National Plan: 1999–2003*. Bethesda (MD): U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Eye Institute, 1998. NIH Publication No. 98-4120.

National Institutes of Health. *Changes in Cigarette-Related Disease Risks and Their Implication for Prevention and Control*. Shopland DR, Burns DM, Garfinkel L, Samet JM, editors. Smoking and Tobacco Control Monograph No. 8. Bethesda (MD): US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute, 1997. NIH Publication No. 97-4213.

Naus A, Engler V, Hetychova M, Vavreckova O. Work injuries and smoking. *Industrial Medicine and Surgery* 1966;35(10):880–1.

Nelson HD, Nevitt MC, Scott JC, Stone KL, Cummings SR. Smoking, alcohol, and neuromuscular and physical function of older women: Study of Osteoporotic Fractures Research Group. *Journal of the American Medical Association* 1994;272(23):1825–31.

Nettleman MD, Banitt L, Barry W, Awan I, Gordon EE. Predictors of survival and the role of gender in postoperative myocardial infarction. *American Journal of Medicine* 1997;103(5):357–62.

Newbrun E. Indices to measure gingival bleeding. *Journal of Periodontology* 1996;67(6):555–61.

Newcomb MD, Bentler PM. The impact of late adolescent substance use on young adult health status and utilization of health services: a structural-equation model over four years. *Social Science and Medicine* 1987;24(1):71–82.

Newman MG, Kornman KS, Holtzman S. Association of clinical risk factors with treatment outcomes. *Journal of Periodontology* 1994;65(5 Suppl):489–97.

Nguyen TV, Kelly PJ, Sambrook PN, Gilbert C, Pocock NA, Eisman JA. Lifestyle factors and bone density in the elderly: implications for osteoporosis prevention. *Journal of Bone and Mineral Research* 1994;9(9): 1339–46.

Niedhammer I, Bugel I, Goldberg M, Leclerc A, Guéguen A. Psychosocial factors at work and sickness absence in the Gazel cohort: a prospective study. *Occupational and Environmental Medicine* 1998; 55(11):735–41.

Nielsen H. A quantitative and qualitative study of blood monocytes in smokers. *European Journal of Respiratory Diseases* 1985;66(5):327–32.

Nierenberg DW, Stukel TA, Baron JA, Dain BJ, Greenberg ER. Determinants of plasma levels of beta-carotene and retinol. *American Journal of Epidemiology* 1989;130(3):511–21.

NIH Consensus Development Panel on *Helicobacter pylori* in Peptic Ulcer Disease. *Helicobacter pylori* in peptic ulcer disease. *Journal of the American Medical Association* 1994;272(1):65–9.

NIH Consensus Development Panel on Impotence. Impotence: Consensus Development Panel on Impotence. *Journal of the American Medical Association* 1993;270(1):83–90.

Noble RC, Penny BB. Comparison of leukocyte count and function in smoking and nonsmoking young men. *Infection and Immunity* 1975;12(3):550–5.

Norderyd O, Hugoson A. Risk of severe periodontal disease in a Swedish adult population: a cross-sectional study. *Journal of Clinical Periodontology* 1998; 25(12):1022–8.

Norderyd O, Hugoson A, Grusovin G. Risk of severe periodontal disease in a Swedish adult population: a longitudinal study. *Journal of Clinical Periodontology* 1999;26(9):608–15.

North F, Syme SL, Feeney A, Head J, Shipley MJ, Marmot MG. Explaining socioeconomic differences in sickness absence: the Whitehall II Study. *British Medical Journal* 1993;306(6874):361–6.

Oakes TW, Friedman GD, Seltzer CC, Siegelaub AB, Collen MF. Health service utilization by smokers and nonsmokers. *Medical Care* 1974;12(11):958–66.

Obwegeser R, Oguogho A, Ulm M, Berghammer P, Sinzinger H. Maternal cigarette smoking increases F_2-isoprostanes and reduces prostacyclin and nitric oxide in umbilical vessels. *Prostaglandins and Other Lipid Mediators* 1999;57(4):269–79.

O'Connor HJ, Kanduru C, Bhutta AS, Meehan JM, Feeley KM, Cunnane K. Effect of *Helicobacter pylori* eradication on peptic ulcer healing. *Postgraduate Medical Journal* 1995;71(832):90–3.

Okuno T. Smoking and blood changes [letter]. *Journal of the American Medical Association* 1973;225(11): 1387–8.

Olsen GW, Kusch GD, Stafford BA, Gudmundsen SL, Currier MF. The positive known association design:

a quality assurance method for occupational health surveillance data. *Journal of Occupational Medicine* 1991;33(9):998–1000.

O'Riordan T, Mathai E, Tobin E, McKenna D, Keane C, Sweeney E, O'Morain C. Adjuvant antibiotic therapy in duodenal ulcers treated with colloidal bismuth subcitrate. *Gut* 1990;31(9):999–1002.

Orleans CT, Schoenbach VJ, Salmon MA, Strecher VJ, Kalsbeek W, Quade D, Brooks EF, Konrad TR, Blackmon C, Watts CD. A survey of smoking and quitting patterns among black Americans. *American Journal of Public Health* 1989;79(2):176–81.

Ortego-Centeno N, Muñoz-Torres M, Hernández-Quero J, Jurado-Duce A, de la Higuera Torres-Puchol J. Bone mineral density, sex steroids, and mineral metabolism in premenopausal smokers. *Calcified Tissue International* 1994;55(6):403–7.

Ortego-Centeno N, Muñoz-Torres M, Jódar E, Hernández-Quero J, Jurado-Duce A, de la Higuera Torres-Puchol J. Effect of tobacco consumption on bone mineral density in healthy young males. *Calcified Tissue International* 1997;60(6):496–500.

Paetkau ME, Boyd TAS, Grace M, Bach-Mills J, Winship B. Senile disciform macular degeneration and smoking. *Canadian Journal of Ophthalmology* 1978;13(2): 67–71.

Paetkau ME, Boyd TAS, Winship B, Grace M. Cigarette smoking and diabetic retinopathy. *Diabetes* 1977;26(1):46–9.

Paganini-Hill A, Chao A, Ross RK, Henderson BE. Exercise and other factors in the prevention of hip fracture: the Leisure World Study. *Epidemiology* 1991;2(1):16–25.

Paganini-Hill A, Ross RK, Gerkins VR, Henderson BE, Arthur M, Mack TM. Menopausal estrogen therapy and hip fractures. *Annals of Internal Medicine* 1981; 95(1):28–31.

Palmer RM, Matthews JP, Wilson RF. Non-surgical periodontal treatment with and without adjunctive metronidazole in smokers and non-smokers. *Journal of Clinical Periodontology* 1999;26(3):158–63.

Palmore E. Health practices and illness among the aged. *Gerontologist* 1970;10(4):313–6.

Pampalon R, Duncan C, Subramanian SV, Jones K. Geographies of health perception in Quebec: a multilevel perspective. *Social Science and Medicine* 1999;48(10):1483–90.

Pamuk ER, Byers T, Coates RJ, Vann JW, Sowell AL, Gunter EW, Glass D. Effect of smoking on serum nutrient concentrations in African-American women. *American Journal of Clinical Nutrition* 1994; 59(4):891–5.

Panda K, Chattopadhyay R, Chattopadhyay D, Chatterjee IB. Vitamin C prevents cigarette smoke-induced oxidative damage in vivo. *Free Radical Biology and Medicine* 2000;29(2):115–24.

Panda K, Chattopadhyay R, Ghosh M, Chattopadhyay D, Chatterjee IB. Vitamin C prevents cigarette smoke induced oxidative damage of proteins and increased proteolysis. *Free Radical Biology and Medicine* 1999;27(9/10):1064–79.

Papantonopoulos GH. Smoking influences decision making in periodontal therapy: a retrospective clinical study. *Journal of Periodontology* 1999;70(10): 1166–73.

Parazzini F, Fabris FM, Bortolotti A, Calabrò A, Chatenoud L, Colli E, Landoni M, Lavezzari M, Turchi P, Sessa A, Mirone V. Frequency and determinants of erectile dysfunction in Italy. *European Urology* 2000;37(1):43–9.

Parkes KR. Smoking as a moderator of the relationship between affective state and absence from work. *Journal of Applied Psychology* 1983;68(4):698–708.

Parulkar VG, Balsubramaniam P, Barua MJ, Bhatt JV. Smoking and differential leucocyte (w.b.c.) count. *Journal of Postgraduate Medicine* 1975;21(2):75–7.

Parulkar VG, Barua MJ, Bhatt JV. Smoking and leucocyte counts. *Journal of Postgraduate Medicine* 1973;19(3):132–5.

Parvinen T. Stimulated salivary flow rate, pH and lactobacillus and yeast concentrations in non-smokers and smokers. *Scandinavian Journal of Dental Research* 1984;92(4):315–8.

Pearson DC, Grothaus LC, Thompson RS, Wagner EH. Smokers and drinkers in a health maintenance organization population: lifestyles and health status. *Preventive Medicine* 1987;16(6):783–95.

Penner M, Penner S. Excess insured health care costs from tobacco-using employees in a large group plan. *Journal of Occupational Medicine* 1990;32(6):521–3.

Pepelassi EA, Tsiklakis K, Diamanti-Kipioti A. Radiographic detection and assessment of the periodontal endosseous defects. *Journal of Clinical Periodontology* 2000;27(4):224–30.

Pereira ED, Fernandes AL, da Silva Ancao M, de Arauja Pereres C, Atallah AN, Faresin SM. Prospective assessment of the risk of postoperative pulmonary complications in patients submitted to upper abdominal surgery. *Sao Paulo Medical Journal* 1999; 117(4):151–60.

Persson RE, Hollender LG, Persson GR. Assessment of alveolar bone levels from intraoral radiographs in subjects between ages 15 and 94 years seeking dental care. *Journal of Clinical Periodontology*

1998;25(8):647–54. [See also comments in *Journal of Clinical Periodontology* 1999;26(4):264–6.]

Peters JM, Ferris BG Jr. Smoking and morbidity in a college-age group. *American Review of Respiratory Disease* 1967;95(5):783–9.

Petitti DB, Kipp H. The leukocyte count: associations with intensity of smoking and persistence of effect after quitting. *American Journal of Epidemiology* 1986; 123(1):89–95.

Pfeilschifter J, Ziegler R. Smoking and endocrine ophthalmopathy: impact of smoking severity and current vs lifetime cigarette consumption. *Clinical Endocrinology* 1996;45(4):477–81.

Pilz H, Oguogho A, Chehne F, Lupattelli G, Palumbo B, Sinzinger H. Quitting cigarette smoking results in a fast improvement of in vivo oxidation injury (determined via plasma, serum, and urinary isoprostane). *Thrombosis Research* 2000;99(3):209–21.

Pines A, Skulkeo K, Pollak E, Peritz E, Steif J. Rates of sickness absenteeism among employees of a modern hospital: the role of demographic and occupational factors. *British Journal of Industrial Medicine* 1985;42(5):326–35.

Pinsky JL, Leaverton PE, Stokes J III. Predictors of good function: the Framingham Study. *Journal of Chronic Diseases* 1987;40(Suppl 1):159S–162S.

Poikolainen K, Vartiainen E. Determinants of gamma-glutamyltransferase: positive interaction with alcohol and body mass index, negative association with coffee. *American Journal of Epidemiology* 1997;146(12): 1019–24.

Poikolainen K, Vartiainen E, Korhonen H. Alcohol intake and subjective health. *American Journal of Epidemiology* 1996;144(4):346–50.

Ponte F, Giuffré G, Giammanco R, Dardanoni G. Risk factors of ocular hypertension and glaucoma: the Casteldaccia Eye Study. *Documenta Ophthalmologica* 1994;85(3):203–10.

Pope CR. Life-styles, health status and medical care utilization. *Medical Care* 1982;20(4):402–13.

Post WK, Burdorf A, Bruggeling TG. Relations between respiratory symptoms and sickness among workers in the animal feed industry. *Occupational and Environmental Medicine* 1994;51(7):440–6.

Practicò D, Barry OP, Lawson JA, Adiyaman M, Hwang S-W, Khanapure SP, Iuliano L, Rokach J, FitzGerald GA. $IPF_{2\alpha\text{-}I}$: an index of lipid peroxidation in humans. *Proceedings of the National Academy of Sciences of the United States of America* 1998;95(7):3449–54.

Preber H, Bergström J. Occurrence of gingival bleeding in smoker and non-smoker patients. *Acta Odontologica Scandinavica* 1985;43(5):315–20.

Preber H, Bergström J. Cigarette smoking in patients referred for periodontal treatment. *Scandinavian Journal of Dental Research* 1986;94(2):102–8.

Preber H, Bergström J. Effect of cigarette smoking on periodontal healing following surgical therapy. *Journal of Clinical Periodontology* 1990;17(5):324–8.

Preber H, Bergström J, Linder LE. Occurrence of periopathogens in smoker and non-smoker patients. *Journal of Clinical Periodontology* 1992;19(9 Pt 1): 667–71.

Preber H, Kant T. Effect of tobacco-smoking on periodontal tissue of 15-year-old schoolchildren. *Journal of Periodontal Research* 1973;8(5):278–83.

Preber H, Kant T, Bergström J. Cigarette smoking, oral hygiene and periodontal health in Swedish army conscripts. *Journal of Clinical Periodontology* 1980;7(2): 106–13.

Preber H, Linder L, Bergström J. Periodontal healing and periopathogenic microflora in smokers and non-smokers. *Journal of Clinical Periodontology* 1995; 22(12):946–52.

Prevent Blindness America. Vision Problems in the U.S.: Prevalence of Adult Vision Impairment and Age-Related Eye Disease in America; <http://www.preventblindness.org/resources/vision_data.html>; accessed: October 28, 2002.

Prokopczyk B, Cox J, Hoffman D, Waggoner SE. Identification of tobacco-specific carcinogen in the cervical mucus of smokers and nonsmokers. *Journal of the National Cancer Institute* 1997;89(12):868–73.

Pronk NP, Goodman MJ, O'Connor PJ, Martinson BC. Relationship between modifiable health risks and short-term health care charges. *Journal of the American Medical Association* 1999;282(23):2235–9.

Prummel MF, Wiersinga WM. Smoking and risk of Graves' disease. *Journal of the American Medical Association* 1993;269(4):479–82.

Quigley HA, Enger C, Katz J, Sommer A, Scott R, Gilbert D. Risk factors for the development of glaucomatous visual field loss in ocular hypertension. *Archives of Ophthalmology* 1994;112(5):644–9.

Quinn SM, Zhang JB, Gunsolley JC, Schenkein HA, Tew JG. The influence of smoking and race on adult periodontitis and serum IgG2 levels. *Journal of Periodontology* 1998;69(2):171–7.

Raichlen JS, Healy B, Achuff SC, Pearson TA. Importance of risk factors in the angiographic progression of coronary artery disease. *American Journal of Cardiology* 1986;57(1):66–70.

Ramakrishnan S, Sulochana KN, Selvaraj T, Abdul Rahim A, Lakshmi M, Arunagiri K. Smoking of beedies and cataract: cadmium and vitamin C in the

lens and blood. *British Journal of Ophthalmology* 1995; 79(3):202–6.

Rand LI, Krolewski AS, Aiello LM, Warram JH, Baker RS, Maki T. Multiple factors in the prediction of risk of proliferative diabetic retinopathy. *New England Journal of Medicine* 1985;313(23):1433–8.

Raulin LA, McPherson JC III, McQuade MJ, Hanson BS. The effect of nicotine on the attachment of human fibroblasts to glass and human root surfaces *in vitro*. *Journal of Periodontology* 1988;59(5):318–25.

Rauws E, Tytgat G. *Helicobacter pylori* in duodenal and gastric ulcer disease. *Baillière's Clinical Gastroenterology* 1995;9(3):529–47.

Ravald N, Birkhed D, Hamp S-E. Root caries susceptibility in periodontally treated patients: results after 12 years. *Journal of Clinical Periodontology* 1993;20(2): 124–9.

Ray NF, Chan JK, Thamer M, Melton LJ III. Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995: report from the National Osteoporosis Foundation. *Journal of Bone and Mineral Research* 1997;12(1):24–35.

Recker RR, Davies KM, Hinders SM, Heaney RP, Stegman MR, Kimmel DB. Bone gain in young adult women. *Journal of the American Medical Association* 1992;268(17):2403–8.

Reed WL. Physical health status as a consequence of health practices. *Journal of Community Health* 1983; 89(4):217–28.

Reed DM, Foley DJ, White LR, Heimovitz H, Burchfiel CM, Masaki K. Predictors of healthy aging in men with high life expectancies. *American Journal of Public Health* 1998;88(10):1463–8.

Reilly M, Delanty N, Lawson JA, FitzGerald GA. Modulation of oxidant stress in vivo in chronic cigarette smokers. *Circulation* 1996;94(1):19–25.

Renvert S, Dahlén G, Wikström M. The clinical and microbiological effects of non-surgical periodontal therapy in smokers and non-smokers. *Journal of Clinical Periodontology* 1998;25(2):153–7.

Repine JE, Bast A, Lankhorst I. Oxidative stress in chronic obstructive pulmonary disease: Oxidative Stress Study Group. *American Journal of Respiratory and Critical Care Medicine* 1997;156(2 Pt 1):341–57.

Reynolds KL, Heckel HA, Witt CE, Martin JW, Pollard JA, Knapik JJ, Jones BH. Cigarette smoking, physical fitness, and injuries in infantry soldiers. *American Journal of Preventive Medicine* 1994;10(3):145–50.

Reznick AZ, Cross CE, Hu M-L, Suzuki YJ, Khwaja S, Safadi A, Motchnik PA, Packer L, Halliwell B. Modification of plasma proteins by cigarette smoke as measured by protein carbonyl formation. *Biochemistry Journal* 1992;286(Pt 2):607–11.

Rice DP, Hodgson TA, Sinsheimer P, Browner W, Kopstein A. The economic costs of the health effects of smoking, 1984. *The Milbank Quarterly* 1986;64(4): 489–547.

Riebel GD, Boden SD, Whitesides TE, Hutton WC. The effect of nicotine on incorporation of cancellous bone graft in an animal model. *Spine* 1995;20(20): 2198–202.

Rimer BK, Orleans CT, Keintz MK, Cristinzio S, Fleisher L. The older smoker: status, challenges and opportunities for intervention. *Chest* 1990;97(3): 547–53.

Rimm EB, Giovannucci EL, Willett WC, Colditz GA, Ascherio A, Rosner B, Stampfer MJ. Prospective study of alcohol consumption and risk of coronary disease in men. *Lancet* 1991;338(8765):464–8.

Rockman CB, Cappadona C, Riles TS, Lamparello PJ, Giangola G, Adelman MA, Landis R. Causes of the increased stroke rate after carotid endarterectomy in patients with previous strokes. *Annals of Vascular Surgery* 1997;11(1):28–34.

Rosen MP, Greenfield AJ, Walker TG, Grant P, Dubrow J, Bettmann MA, Fried LE, Goldstein I. Cigarette smoking: an independent risk factor for atherosclerosis in the hypogastric-cavernous arterial bed of men with arteriogenic impotence. *Journal of Urology* 1991;145(4):759–63.

Rosenberg ES, Cutler SA. The effect of cigarette smoking on the long-term success of guided tissue regeneration: a preliminary study. *Annals of the Royal Australasian College of Dental Surgeons* 1994;12: 89–93.

Ross MA, Crosley LK, Brown KM, Duthie SJ, Collins AC, Arthur JR, Duthie GG. Plasma concentrations of carotenoids and antioxidant vitamins in Scottish males: influences of smoking. *European Journal of Clinical Nutrition* 1995;49(11):861–5.

Rundgren A, Mellström D. The effect of tobacco smoking on the bone mineral content of the ageing skeleton. *Mechanisms of Ageing and Development* 1984; 28(2-3):273–7.

Ryan J, Zwerling C, Jones M. Cigarette smoking at hire as a predictor of employment outcome. *Journal of Occupational and Environmental Medicine* 1996;38(9): 928–33.

Ryan J, Zwerling C, Orav EJ. Occupational risks associated with cigarette smoking: a prospective study. *American Journal of Public Health* 1992;82(1):29–32.

Ryder MI, Fujitaki R, Johnson G, Hyun W. Alterations of neutrophil oxidative burst by in vitro smoke exposure: implications for oral and systemic diseases. *Annals of Periodontology* 1998;3(1):76–87.

Saenz de Tejada I, Goldstein I, Azadzoi K, Krane RJ, Cohen RA. Impaired neurogenic and endothelium-mediated relaxation of penile smooth muscle from diabetic men with impotence. *New England Journal of Medicine* 1989;320(16):1025–30.

Sakki TK, Knuuttila MLE, Vimpari SS, Hartikainen MSL. Association of lifestyle with periodontal health. *Community Dentistry and Oral Epidemiology* 1995;23(3):155–8.

Salvi M, Pedrazzoni M, Girasole G, Guiliani N, Minelli R, Wall JR, Roti E. Serum concentrations of pro-inflammatory cytokines in Graves' disease: effect of treatment, thyroid function, ophthalmopathy, and smoking. *European Journal of Endocrinology* 2000; 143(2):197–202.

Samuels LE, Sharma S, Kaufman MS, Morris RJ, Brockman SK. Coronary artery bypass grafting in patients in their third decade of life. *Journal of Cardiac Surgery* 1996;11(6):402–7.

Santavirta S, Konttinen YT, Heliövaara M, Knekt P, Lüthje P, Aromaa A. Determinants of osteoporotic thoracic vertebral fracture: screening of 57,000 Finnish women and men. *Acta Orthopaedica Scandinavica* 1992;63(2):198–202.

Sarks SH, Sarks JP. Age-related macular degeneration: atrophic form. In: Ryan SJ, Schachat AP, Murphy RB, editors. *Retina*. 2nd ed. Vol. 2. St. Louis: Mosby, 1994:1071–102.

Sasajima T, Kubo Y, Inaba M, Goh K, Azuma N. Role of infrainguinal bypass in Buerger's disease: an eighteen-year experience. *European Journal of Vascular and Endovascular Surgery* 1997;13(2):186–92.

Sayers NM, James JA, Drucker DB, Blinkhorn AS. Possible potentiation of toxins from *Prevotella intermedia*, *Prevotella nigrescens*, and *Porphyromonas gingivalis* by cotinine. *Journal of Periodontology* 1999;70(11): 1269–75.

Scane AC, Francis RM, Sutcliffe AM, Francis MJD, Rawlings DJ, Chapple CL. Case-control study of the pathogenesis and sequelae of symptomatic vertebral fractures in men. *Osteoporosis International* 1999; 9(1):91–7.

Scheffler E, Huber L, Fruhbis J, Schulz I, Ziegler R, Dresel HA. Alteration of plasma low density lipoprotein from smokers. *Atherosclerosis* 1990;82(3): 261–5.

Scheffler E, Wiest E, Woehrle J, Otto I, Schulz I, Huber L, Ziegler R, Dresel HA. Smoking influences the atherogenic potential of low-density lipoprotein. *Clinical Investigations* 1992;70(3-4):263–8.

Schenkein HA, Gunsolley JC, Koertge TE, Schenkein JG, Tew JG. Smoking and its effects on early-onset periodontitis. *Journal of the American Dental Association* 1995;126(8):1107–13.

Schlemper RJ, van der Werf SDJ, Vandenbroucke JP, Biemond I, Lamers CBHW. Risk factors of peptic ulcer disease: different impact of *Helicobacter pylori* in Dutch and Japanese populations? *Journal of Gastroenterology and Hepatology* 1996;11(9):825–31.

Schnurr PP, Spiro A III. Combat exposure, posttraumatic stress disorder symptoms, and health behaviors as predictors of self-reported physical health in older veterans. *Journal of Nervous and Mental Disease* 1999;187(6):353–9.

Schoenborn CA, Horm J. Negative moods as correlates of smoking and heavier drinking: implications for health promotion. *Advance Data* 1993;236:1–16.

Schubert TT, Bologna SD, Nensey Y, Schubert AB, Mascha EJ, Ma CK. Ulcer risk factors: interactions between *Helicobacter pylori* infection, nonsteroidal use, and age. *American Journal of Medicine* 1993;94(4): 413–8.

Schulte-Hobein B, Schwartz-Bickenbach D, Abt S, Plum C, Nau H. Cigarette smoke exposure and development of infants throughout the first year of life: influence of passive smoking and nursing on cotinine levels in breast milk and infant's urine. *Acta Paediatrica* 1992;81(6–7):550–7.

Schwartz J, Weiss ST. Host and environmental factors influencing the peripheral blood leukocyte count. *American Journal of Epidemiology* 1991;134(12): 1402–9.

Schwartz-Bickenbach D, Schulte-Hobein B, Abt S, Plum C, Nau H. Smoking and passive smoking during pregnancy and early infancy: effects on birth weight, lactation period, and cotinine concentrations in mother's milk and infant's urine. *Toxicology Letters* 1987;35(1):73–81.

Secker-Walker RH, Solomon LJ, Flynn BS, Dana GS. Comparisons of the smoking cessation counseling activities of six types of health professionals. *Preventive Medicine* 1994;23(6):800–8.

Seddon JM, Willett WC, Speizer FE, Hankinson SE. A prospective study of cigarette smoking and age-related macular degeneration in women. *Journal of the American Medical Association* 1996;276(14): 1141–6.

Seeley DG, Kelsey J, Jergas M, Nevitt MC. Predictors of ankle and foot fractures in older women. *Journal of Bone and Mineral Research* 1996;11(9):1347–55.

Segovia J, Bartlett RF, Edwards AC. The association between self-assessed health status and individual health practices. *Canadian Journal of Public Health* 1989; 80(1):34–7.

Seidell JC, Bakx KC, Deurenberg P, Burema J, Hautvast JG, Huygen FJ. The relation between overweight and subjective health according to age, social class, slimming behavior and smoking habits in Dutch adults. *American Journal of Public Health* 1986;76(12): 1410–5.

Shabsigh R, Fishman IJ, Schum C, Dunn JK. Cigarette smoking and other vascular risk factors in vasculogenic impotence. *Urology* 1991;38(3):227–31.

Sheiham A. Periodontal disease and oral cleanliness in tobacco smokers. *Journal of Periodontology* 1971;42(5):259–63.

Shephard RJ, Ponsford E, Basu PK, LaBarre R. Effects of cigarette smoking on intraocular pressure and vision. *British Journal of Ophthalmology* 1978;62(10): 682–7.

Shiloah J, Patters MR, Waring MB. The prevalence of pathogenic periodontal microflora in healthy young adult smokers. *Journal of Periodontology* 2000;71(4): 562–7.

Shine B, Fells P, Edwards OM, Weetman AP. Association between Graves' ophthalmopathy and smoking. *Lancet* 1990;335(8700):1261–3.

Shizukuishi S, Hayashi N, Tamagawa H, Hanioka T, Maruyama S, Takeshita T, Morimoto K. Lifestyle and periodontal health status of Japanese factory workers. *Annals of Periodontology* 1998;3(1):303–11.

Silcox DH 3rd, Daftari T, Boden SD, Schimandle JH, Hutton WC, Whitesides TE Jr. The effect of nicotine on spinal fusion. *Spine* 1995;20(14):1549–53.

Silverman NA, Potvin C, Alexander JC Jr, Chretien PB. In vitro lymphocyte reactivity and T-cell levels in chronic cigarette smokers. *Clinical and Experimental Immunology* 1975;22(2):285–92.

Sinclair DR, Chung F, Mezei G. Can postoperative nausea and vomiting be predicted? *Anesthesiology* 1999;91(1):109–18.

Sinha RN, Patrick AW, Richardson L, Wallymahmed M, MacFarlane IA. A six-year follow-up study of smoking habits and microvascular complications in young adults with type 1 diabetes. *Postgraduate Medical Journal* 1997;73(859):293–4.

Sippel JM, Pedula KL, Vollmer WM, Buist AS, Osborne ML. Associations of smoking with hospital-based care and quality of life in patients with obstructive airway disease. *Chest* 1999;115(3):691–6.

Sjolie AK. Ocular complications in insulin treated diabetes mellitus: an epidemiological study. *Acta Ophthalmologica Supplement* 1985;172:1–77.

Slemenda CW, Christian JC, Reed T, Reister TK, Williams CJ, Johnston CC Jr. Long-term bone loss in men: effects of genetic and environmental factors. *Annals of Internal Medicine* 1992;117(4):286–91.

Slemenda CW, Hui SL, Longcope C, Johnston CC Jr. Cigarette smoking, obesity, and bone mass. *Journal of Bone and Mineral Research* 1989;4(5):737–41.

Slemenda CW, Longcope C, Zhou L, Hui SL, Peacock M, Johnston CC. Sex steroids and bone mass in older men: positive associations with serum estrogens and negative associations with androgens. *Journal of Clinical Investigation* 1997;100(7):1755–9.

Smeets-Goevaers CG, Lesusink GL, Papapoulos SE, Maartens LW, Keyzer JJ, Weerdenburg JP, Beijers LM, Zwinderman AH, Knottnerus JA, Pols HA, Pop VJ. The prevalence of low bone mineral density in Dutch perimenopausal women: the Eindhoven perimenopausal osteoporosis study. *Osteoporosis International* 1998;8(5):404–9.

Smith DJ. Absenteeism and "presenteeism" in industry. *Archives of Environmental Health* 1970;21(5): 670–7.

Smith GC, Athanasou JA, Reid CC, Ng TKW, Ferguson DA. Sickness absence, respiratory impairment and smoking in industry. *Medical Journal of Australia* 1981;1(5):235–7.

Smith W, Mitchell P, Leeder SR. Smoking and age-related maculopathy: the Blue Mountains Eye Study. *Archives of Ophthalmology* 1996;114(12):1518–23.

Söder B, Jin LJ, Söder P-Ö, Wikner S. Clinical characteristics of destructive periodontitis in a risk group of Swedish urban adults. *Swedish Dental Journal* 1995;19(1-2):9–15.

Söder B, Nedlich U, Jin LJ. Longitudinal effect of non-surgical treatment and systemic metronidazole for 1 week in smokers and non-smokers with refractory periodontitis: a 5-year study. *Journal of Periodontology* 1999;70(7):761–71.

Söder P-Ö, Jin LJ, Söder B, Wikner S. Periodontal status in an urban adult population in Sweden. *Community Dentistry and Oral Epidemiology* 1994;22(2): 106–11.

Solomon HA, Priore RL, Bross ID. Cigarette smoking and periodontal disease. *Journal of the American Dental Association* 1968;77(5):1081–4.

Sommer A, Tielsch JM, Katz J, Quigley HA, Gottsch JD, Javitt JC, Martone JF, Royall RM, Witt KA, Ezrine S. Racial differences in the cause-specific prevalence of blindness in east Baltimore. *New England Journal of Medicine* 1991;325(20):1412–7.

Sonnenberg A. Smoking and mortality from peptic ulcer in the United Kingdom. *Gut* 1986;27(11): 1369–72.

Sonnenberg A, Everhart JE. The prevalence of self-reported peptic ulcer in the United States. *American Journal of Public Health* 1996;86(2):200–5.

Sorensen LT, Jorgensen T, Kirkeby LT, Skodval J, Vennits B, Wille-Jorgensen P. Smoking and alcohol abuse are major risk factors for anastomotic leakage in colorectal surgery. *British Journal of Surgery* 1999;86(7):927–31.

Sowers MR, Clark MK, Hollis B, Wallace RB, Jannausch M. Radial bone mineral density in pre- and perimenopausal women: a prospective study of rates and risk factors for loss. *Journal of Bone and Mineral Research* 1992;7(6):647–57.

Sowers MR, Wallace RB, Lemke JH. Correlates of mid-radius bone density among postmenopausal women: a community study. *American Journal of Clinical Nutrition* 1985;41(5):1045–53.

Sparrow D, Glynn RJ, Cohen M, Weiss ST. The relationship of the peripheral leukocyte count and cigarette smoking to pulmonary function among adult men. *Chest* 1984;86(3):383–6.

Spelman DW, Russo P, Harrington G, Davis BB, Rabinov M, Smith JA, Spicer WJ, Esmore D. Risk factors for surgical wound infection and bacteraemia following coronary artery bypass surgery. *Australian and New Zealand Journal of Surgery* 2000; 70(1):47–51.

Stamm JW, Banting DW, Imrey PB. Adult root caries survey of two similar communities with contrasting natural water fluoride levels. *Journal of the American Dental Association* 1990;120(2):143–9.

Stansfeld SA, Smith GD, Marmot M. Association between physical and psychological morbidity in the Whitehall II Study. *Journal of Psychosomatic Research* 1993;37(3):227–38.

Steers RM, Rhodes SR. Major influences on employee attendance: a process model. *Journal of Applied Psychology* 1978;63(4):391–407.

Steinberg EP, Javitt JC, Sharkey PD, Zuckerman A, Legro MW, Anderson GF, Bass EB, O'Day D. The content and cost of cataract surgery. *Archives of Ophthalmology* 1993;111(8):1041–9.

Steinhardt M, Greenhow L, Stewart J. The relationship of physical activity and cardiovascular fitness to absenteeism and medical care claims among law enforcement officers. *American Journal of Health Promotion* 1991;5(6):455–60.

Stoltenberg JL, Osborn JB, Pihlstrom BL, Herzberg MC, Aeppli DM, Wolff LF, Fischer GE. Association between cigarette smoking, bacterial pathogens, and periodontal status. *Journal of Periodontology* 1993; 64(12):1225–30.

Strawbridge WJ. The attribution of health problems to aging. *American Journal of Public Health* 1993;83(9): 1351–2.

Stryker WS, Kaplan LA, Stein EA, Stampfer MJ, Sober A, Willett WC. The relation of diet, cigarette smoking, and alcohol consumption to plasma beta-carotene and alpha-tocopherol levels. *American Journal of Epidemiology* 1988;127(2):283–96.

Summers CJ, Oberman A. Association of oral disease with 12 selected variables. I: periodontal disease. *Journal of Dental Research* 1968;47(3):457–62.

Sunyer J, Muñoz A, Peng Y, Margolick J, Chmiel JS, Oishi J, Kingsley L, Samet JM. Longitudinal relation between smoking and white blood cells. *American Journal of Epidemiology* 1996;144(8):734–41.

Suzuki Y, Kadowaki H, Atsumi Y, Hosokawa K, Katagiri H, Kadowaki T, Oka Y, Uyama K, Mokubo A, Asahina T, Murata C, Matsuoka K. A case of diabetic amyotrophy associated with 3243 mitochondrial tRNA(leu; UUR) mutation and successful therapy with coenzyme Q10. *Endocrine Journal* 1995; 42(2):141–5.

Svanes C, Soreide JA, Skarstein A, Fevang BT, Bakke P, Vollset SE, Svanes K, Sooreide O. Smoking and ulcer perforation. *Gut* 1997;41(2):177–80.

Swenson HM. The effect of cigarette smoking on plaque formation. *Journal of Periodontology* 1979; 50(3):146–7.

Taani DSQ. Association between cigarette smoking and periodontal health. *Quintessence International* 1997;28(8):535–9.

Tagesson C, Chabiuk D, Axelson O, Baranski B. Increased urinary excretion of the oxidative DNA adduct, 8-hydroxydeoxyguanosine, as a possible early indicator of occupational cancer hazards in the asbestos, rubber and azo-dye industries. *Polish Journal of Occupational Medicine and Environmental Health* 1993;6(4):357–68.

Tagesson C, Källberg M, Wingren G. Urinary malondialdehyde and 8-hydroxydeoxyguanosine as potential markers of oxidative stress in industrial art glass workers. *International Archives of Occupational and Environmental Health* 1996;69(1):5–13.

Taha AS, Angerson W, Nakshabendi I, Beekman H, Morran C, Sturrock RD, Russell RI. Gastric and duodenal mucosal blood flow in patients receiving non-steroidal anti-inflammatory drugs—influence of age, smoking, ulceration and *Helicobacter pylori*. *Alimentary Pharmacology and Therapeutics* 1993;7(1): 41–5.

Takada H, Washino K, Iwata H. Risk factors for low bone mineral density among females: the effect of lean body mass. *Preventive Medicine* 1997;26(5 Pt 1):633–8.

Takeishi M, Shaw WW, Ahn CY, Borud L. TRAM flaps in patients with abdominal scars. *Plastic Reconstruction and Surgery* 1997;97(3):713–22.

Takeuchi T, Nakajima M, Ohta Y, Mure K, Takeshita T, Morimoto K. Evaluation of 8-hydroxydeoxyguanosine, a typical oxidative DNA damage, in human leukocytes. *Carcinogenesis* 1994;15(8):1519–23.

Talamini G, Zamboni G, Cavallini G. Antral mucosal *Helicobacter pylori* infection density as a risk factor of duodenal ulcer. *Digestion* 1997;58(3):211–7.

Tamakoshi A, Yuzawa M, Matsui M, Uyama M, Fujiwara NK, Ohno Y. Smoking and neovascular form of age related macular degeneration in late middle aged males: findings from a case-control study in Japan. *British Journal of Ophthalmology* 1997;81(10):901–4.

Taylor PJ. Personal factors associated with sickness absence: a study of 194 men with contrasting sickness absence experience in a refinery population. *British Journal of Industrial Medicine* 1968;25(2): 106–18.

Taylor A, Jacques PF, Epstein EM. Relations among aging, antioxidant status, and cataract. *American Journal of Clinical Nutrition* 1995;62(6 Suppl):1439S–1447S.

Taylor A, Jacques PF, Nowell T, Perrone G, Blumberg J, Handelman J, Jozwiak B, Nadler D. Vitamin C in human and guinea pig aqueous, lens and plasma in relation to intake. *Current Eye Research* 1997;16(9): 857–64.

Tell GS, Grimm RH Jr, Vellar OD, Theodorsen L. The relationship of white cell count, platelet count, and hematocrit to cigarette smoking in adolescents: the Oslo Youth Study. *Circulation* 1985;72(5):971–4.

Tellez M, Cooper J, Edmonds C. Graves' ophthalmopathy in relation to cigarette smoking and ethnic origin. *Clinical Endocrinology* 1992;36(3):291–4.

Telmer S, Christiansen JS, Andersen AR, Nerup J, Deckert T. Smoking habits and prevalence of clinical diabetic microangiopathy in insulin-dependent diabetics. *Acta Medica Scandinavica* 1984;215(1): 63–8.

ten Cate B. The role of saliva in mineral equilibrium—caries and calculus formation. In: Edgar WM, O'Mullane DM, editors. *Saliva and Oral Health*. 2nd ed. London: British Dental Association, 1996: 123–36.

Tengs TO, Osgood ND. The link between smoking and impotence: two decades of evidence. *Preventive Medicine* 2001;32(6):447–52.

Terry PE, Fowler EJ, Fowles JB. Are health risks related to medical care charges in the short-term? Challenging traditional assumptions. *American Journal of Health Promotion* 1998;12(5):340–7.

Thomas CB. Characteristics of smokers compared with nonsmokers in a population of healthy young adults, including observations on family history, blood pressure, heart rate, body weight, cholesterol and certain psychologic trails. *Annals of Internal Medicine* 1960;53(4):697–718.

Thomas S, Raja RV, Kutty R, Strayer MS. Pattern of caries experience among an elderly population in south India. *International Dental Journal* 1994;44(6): 617–22.

Thylefors B, Negrel AD, Pararajasegaram R, Dadzie KY. Global data on blindness. *Bulletin of the World Health Organization* 1995;73(1):115–21.

Tibblin E, Bengtsson C, Hallberg L, Lennartsson J. Haemoglobin concentration and peripheral blood cell counts in women: the population study of women in Goteborg 1968–1969. *Scandinavian Journal of Haematology* 1979;22(1):5–16.

Tillmann M, Silcock J. A comparison of smokers' and ex-smokers' health-related quality of life. *Journal of Public Health Medicine* 1997;19(3):268–73.

Tipton DA, Dabbous MK. Effects of nicotine on proliferation and extracellular matrix production of human gingival fibroblasts in vitro. *Journal of Periodontology* 1995;66(12):1056–64.

Tomar SL, Asma S. Smoking-attributable periodontitis in the United States: findings from NHANES III. *Journal of Periodontology* 2000;71(5):743–51.

Tomar SL, Husten CG, Manley MW. Do dentists and physicians advise tobacco users to quit? *Journal of the American Dental Association* 1996;127(2):259–65.

Tomar SL, Swango PA, Kleinman DV, Burt BA. Loss of periodontal attachment in HIV-seropositive military personnel. *Journal of Periodontology* 1995;66(6): 421–8.

Tomar SL, Winn DM. Chewing tobacco use and dental caries among U.S. men. *Journal of the American Dental Association* 1999;130(11):1601–10.

Tonetti MS, Pini-Prato G, Cortellini P. Effect of cigarette smoking on periodontal healing following GTR in infrabony defects: a preliminary retrospective study. *Journal of Clinical Periodontology* 1995;22(3): 229–34.

Tracy RP, Psaty BM, Macy E, Bovill EG, Cushman M, Cornell ES, Kuller LH. Lifetime smoking exposure affects the association of C-reactive protein with cardiovascular disease risk factors and subclinical disease in healthy elderly subjects. *Arteriosclerosis, Thrombosis, and Vascular Biology* 1997;17(10):2167–76.

Trombelli L, Scabbia A. Healing response of gingival recession defects following guided tissue regeneration procedures in smokers and non-smokers. *Journal of Clinical Periodontology* 1997;24(8):529–33.

Tsai SP, Gilstrap EL, Colangelo TA, Menard AK, Ross CE. Illness absence at an oil refinery and petrochemical plant. *Journal of Occupational and Environmental Medicine* 1997;39(5):455–62.

Turner WED. Sickness absence in the freezing industry. *New Zealand Medical Journal* 1988;101(856 Pt 1):663–6.

Turner LW, Fu Q, Taylor JE, Wang MQ. Osteoporotic fracture among older U.S. women: risk factors quantified. *Journal of Aging and Health* 1998;10(3):372–91.

Tytgat GNJ, Noach LA, Rauws EAJ. *Helicobacter pylori* infection and duodenal ulcer disease. *Gastroenterology Clinics of North America* 1993;22(1):127–39.

Unge P, Gad A, Eriksson K, Bergman B, Carling L, Ekström P, Glise H, Gnarpe H, Junghard O, Lindholmer C, Sandzén B, Strandberg L, Stubberöd A, Weywad L. Amoxicillin added to omeprazole prevents relapse in the treatment of duodenal ulcer patients. *European Journal of Gastroenterology and Hepatology* 1993;5(5):325–31.

U.S. Department of Health and Human Services. *The Health Consequences of Smoking for Women. A Report of the Surgeon General*. Washington: U.S. Department of Health and Human Services, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health, 1980.

U.S. Department of Health and Human Services. *The Health Consequences of Smoking: Chronic Obstructive Lung Disease. A Report of the Surgeon General*. Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, 1984. DHHS Publication No. (PHS) 84-50205.

U.S. Department of Health and Human Services. *The Health Consequences of Smoking: Nicotine Addiction. A Report of the Surgeon General.* Atlanta: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1988. DHHS Publication No. (CDC) 88-8406.

U.S. Department of Health and Human Services. *The Health Benefits of Smoking Cessation. A Report of the Surgeon General.* Atlanta: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1990. DHHS Publication No. (CDC) 90-8416.

U.S. Department of Health and Human Services. *Preventing Tobacco Use Among Young People: A Report of the Surgeon General*. Atlanta: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1994.

U.S. Department of Health and Human Services. *Oral Health in America: A Report of the Surgeon General*. Rockville (MD): U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Dental and Craniofacial Research, 2000.

U.S. Department of Health and Human Services. *Women and Smoking. A Report of the Surgeon General*. Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, Office of the Surgeon General, 2001.

U.S. Department of Health, Education, and Welfare. *Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service*. Washington: U.S. Department of Health, Education, and Welfare, Public Health Service, 1964. PHS Publication No. 1103.

U.S. Department of Health, Education, and Welfare. *The Health Consequences of Smoking. A Public Health Service Review: 1967*. Washington: U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, 1967. PHS Publication No. 1696.

U.S. Department of Health, Education, and Welfare. *The Health Consequences of Smoking. A Report of the Surgeon General*. Rockville (MD): U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, 1971. DHEW Publication No. (HSM) 71-7513.

U.S. Department of Health, Education, and Welfare. *The Health Consequences of Smoking. A Report of the Surgeon General*. Rockville (MD): U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, 1972. DHEW Publication No. (HSM) 72-7516.

U.S. Department of Health, Education, and Welfare. *The Health Consequences of Smoking. A Report of the Surgeon General, 1975*. Washington: U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, 1975. DHEW Publication No. (CDC) 76-8704.

U.S. Department of Health, Education, and Welfare. *Smoking and Health. A Report of the Surgeon General*. Rockville (MD): U.S. Department of Health, Education, and Welfare, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health, 1979. DHEW Publication No. (PHS) 79-50066.

Utley JR, Leyland SA, Fogarty CM, Smith WP, Knight EB, Feldman GJ, Wilde EF. Smoking is not a predictor of mortality and morbidity following coronary artery bypass grafting. *Journal of Cardiac Surgery* 1996;11(6):377–84.

Välimäki MJ, Kärkkäinen M, Lamberg-Allardt C, Laitinen K, Alhava E, Heikkinen J, Impivaara O, Mäkelä P, Palmgren J, Seppänen R, Vuori I, and the Cardiovascular Risk in Young Finns Study Group. Exercise, smoking, and calcium intake during adolescence and early adulthood as determinants of peak bone mass. *British Medical Journal* 1994; 309(6949):230–5.

Van Der Hulst RWM, Rauws EAJ, Köycü B, Keller JJ, Bruno MJ, Tijssen JGP, Tytgat GNJ. Prevention of ulcer recurrence after eradication of *Helicobacter pylori*: a prospective long-term follow-up study. *Gastroenterology* 1997;113(4):1082–6.

Van Peenen PFD, Blanchard AG, Wolkonsky PM, Gill TM. Health insurance claims of petrochemical company employees. *Journal of Occupational Medicine* 1986;28(3):237–40.

Van Tuinen M, Land G. Smoking and excess sick leave in a department of health. *Journal of Occupational Medicine* 1986;28(1):33–5.

van Zeeland AA, de Groot AJL, Hall J, Donato F. 8-Hydroxydeoxyguanosine in DNA from leukocytes of healthy adults: relationship with cigarette smoking, environmental tobacco smoke, alcohol and coffee consumption. *Mutation Research* 1999;439(2): 249–57.

Vanuxem D, Sampol J, Weiller PJ, M'Barki M, Grimaud C. Influence of chronic smoking on leukocytes [French]. *Respiration* 1984;46(3):258–64.

Varenna M, Binelli L, Zucchi F, Ghiringhelli D, Gallazzi M, Sinigaglia L. Prevalence of osteoporosis by educational level in a cohort of postmenopausal women. *Osteoporosis International* 1999;9(3):236–41.

Vasse RM, Nijhuis FJN, Kok G. Associations between work stress, alcohol consumption and sickness absence. *Addiction* 1998;93(2):231–41.

Vinding T, Appleyard M, Nyboe J, Jensen G. Risk factor analysis for atrophic and exudative age-related macular degeneration: an epidemiological study of 1000 aged individuals. *Acta Ophthalmologica* 1992; 70(1):66–72.

Vingerling JR, Hofman A, Grobbee DE, de Jong PT. Age-related macular degeneration and smoking: the Rotterdam Study. *Archives of Ophthalmology* 1996; 114(10):1193–6.

Virag R, Bouilly P, Frydman D. Is impotence an arterial disorder? A study of arterial risk factors in 440 impotent men. *Lancet* 1985;1(8422):181–4.

Vogel JM, Davis JW, Nomura A, Wasnich RD, Ross PD. The effects of smoking on bone mass and the rates of bone loss among elderly Japanese-American men. *Journal of Bone and Mineral Research* 1997;12(9): 1495–501.

Vogt TM, Schweitzer SO. Medical costs of cigarette smoking in a health maintenance organization. *American Journal of Epidemiology* 1985;122(6): 1060–6.

Wabrek AJ, Shelley MA, Horowitz LM, Bastarache MM, Giuca JE. Noninvasive penile arterial evaluation in 120 males with erectile dysfunction. *Urology* 1983;22(3):230–4.

Wagner EH, Curry SJ, Grothaus L, Saunders DW, McBride CM. The impact of smoking and quitting on health care use. *Archives of Internal Medicine* 1995; 155(16):1789–95.

Wagner G, Béjin A, Fugl-Meyer AR, Glina S, Kimoto Y, Lukacs CSB, Mulcahy J, O'Leary M. Symptom score and quality of life. In: Jardin A, Wagner G, Khoury S, Giuliano F, Padma-Nathan H, Rosen R, editors. *Erectile Dysfunction*. Plymouth (United Kingdom): Health Publication, 2000:105–13.

Wakai K, Kawamura T, Umemura O, Hara Y, Machida J-I, Anno T, Ichihara Y, Mizuno Y, Tamakoshi A, Lin Y, Nakayama T, Ohno Y. Associations of medical status and physical fitness with periodontal disease. *Journal of Clinical Periodontology* 1999;26(10):664–72.

Wakefield M, Ruffin R, Campbell D, Roberts L, Wilson D. Smoking-related beliefs and behaviour among adults with asthma in a representative population sample. *Australian and New Zealand Journal of Medicine* 1995;25(1):12–7.

Walker JM, Cove DH, Beevers DG, Dodson PM, Leatherdale BA, Fletcher RF, Wright AD. Cigarette smoking, blood pressure and the control of blood glucose in the development of diabetic retinopathy. *Diabetes Research* 1985;2(4):183–6.

Wang J-Y, Liu S-B, Chen S-Y, Dobson A. Risk factors for peptic ulcer in Shanghai. *International Journal of Epidemiology* 1996;25(3):638–43.

Warner DO, Warner MA, Offord KP, Schroeder DR, Maxson P, Scanlon PD. Airway obstruction and perioperative complications in smokers undergoing abdominal surgery. *Anesthesiology* 1999;90(2): 372–9.

Warner KE, Smith RJ, Smith DG, Fries BE. Health and economic implications of a work-site smoking-cessation program: a simulation analysis. *Journal of Occupational and Environmental Medicine* 1996; 38(10):981–92.

Wasada T, Kawahara R, Katsumori K, Naruse M, Omori Y. Plasma concentration of immunoreactive vascular endothelial growth factor and its relation to smoking. *Metabolism* 1998;47(1):27–30.

Watterson PA, Bostwick J 3rd, Hester TR Jr, Bried JT, Taylor GI. TRAM flap anatomy correlated with a 10-year clinical experience with 556 patients. *Plastic Reconstruction and Surgery* 1995;95(7):1185–94.

Weaver MT, Forrester BG, Brown KC, Phillips JA, Hilyer JC, Capilouto EI. Health risk influence on medical care costs and utilization among 2,898 municipal employees. *American Journal of Preventive Medicine* 1998;15(3):250–3.

Weil J, Langman MJS, Wainwright P, Lawson DH, Rawlins M, Logan RFA, Brown TP, Vessey MP, Murphy M, Colin-Jones DG. Peptic ulcer bleeding: accessory risk factors and interactions with non-steroidal anti-inflammatory drugs. *Gut* 2000;46(1): 27–31.

Weinkam JJ, Rosenbaum W, Sterling TD. Smoking and hospital utilization. *Social Science and Medicine* 1987;24(11):983–6.

Weiss NS, Liff JM, Ure CL, Ballard JH, Abbott GH, Daling JR. Mortality in women following hip fracture. *Journal of Chronic Diseases* 1983;36(12):879–82.

West KM, Erdreich LS, Stober JA. Absence of a relationship between smoking and diabetic microangiopathy. *Diabetes Care* 1980;3(2):250–2.

West S, Munoz B, Emmett EA, Taylor HR. Cigarette smoking and risk of nuclear cataracts. *Archives of Ophthalmology* 1989a;107(8):1166–9.

West S, Muñoz B, Schein OD, Vitale S, Maguire M, Taylor HR, Bressler NM. Cigarette smoking and risk for progression of nuclear opacities. *Archives of Ophthalmology* 1995;113(11):1377–80.

West SK, Muñoz B, Schein OD, Duncan DD, Rubin GS. Racial differences in lens opacities: the Salisbury Eye Evaluation (SEE) Project. *American Journal of Epidemiology* 1998;148(11):1033–9.

West SK, Rosenthal FS, Bressler NM, Bressler SB, Munoz B, Fine SL, Taylor HR. Exposure to sunlight and other risk factors for age-related macular degeneration. *Archives of Ophthalmology* 1989b;107(6): 875–9.

West SK, Valmadrid CT. Epidemiology of risk factors for age-related cataract. *Survey of Ophthalmology* 1995;39(4):323–34.

Wetterslev J, Hansen EG, Kamp-Jensen M, Roikjaer O, Kanstrup IL. PaO2 during anaesthesia and years of smoking predict late postoperative hypoxaemia and complications after upper abdominal surgery in patients without preoperative cardiopulmonary dysfunction. *Acta Anaesthesiologica Scandinavica* 2000;44(1):9–16.

Wetzler HP, Ursano RJ. A positive association between physical health practices and psychological well-being. *Journal of Nervous and Mental Disease* 1988; 176(5):280–3.

Wickham CAC, Walsh K, Cooper C, Barker DJP, Margetts BM, Morris J, Bruce SA. Dietary calcium, physical activity, and risk of hip fracture: a prospective study. *British Medical Journal* 1989;299(6704): 889–92.

Wiley JA, Camacho TC. Life-style and future health: evidence from the Alameda County Study. *Preventive Medicine* 1980;9(1):1–21.

Williams AR, Weiss NS, Ure CL, Ballard J, Daling JR. Effect of weight, smoking, and estrogen use on the risk of hip and forearm fractures in postmenopausal women. *Obstetrics and Gynecology* 1982;60(6):695–9.

Wilson MR, Hertzmark E, Walker AM, Childs-Shaw K, Epstein DL. A case-control study of risk factors in open angle glaucoma. *Archives of Ophthalmology* 1987;105(8):1066–71.

Wilson RW. Cigarette smoking, disability days and respiratory conditions. *Journal of Occupational Medicine* 1973;15(3):236–40.

Wilson RW, Elinson J. National Survey of Personal Health Practices and Consequences: background, conceptual issues, and selected findings. *Public Health Reports* 1981;96(3):218–25.

Winsa B, Mandahl A, Karlsson FA. Graves' disease, endocrine ophthalmopathy and smoking. *Acta Endocrinologica* 1993;128(2):156–60.

Witteman EM, Hopman WP, Becx MC, De Koning RW, Tytgat GN, Janssen AJ, Jansen JB. Short report: smoking habits and the acquisition of metronidazole resistance in patients with *Helicobacter pylori*-related gastritis. *Alimentary Pharmacology and Therapeutics* 1993;7(6):683–7.

Wood EA, Olmstead GW, Craig JL. An evaluation of lifestyle risk factors and absenteeism after two years in a worksite health promotion program. *American Journal of Health Promotion* 1989;4(2):128–33.

Wooden M, Bush R. Smoking cessation and absence from work. *Preventive Medicine* 1995;24(5):535–40.

World Health Organization. *Periodontal Disease*. Technical Report Series No. 207. Geneva: World Health Organization, 1961.

Wouters FR, Salonen LWE, Frithiof L, Helldén LB. Significance of some variables on interproximal alveolar bone height based on cross-sectional epidemiologic data. *Journal of Clinical Periodontology* 1993;20(3):199–206.

Xia HH, Talley NJ. Natural acquisition and spontaneous elimination of *Helicobacter pylori* infection: clinical implications. *American Journal of Gastroenterology* 1997;92(10):1780–7.

Xie Y, Garban H, Ng C, Rajfer J, Gonzalez-Cadavid NF. Effect of long-term passive smoking on erectile function and penile nitric oxide synthase in the rat. *Journal of Urology* 1997;157(3):1121–6.

Yarnell JWG, Sweetnam PM, Rogers S, Elwood PC, Bainton D, Baker IA, Eastham R, O'Brien JR, Etherington MD. Some long term effects of smoking on the haemostatic system: a report from the Caerphilly and Speedwell Collaborative Surveys. *Journal of Clinical Pathology* 1987;40(8):909–13.

Yeung DL. Relationships between cigarette smoking, oral contraceptives, and plasma vitamins A, E, C, and plasma triglycerides and cholesterol. *American Journal of Clinical Nutrition* 1976;29(11):1216–21.

York JL, Hirsch JA. Drinking patterns and health status in smoking and nonsmoking alcoholics. *Alcoholism, Clinical and Experimental Research* 1995;19(3): 666–73.

Zalokar JB, Richard JL, Claude JR. Leukocyte count, smoking, and myocardial infarction. *New England Journal of Medicine* 1981;304(8):465–8.

Zambon JJ, Grossi SG, Machtei EE, Ho AW, Dunford R, Genco RJ. Cigarette smoking increases the risk for subgingival infection with periodontal pathogens. *Journal of Periodontology* 1996;67(10 Suppl): 1050–4.

Zitterbart PA, Matranga LF, Christen AG, Park KK, Potter RH. Association between cigarette smoking and the prevalence of dental caries in adult males. *General Dentistry* 1990;38(6):426–31.