# CONTENTS

# PART I. PEPTIC ULCER DISEASE

## Introduction

Numerous studies have demonstrated the association between smoking and the occurrence of peptic ulcer disease. This association was noted in the 1964, 1971, and 1972 Surgeon General's Reports (US PHS 1964; US DHEW 1971, 1972). The 1979 Report stated that the evidence of an association between cigarette smoking and peptic ulcer was strong enough to suggest a causal relationship (US DHEW 1979). That Report concluded that cigarette smoking was associated with the incidence of peptic ulcer disease and with increased risk of dying from peptic ulcer disease; the evidence that smoking retards healing of peptic ulcers was regarded as highly suggestive. The 1989 Report (US DHHS 1989) stated that smoking cessation may reduce peptic ulcer incidence and is an important component of peptic ulcer treatment, even with the effective drug therapy presently available. This Section focuses on smoking cessation and the occurrence and course of peptic ulcer disease.

## Impact of Smoking and Smoking Cessation on Ulcer Occurrence

### Smoking and Gastrointestinal Physiology

Kikendall, Evaul, and Johnson (1984) reviewed the effect of cigarette smoking on aspects of gastrointestinal physiology relevant to peptic ulcer disease. The literature available at the time of their review supported the following concepts. Chronic cigarette smokers have higher maximal acid output than nonsmokers. Smoking 1 cigarette or more has no consistent immediate effect on acid secretion. Smoking 1 cigarette immediately decreases alkaline pancreatic secretion and immediately results in a pronounced fall in duodenal bulb pH, especially in subjects with gastric acid hypersecretion. Smoking has a variable effect on gastric emptying, depending on experimental design. Smoking increases duodenogastric reflux. Smoking decreases gastric mucosal blood flow. Smoking during waking hours inhibits the antisecretory effects of a nocturnal dose of cimetidine, ranitidine, or poldine.

Subsequent to this review, the two latter concepts have been seriously challenged. Robert, Leung, and Guth (1986) found that neither nicotine nor smoking inhibited basal gastric mucosal blood flow in rats. Several investigators could not confirm that smoking antagonized the antisecretory effect of cimetidine or ranitidine (Deakin, Ramage, Williams 1988; Bianchi Porro et al. 1983; Bauerfeind et al. 1987).

However, several of the findings from this earlier review (Kikendall, Evaul, Johnson 1984) have been confirmed by more recent reports. Parente and associates (1985) confirmed higher pentagastrin-stimulated acid secretion among chronic heavy smokers than among nonsmokers. Smokers also had higher basal serum pepsinogen-I levels. These differences were statistically significant and large enough to be of clinical importance. Higher maximal gastric acid secretory rates among smokers compared

with nonsmokers were also demonstrated by Whitfield and Hobsley (1985) in a study of 201 patients with duodenal ulcer.

Additionally, Mueller-Lissner (1986) noted that chronic smokers who abstained from smoking for 12 hours had more duodenogastric bile reflux than nonsmokers and confirmed that smoking cigarettes acutely augments the already elevated rate of bile reflux. Quimby and coworkers (1986) reported that active smoking transiently decreased gastric mucosal prostaglandin synthesis.

In summary, the known effects of smoking on gastroduodenal physiology provide multiple potential mechanisms for enhancement of an ulcer diathesis by active smoking. Several of the effects of smoking, most notably the inhibition of alkaline pancreatic secretion, the reduction of duodenal bulb pH, and the reduction of prostaglandin synthesis, are transient effects that could be reversed quickly by abstinence from smoking.

## Trends in Peptic Ulcer Disease

During the past several decades, the rates of hospitalization for and mortality from peptic ulcer disease in the United States have declined dramatically (Kurata et al. 1983). Although changes in coding practices and/or diagnostic procedures could explain some of the decline, the trends in mortality from peptic ulcer have paralleled the decreasing prevalence of smoking. Kurata and coworkers (1986) studied trends in ulcer mortality and smoking in the United States between 1920 and 1980 and estimated that the portion of duodenal-ulcer-related mortality attributable to smoking was between 43 and 63 percent for men and 25 and 50 percent for women. In contrast, Sonnenberg (1986) concluded that smoking was not the main determinant of the birth cohort phenomenon of declining peptic ulcer mortality in the United Kingdom. This study descriptively compared the death rates for duodenal and gastric ulcer with the annual cigarette consumption in the United Kingdom according to birth cohorts and found a lack of correlation between ulcer mortality and cigarette consumption (Sonnenberg 1986). Thus, factors in addition to cigarette smoking may also underlie the recent trends in these indicators of peptic ulcer disease.

Two factors that have received considerable attention in recent years are *Helicobacter pylori* gastritis (Graham 1989) and the use of nonsteroidal anti-inflammatory drugs (Griffin, Ray, Schaffner 1988). Martin and associates (1989), in an endoscopic study, found that smoking was a risk factor for peptic ulcer disease among patients who had *Helicobacter pylori* gastritis. Willoughby and colleagues (1986) found that smoking was associated with peptic ulcer disease among subjects with rheumatoid arthritis, most of whom were taking nonsteroidal anti-inflammatory drugs. Ehsanullah and colleagues (1988) and Yeomans and associates (1988) also showed an association of smoking with the acute gastric erosions and submucosal hemorrhages induced by these drugs. These studies demonstrated that smoking is associated with ulcer disease related to both *Helicobacter pylori* and nonsteroidal anti-inflammatory drugs.

## Morbidity From Peptic Ulcers

In an analysis of prospective cohort data on ulcer incidence in women from the National Health and Nutrition Examination Survey I Epidemiologic Followup Study, the relative risk for developing peptic ulcer was 1.3 among former smokers (95-percent confidence interval (CI), 0.7–2.9) and 1.9 among current smokers (95-percent CI, 1.2–2.6) compared with lifetime nonsmokers (Anda et al. 1990). In this study, former smokers were defined as persons who had smoked at least 100 cigarettes in their lifetime but who were not smoking at the time of the baseline interview. The mean length of followup in this cohort was 9 years. This analysis used the Cox proportional hazards model to adjust for the potential confounding effects of age, sex, socioeconomic status, regular aspirin use, alcohol intake, and coffee consumption.

Ainley and associates (1986) surveyed the smoking behavior of 1,217 patients undergoing endoscopy. This study did not include "normal" or community controls as all patients had indications for endoscopy. Of the smokers, 11.9 percent had gastric ulcers, a diagnosis shared by 7.7 percent of ex-smokers ($p<0.025$) and 4.6 percent of never smokers ($p<0.001$). Of the smokers, 12.8 percent had duodenal ulcer compared with 6.8 percent of ex-smokers ($p<0.01$) and 6.1 percent of never smokers ($p<0.001$).

In a study of nearly 6,000 Japanese men living in Hawaii (Stemmermann et al. 1989), 243 developed gastric ulcers and 99 developed duodenal ulcers in 20 years of followup. Gastric ulcer developed among 6.7 percent of current smokers compared with 3.8 percent of former smokers and 3.2 percent of lifetime nonsmokers ($p<0.0001$). Duodenal ulcer developed more often ($p<0.0001$) among current smokers than among former smokers or never smokers (2.7 vs. 1.4 vs. 0.9 percent, respectively).

These three studies show that smokers are more likely than never smokers and former smokers to develop peptic ulcer disease. Two of the studies show higher frequencies among smokers for both duodenal and gastric ulcer. All three studies demonstrate that the risk of peptic ulcer for former smokers is between that for current smokers and for never smokers. The tendency of symptomatic smokers to stop smoking would bias the results of such studies toward reducing the apparent benefit of cessation (Chapter 2). These studies strongly suggest that the smoker's risk of developing either gastric or duodenal ulcer is diminished after smoking cessation.

In an early analysis of cross-sectional survey data among men aged 20 to 79 in Tecumseh, MI (Higgins and Kjelsberg 1967), the age-adjusted prevalences of self-reported peptic ulcer among nonsmokers (presumably never smokers), ex-smokers, and current smokers were 5.2, 8.0, and 7.1 percent, respectively. The definitions of smoking status were not presented, and the differences were not statistically significant. In this study, the prevalences of peptic ulcer among women who were nonsmokers, ex-smokers, or current smokers were 1.4, 1.5, and 2.8 percent, respectively; these differences were reported as statistically significant between smokers and nonsmokers (Higgins and Kjelsberg 1967). Earlier studies such as this, which were conducted before the advent of endoscopy, had relatively poor diagnostic accuracy and may consequently have been biased toward underestimating the effects of smoking.

Additional reports linked smoking to some of the complications of peptic ulcer disease. For example, 86 percent of 128 patients presenting with perforated duodenal

ulcer were cigarette smokers compared with 51 percent ($p<0.01$) of retrospectively matched controls (Smedley et al. 1988). Other reports noted that smokers comprised 87 percent (Heuman, Larsson, Norrby 1983) and 86 percent (Hodnett et al. 1989) of patients with perforated duodenal ulcers and 83 percent of males undergoing surgery for peptic ulcer (Ross et al. 1982). These latter studies were uncontrolled, and the high percentages of smokers have not been confirmed in some other surgical series. Nevertheless, these latter studies support the findings of Smedley and associates (1988) and suggest that smokers with peptic ulcer who continue to smoke may be at greater risk for ulcer complications than nonsmokers.

### Mortality From Peptic Ulcers

The American Cancer Society Cancer Prevention Study I (ACS CPS-I) found that the relative risk of mortality for peptic ulcer among men was 3.1 for current smokers (95-percent CI, 2.2–4.2) and 1.5 for former smokers (95-percent CI, 1.0–2.3) compared with lifetime nonsmokers (US DHHS 1989).

In the U.S. Veterans Study, the duodenal ulcer mortality ratios for current and ex-smokers compared with never smokers were 3.2 and 1.8, respectively (Kahn 1966). Ex-smokers in this report were persons who stopped smoking for reasons other than physician's orders but were otherwise not clearly defined. The mortality ratios for gastric ulcer among current and ex-smokers were 4.1 and 3.4, respectively. Although these differences in mortality were not statistically significant, the trends were similar to those in ACS CPS-I and supported the results of that study.

## Effects of Smoking on Ulcer Healing and Recurrence

### Healing of Duodenal Ulcers

Numerous trials evaluating ulcer therapy have suggested that smoking adversely affects ulcer healing. Kikendall, Evaul, and Johnson (1984) reviewed the results of 18 studies that assessed the impact of smoking on healing of duodenal ulcers. In most of these studies, the percentage of healed ulcers was lower among current smokers than among nonsmokers (Table 1). These studies were not explicitly designed to study smoking, and the nonsmoking category presumably included never as well as former smokers. When the data from these studies were subjected to meta-analysis, the percentage of healed ulcers was lower among smokers than among nonsmokers in patients treated with $H_2$-blockers ($p<0.0001$) and in patients given placebo ($p<0.0001$) (Table 2). The median difference in percentage of subjects completely healed was 22 percentage points in favor of nonsmokers in groups treated with $H_2$-blockers, 21.5 percentage points in groups receiving other active therapy, and 22 percentage points in groups receiving placebo. The data for groups receiving active therapy other than $H_2$-blockers were not subjected to statistical analysis because the data were not homogeneous, but the data in Table 1 show that nonsmokers in most of these other treatment groups fared better than their smoking peers. Most trials published since this

1984 review show similar trends toward greater likelihood of healing of duodenal ulcers in nonsmokers.

Recently, several reports have suggested that sucralfate (Lam et al. 1987) and misoprostol (Lam et al. 1986) may have particular value in treating duodenal ulcers among patients who smoke. Lam (1989) has compiled a list of six studies showing comparable duodenal ulcer healing rates for smokers and nonsmokers treated with sucralfate. Although a few studies offer contrary data (Van Deventer, Schneidman, Walsh 1985; Martin 1989), much of the evidence suggests that sucralfate heals duodenal ulcers in smokers and nonsmokers at comparable rates.

The claim that the efficacy of prostaglandins for duodenal ulcer healing is unaffected by smoking is based on the results of a single study (Lam et al. 1986). The design of this study is unusual because patients who smoked were encouraged to abstain from smoking during the study; therefore, healing efficacy in smokers may have been due to the combined effects of misoprostol and smoking cessation. Other duodenal ulcer treatment trials (Bianchi Porro and Parente 1988; Brand et al. 1985; Nicholson 1985) showed improved healing among nonsmokers. Nicholson (1985) treated duodenal ulcer patients with 200 μg misoprostol 4 times daily and documented healing in 73 of 138 smokers (53 percent) and 66 of 93 nonsmokers (71 percent, $p<0.01$). Thus, the evidence is tenuous at best that oral prostaglandins can overcome the adverse effects of smoking on the healing of duodenal ulcers.

Other recently reported clinical trials are not systematically reviewed in this Chapter. Most of the recent trials that have analyzed the effects of smoking on duodenal ulcer healing show lower healing rates among smokers than among nonsmokers.

In contrast to the numerous comparisons of duodenal ulcer healing rates among smokers and nonsmokers, only one study has examined specifically the effect of smoking cessation on duodenal ulcer healing (Hull and Beale 1985). In this study, 70 male smokers with duodenal ulcers were advised to stop smoking and were treated with cimetidine for 3 months. Those who stopped were no more likely than those who continued smoking to have healed their ulcers on endoscopic exam at 3 months (75 vs. 81 percent, respectively, not significant). Cimetidine treatment was then stopped. Three months later, 72 percent of those who quit smoking and 39 percent of smokers were ulcer-free at repeat endoscopy ($p<0.05$) (Hull and Beale 1985). Although these results require confirmation, the findings suggest either that some of the adverse effects of smoking on duodenal ulcer disease may persist for a few weeks after cessation of smoking or that cimetidine therapy may mitigate these effects.

### Recurrence of Duodenal Ulcers

A number of prospective clinical trials of maintenance therapy for duodenal ulcer have assessed the impact of smoking on ulcer recurrence. In one of the larger trials (Sontag et al. 1984), 370 subjects with previously documented duodenal ulcer, who had no active ulcer at enrollment endoscopy, were randomized to placebo or cimetidine. Endoscopy was repeated at 6 and 12 months or whenever dyspepsia occurred during the 12 months of followup. In the placebo group, smokers were more likely than nonsmokers to experience recurrence (72 vs. 21 percent, $p<0.001$). In addition,

**TABLE 1.—Percentage of healed duodenal ulcers among smoking and nonsmoking patients**

| Reference | Drug | Duration of Rx (wk) | Patients with healed ulcers | | | | p-value | Difference in % healed |
|---|---|---|---|---|---|---|---|---|
| | | | Smokers | | Nonsmokers | | | |
| | | | N[a] | %[b] | N[a] | %[b] | | |
| Exclusively $H_2$-blocker therapy | | | | | | | | |
| Bianchi Porro et al. (1981) | $H_2$-blockers | 4 | 76 | 66 | 36 | 86 | <0.05 | 20 |
| Korman et al. (1983) | $H_2$-blockers | 4–6 | 71 | 63 | 64 | 95 | <0.01 | 32 |
| Korman, Hansky et al. (1982) | Ranitidine | 4 | 13 | 62 | 12 | 100 | <0.05 | 38 |
| Hetzel et al. (1978) | Cimetidine | 6 | 43 | 86 | 43 | 80 | NS | –6 |
| Korman et al. (1981) | Cimetidine | 6 | 10 | 50 | 15 | 100 | <0.05 | 50 |
| Marks et al. (1980) | Cimetidine | 6 | 19 | 78 | 10 | 60 | NS | –18 |
| Bardhan et al. (1979) | Cimetidine | 4 | 94 | 65 | 40 | 65 | NS | 0 |
| Gugler et al. (1982) | Cimetidine | 8 | 34 | 64 | 16 | 94 | <0.05 | 29 |
| Gugler et al. (1982) | Oxmetidine | 8 | 35 | 71 | 14 | 93 | NS | 22 |
| Korman, Hetzel et al. (1982) | Oxmetidine | 4 | 27 | 70 | 15 | 87 | NS | 17 |
| Korman, Hetzel et al. (1982) | Cimetidine | 4 | 28 | 68 | 13 | 92 | <0.05 | 24 |

**TABLE 1.—Continued**

| Reference | Drug | Duration of Rx (wk) | Patients with healed ulcers | | | | p-value | Difference in % healed |
|---|---|---|---|---|---|---|---|---|
| | | | Smokers | | Nonsmokers | | | |
| | | | N[a] | %[b] | N[a] | %[b] | | |
| Active therapy other than $H_2$-blockers | | | | | | | | |
| Bianchi Porro et al. (1980) | Cimetidine or pirenzepine | 4 | 63 | 71 | 27 | 81 | NS | 10 |
| Sonnenberg et al. (1981) | Cimetidine, pirenzepine, or placebo | 4 | 66 | 54 | 68 | 73 | <0.05 | 19 |
| Barbara et al. (1979) | Pirenzepine | 4 | 16 | 69 | 28 | 43 | NS | −26 |
| Vantrappen et al. (1982) | Arbaprostil | 4 | 68 | 65 | 14 | 79 | NS | 14 |
| Peterson et al. (1977) | Antacid | 4 | 28 | 75 | 8 | 88 | NS | 13 |
| Korman et al. (1981) | Antacid | 6 | 13 | 39 | 12 | 67 | <0.05 | 28 |
| Marks et al. (1980) | Sucralfate | 6 | 20 | 90 | 9 | 67 | NS | −23 |
| Nagy (1978) | Carbenoxolone | — | 11 | 55 | 10 | 80 | NS | 25 |
| Young and St. John (1982) | Carbenoxolone | 6 | 14 | 50 | 6 | 83 | NS | 33 |
| Lam et al. (1979) | Antacid ± sulpiride | — | 17 | 59 | 34 | 91 | <0.05 | 32 |
| Lam et al. (1979) | Placebo or sulpiride | — | 15 | 27 | 35 | 51 | NS | 24 |
| Massarrat and Eisenmann (1981) | Antacid | 8 | 56 | 48 | 24 | 75 | <0.05 | 27 |

**TABLE 1.—Continued**

| Reference | Drug | Duration of Rx (wk) | Patients with healed ulcers | | | | p-value | Difference in % healed |
|---|---|---|---|---|---|---|---|---|
| | | | Smokers | | Nonsmokers | | | |
| | | | N[a] | %[b] | N[a] | %[b] | | |
| Placebo therapy | | | | | | | | |
| Bianchi Porro et al. (1980) | Placebo | 4 | 55 | 31 | 15 | 53 | NS | 22 |
| Nagy (1978) | Placebo | — | 11 | 25 | 11 | 30 | NS | 5 |
| Young and St. John (1982) | Placebo | 6 | 15 | 20 | 5 | 40 | NS | 20 |
| Hetzel et al. (1978) | Placebo | 4 | 42 | 37 | 42 | 42 | NS | 5 |
| Peterson et al. (1977) | Placebo | 4 | 25 | 32 | 13 | 69 | <0.03 | 37 |
| Vantrappen et al. (1982) | Placebo | 4 | 65 | 28 | 26 | 65 | <0.05 | 37 |
| Barbara et al. (1979) | Placebo | 4 | 25 | 28 | 10 | 50 | NS | 22 |
| Korman, Hansky et al. (1982) | Placebo | 4 | 14 | 0 | 11 | 36 | <0.05 | 36 |
| Bianchi Porro et al. (1981) | Placebo | 4 | 62 | 24 | 20 | 50 | <0.01 | 26 |
| Bardhan et al. (1979) | Placebo | 4 | 33 | 24 | 13 | 38 | NS | 14 |

NOTE: NS=not statistically significant.

[a]N=total followed in smoking category.

[b]%=percentage of total who experienced healed ulcers within specified time; p-values calculated by chi-square when not provided in paper.

SOURCE: Kikendall, Evaul, Johnson (1984).

**TABLE 2.—Results of statistical analysis of pooled data from Table 1**

| | Percentage healed | | | | | |
|---|---|---|---|---|---|---|
| | Smokers | | Nonsmokers | | Test statistic | |
| | N[a] | %[b] | N[a] | %[b] | Z | p-value |
| All patient groups | | | | | | |
| $H_2$-blockers | 449 | 70 | 278 | 90 | 7.1 | <0.0001 |
| Placebo | 347 | 28 | 166 | 49 | 4.6 | <0.0001 |
| Subset of large patient groups | | | | | | |
| $H_2$-blockers | 284 | 70 | 183 | 89 | 5.3 | <0.0001 |
| Placebo | 149 | 29 | 88 | 51 | 3.4 | <0.0012 |

[a]N=total followed in smoking category.

[b]%=percentage of total who experienced healed ulcers within specified time.

SOURCE: Kikendall, Evaul, Johnson (1984).

smokers receiving cimetidine were as likely to experience recurrence as nonsmokers receiving placebo, leading the authors to conclude that for smokers, quitting smoking may be more important in the prevention of ulcer recurrence than receiving cimetidine treatment (Sontag et al. 1984). Table 3 displays the results of similar prospective, controlled trials of the recurrence of duodenal ulcer identified in a literature search performed in March 1990. Trials or treatment groups with fewer than 12 smokers or 12 nonsmokers and reports that did not provide the raw data relative to smoking were omitted. Smokers had more recurrences than nonsmokers in every trial or every treatment group, regardless of the treatment (even surgery) and prophylactic therapy used to achieve healing. The difference was statistically significant in about half of the studies.

The only study of larger size that failed to show even a nonsignificant advantage for nonsmokers was an Australian community-based study, not included in Table 3 because the requisite raw data were not published (Nasiry et al. 1987). This study differed from most of those listed in Table 3 in several ways, including larger numbers of exclusions, 41-percent withdrawals, primary reliance on symptoms rather than endoscopy to document recurrences, and lack of systematic effort to control the use of medications that may affect ulcer recurrence. Factors such as these may explain the disparate results.

One trial listed in Table 3 found that incremental increases of cigarette consumption were significantly associated with greater risk of duodenal ulcer recurrence (Korman et al. 1983). Massarrat, Müller, and Schmitz-Moormann (1988) and Piper, McIntosh and Hudson (1985) also found that the number of cigarettes smoked per day was a significant predictor for ulcer recurrence. Although these studies were designed to assess risk factors for recurrence of duodenal ulcer, the latter two studies are not listed in Table 3 because one did not present the necessary raw data (Massarrat, Müller, Schmitz-Moormann 1988) and the other (Piper, McIntosh, Hudson 1985) had a study design that differed from that of the studies listed in Table 3.

**TABLE 3.—Recurrences of duodenal ulcer in smokers and nonsmokers in clinical trials**

| Reference | Prophylaxis | Followup (mo) | Recurrences | | | | p-value |
|---|---|---|---|---|---|---|---|
| | | | Smokers | | Nonsmokers | | |
| | | | N[a] | %[b] | N[a] | %[b] | |
| Sontag et al. (1984) | Cimetidine | 12 | 186 | 34 | 114 | 18 | <0.01 |
| Bianchi Porro et al. (1982) | Cimetidine | 12 | 66 | 59 | 40 | 42 | NS[c] |
| Lauritsen et al. (1987) | Ranitidine | 12 | 48 | 33 | 21 | 19 | NS |
| Gibinski et al. (1984) | Ranitidine | 12 | 62 | 45 | 123 | 11 | <0.005 |
| Cerulli et al. (1987) | Nizatidine | 3 | 139 | 17 | 118 | 4 | 0.001 |
| Brunner (1988) | Roxatidine acetate | 6 | 48 | 48 | 41 | 20 | <0.01 |
| Lauritsen et al. (1987) | Enprostil | 12 | 52 | 65 | 14 | 50 | NS |
| Sonnenberg et al. (1981) | Various | 12 | 33 | 52 | 33 | 33 | NS |
| Battaglia et al. (1984) | Various | 12 | 46 | 30 | 24 | 21 | NS |
| Paakkonen et al. (1989) | Sucralfate | 12 | 13 | 69 | 19 | 47 | NS |
| Bynum and Koch (1989) | Sucralfate | 4 | 58 | 45 | 64 | 39 | NS |
| Classen et al. (1983) | Sucralfate | 6 | 37 | 25 | 51 | 18 | NS |
| Graffner and Lindell (1988) | Parietal cell vagotomy | 60–168 | 190 | 24 | 116 | 7 | <0.01 |
| Rydning et al. (1982) | Diet | 6 | 55 | 69 | 18 | 39 | <0.05 |
| Sontag et al. (1984) | Placebo | 12 | 39 | 72 | 31 | 21 | <0.001 |
| Bolin et al. (1987) | Placebo | 12 | 13 | 85 | 13 | 77 | NS |
| Marks et al. (1989) | Placebo | 12 | 21 | 95 | 12 | 67 | <0.05 |
| Paakkonen et al. (1989) | Placebo | 12 | 16 | 88 | 24 | 67 | NS |
| Bynum and Koch (1989) | Placebo | 4 | 50 | 81 | 67 | 50 | <0.01 |
| Classen et al. (1983) | Placebo | 6 | 39 | 62 | 45 | 41 | NS |
| Cerulli et al. (1987) | Placebo | 3 | 146 | 37 | 110 | 25 | 0.05 |

**TABLE 3.—Continued**

| Reference | Prophylaxis | Followup (mo) | Recurrences | | | | p-value |
|---|---|---|---|---|---|---|---|
| | | | Smokers | | Nonsmokers | | |
| | | | N[a] | %[b] | N[a] | %[b] | |
| Hallerback et al. (1987)[d] | None | 12 | 111 | 80 | 147 | 58 | <0.001 |
| Korman et al. (1983) | None | 12 | 45 | 84 | 60 | 53 | <0.01 |
| Lam et al. (1987) | None | 24 | 60 | 100 | 178 | 74[e] | <0.05 |
| Lee, Samloff, Hardman (1985) | None | 4 | 58 | 69 | 49 | 45 | <0.05 |
| Koelz and Halter (1989) | None | 12 | 25 | 64 | 28 | 50 | NS |

NOTE: NS=not statistically significant.
[a]N=total followed in smoking category.
[b]%=percentage of total who experienced recurrence within the specified time; p-values calculated by chi-square when not provided in paper.
[c]p<0.01 when heavy smokers were compared with nonsmokers.
[d]23% of subjects in this study had gastric ulcer.
[e]Estimated from figure in paper.

## Healing of Gastric Ulcers

Doll, Jones, and Pygott (1958) studied 80 smokers hospitalized with gastric ulcer. Of these, 40 randomly chosen patients were advised to stop smoking; the remaining 40 did not receive advice regarding smoking. As assessed by barium examination, the average reduction in ulcer crater size at 28 days was 78.1 percent among those advised to stop smoking and 56.6 percent among those not advised to stop ($p<0.05$). The reduction in crater size was 83.2 percent among smokers who stopped smoking completely versus 71.8 percent among those advised to stop but who did not do so. Most of the latter group substantially reduced their tobacco consumption during the trial. This study indicates that gastric ulcer patients who stopped or reduced smoking after receiving medical advice responded much better to treatment than smokers who were not advised to stop (Doll, Jones, Pygott 1958). This study, performed in the era before the availability of potent antisecretory agents, suggests that smoking cessation alters the natural history of gastric ulcer among smokers.

These findings have been confirmed by Tatsuta, Iishi, and Okuda (1987). Sixty-four Japanese outpatients with endoscopically proven gastric ulcer were treated with antacids and dicyclomine hydrochloric acid. Additionally, half of the 40 smokers were advised to stop smoking or to reduce smoking by at least one-half. Advice regarding smoking was not given to the remaining smokers. Endoscopy was repeated in 12 weeks by an endoscopist who was unaware of the patients' symptoms or smoking status. Ulcers had healed in 11 of 12 smokers (92 percent) who stopped or reduced smoking and in 7 of 28 smokers (25 percent) who continued to smoke at their pretreatment level ($p<0.001$). Ulcers also healed in 60 percent of nonsmokers (Tatsuta, Iishi, Okuda 1987).

A retrospective study (Herrmann and Piper 1973) that employed air contrast radiography to assess ulcer presence and size in 101 gastric ulcer patients found mean decreases in ulcer size at 3 weeks of 69, 73, and 84 percent, for smokers who continued to smoke, smokers who stopped smoking, and nonsmokers, respectively. Although seeming to support the findings of Doll, Jones, and Pygott (1958) and Tatsuta, Iishi, and Okuda (1987), these differences were not statistically significant (Hermann and Piper 1973). The ulcer size at entry into this study was three times as great among smokers as among nonsmokers, rendering inappropriate a comparison of the time required for complete healing among groups.

Only these three clinical studies have assessed the benefits of smoking cessation on the healing of gastric ulcer; all three demonstrate or suggest a benefit. In contrast, recent randomized therapeutic clinical trials have generally shown no advantage in gastric ulcer healing for nonsmokers compared with smokers (Wright et al. 1982; Kellow et al. 1983; Farley et al. 1985; Euler et al. 1989; McCullough et al. 1989).

## Recurrence of Gastric Ulcers

Tatsuta, Iishi, and Okuda (1987) evaluated the effect of smoking cessation on the recurrence of gastric ulcers for 47 participants who had an endoscopically proven gastric ulcer within the previous 6 months but who were ulcer-free at entry into the trial.

All were treated as outpatients with antacids and dicyclomine hydrochloric acid. Half of the smokers were advised to stop smoking or to reduce cigarette consumption by at least one-half. The remainder were not given this advice. Endoscopy was repeated at 3 and 6 months or whenever symptoms recurred. Data for seven patients who failed to complete the trial were not presented or analyzed. Ulcers recurred among 9 of 12 patients who continued to smoke at their previous level and in 3 of 13 patients who quit or substantially reduced their smoking (75 vs. 23 percent, $p<0.05$). An ulcer recurred in 1 of 15 (7 percent) nonsmokers (Tatsuta, Iishi, Okuda 1987).

This is the only prospective, controlled study that has evaluated the effect of smoking cessation on gastric ulcer recurrence. However, the reports of several clinical trials of maintenance therapy for gastric ulcer have provided data on the impact of smoking on the trial results. All such prospective, controlled clinical trials are displayed in Table 4. Although several of these trials or treatment groups are small, every treatment group shows an advantage for nonsmokers. In two trials, the difference was statistically significant. The median percentage difference in recurrences for smokers compared with nonsmokers is 20 percentage points.

## Summary

The known effects of smoking on gastroduodenal physiology include several mechanisms that might enhance an ulcer diathesis. Most of these mechanisms are rapidly reversible upon cessation of smoking. The association of smoking with increased maximal gastric acid secretory capacity has not been assessed for reversibility.

Epidemiologic studies consistently demonstrate that current smokers compared with nonsmokers are at increased risk for occurrence of and death from duodenal and gastric ulcer. The risks for former smokers are generally found to be between those of current smokers and nonsmokers.

Duodenal ulcers are less likely to heal within specific time intervals among smokers than among nonsmokers, regardless of whether patients are treated with placebo or most active therapies. Both gastric and duodenal ulcers are more likely to recur within specified periods of observation among smokers compared with nonsmokers.

A limited number of clinical trials have been performed to assess the effect of smoking cessation on the course of peptic ulcer disease. These show that smoking cessation, or in some trials, substantial reduction of daily cigarette consumption, is associated with fewer duodenal ulcers at 6 months but not at 3 months, with improved short-term healing of gastric ulcers, and with reduced recurrence of gastric ulcers.

**TABLE 4.—Recurrences of gastric ulcer in smokers and nonsmokers in clinical trials**

| Reference | Prophylaxis | Followup (mo) | Recurrences | | | | p-value |
|---|---|---|---|---|---|---|---|
| | | | Smokers | | Nonsmokers | | |
| | | | N[a] | %[b] | N[a] | %[b] | |
| Barr et al. (1983) | Cimetidine | 24 | 10 | 40 | 14 | 29 | NS |
| Gibinski et al. (1984) | Ranitidine | 12 | 35 | 37 | 43 | 14 | <0.025 |
| Borsch (1988) | Roxatidine acetate | 6 | 31 | 35 | 36 | 28 | NS |
| Marks et al. (1987) | Sucralfate | 6 | 21 | 33 | 8 | 13 | NS |
| Marks et al. (1985) | Sucralfate | 6 | 27 | 19 | 4 | 0 | NS |
| Marks et al. (1987) | Placebo | 6 | 18 | 67 | 9 | 33 | NS |
| Barr et al. (1983) | Placebo | 24 | 15 | 60 | 10 | 40 | NS |
| Marks et al. (1985) | Placebo | 6 | 23 | 78 | 7 | 43 | NS |
| Lauritsen et al. (1989) | None | 6 | 144 | 45 | 73 | 25 | <0.05 |

NOTE: NS=not statistically significant.
[a]N=total followed in smoking category.
[b]%=percentage of total who experienced recurrence within the specified time; p-values calculated by chi-square when not provided in paper.

## PART II. OSTEOPOROSIS AND SKIN WRINKLING

### Osteoporosis

#### Introduction

Osteoporosis is a condition of reduced bone mass that increases the risk of fractures, especially of the hip, distal forearm, and vertebrae, after minimal trauma (Consensus Conference 1984). The most devastating outcome of osteoporosis is hip fracture, occurring in over 200,000 persons each year in the United States (Haupt and Graves 1982; Lewinnek et al. 1980). Mortality in the first years after hip fracture is increased 15 to 20 percent (Cummings and Black 1986; Gallagher et al. 1980; Jensen and Tøndevold 1979; Lewinnek et al. 1980; Miller 1978). Results from three studies indicate that approximately 15 to 25 percent of previously functionally independent persons who sustained a hip fracture remained in a long-term facility after 1 year, and 25 to 35 percent of those who returned home after a hip fracture required help in performing daily activities (Campbell 1976; Jensen and Bagger 1982; Thomas and Stevens 1974).

Osteoporotic forearm and vertebral fractures also have been found common among the elderly. Most cases do not require hospitalization or result in long-term disability (Ga vay et al. 1979; Owen et al. 1982); however, the cost of caring for these fractures has been estimated to be $140 million per year (Melton and Riggs 1983).

Established risk factors for osteoporotic fractures include advanced age, white race, female sex, number of years since natural or surgical menopause, slender body build, prolonged immobilization, alcohol use, and use of certain medications (Cummings et al. 1985). Postmenopausal estrogen replacement therapy decreases the risk of osteoporotic fractures; this risk reduction is greater with longer duration of treatment (Weiss et al. 1980).

#### Pathophysiologic Framework

Smoking may alter risk of osteoporosis and fracture through several mechanisms. First, bone loss accelerates at menopause (Lindquist and Bengtsson 1979; Lindquist et al. 1981; Paganini-Hill et al. 1981; Richelson et al. 1984; Mazess 1982), and smokers undergo menopause 1 to 2 years earlier than never smokers (Chapter 8). Second, a thin body build increases risk of osteoporotic fracture (Daniell 1976; Hutchinson, Polansky, Feinstein 1979; Kiel et al. 1987; Paganini-Hill et al. 1981; Williams et al. 1982; Wyshak 1981), and smokers generally weigh less than nonsmokers (Chapter 10). Third, smoking has been reported to reduce the endogenous production of estrogen (MacMahon et al. 1982) and increase its metabolism (Jensen, Christiansen, Rødbro 1985; Michnovicz et al. 1986).

Smoking also may decrease the effectiveness of exogenous estrogens (Daniell 1987). Endogenous estrogen metabolism is widely believed to affect the risk of osteoporosis and fracture, and exogenous estrogen use is firmly linked with lower rates of postmenopausal bone loss and lower risk of hip, forearm, and vertebral fracture among

women (Ettinger, Genant, Cann 1985; Hutchinson, Polansky, Feinstein 1979; Kreiger et al. 1982; Paganini-Hill et al. 1981; Weiss et al. 1980; Riis, Thomsen, Christiansen 1987; Kiel et al. 1987). However, a 1- to 2-year shift in age at menopause probably does not alter the risk of osteoporotic fracture substantially. Not all researchers have found differences in endogenous estrogen levels between smokers and nonsmokers (Crawford et al. 1981; Friedman, Ravnikar, Barbieri 1987). Although therapy with exogenous estrogen reduces the risk of osteoporotic fractures among women (Ettinger, Genant, Cann 1985; Hutchinson, Polansky, Feinstein 1979; Kreiger et al. 1982; Paganini-Hill et al. 1981; Weiss et al. 1980; Riis, Thomsen, Christiansen 1987; Kiel et al. 1987), it is not certain whether levels of endogenous estrogen are lower in women with osteoporosis than in women without osteoporosis (Cauley et al. 1986; Davidson et al. 1983). The likely effects on osteoporosis and fracture risk of smoking-related changes in circulating levels of male sex hormones, if such changes occur (Chapter 8, Part I), are impossible to predict.

### Bone Mineral Content in Smokers Compared With Nonsmokers

Susceptibility to fractures is increased by a reduction in bone mass. Smoking has been studied extensively in relation to various measurements of bone mass.

Using radiographs of the hand, Daniell (1976) measured percent cortical area (PCA) of the second metacarpal midpoint in 103 women aged 40 to 49 years and in 208 women aged 60 to 69 years. Smoking was associated with lower PCA among older women, but there was no difference in PCA between smokers and nonsmokers among younger women. PCA loss was estimated in 80 of the women aged 60 to 69 by comparison with averages for the younger women. Smokers had significantly greater PCA loss per year after menopause compared with nonsmokers (1.02 vs. 0.69 percent/ year, respectively, $p<0.001$). Nonobese smokers had greater PCA loss per year compared with nonobese nonsmokers, but obese smokers and obese nonsmokers did not differ in PCA loss. In both smokers and nonsmokers, nonobese women lost more PCA per year after menopause than obese women. None of these comparisons controlled for age or years since menopause.

Since this first report describing "osteoporosis of the slender smokers," at least 21 other studies comparing bone mass in smokers and nonsmokers have been published (Table 5). Nine of the nineteen studies found lower bone mass in smokers compared with nonsmokers (Aloia et al. 1988; Holló, Gergely, Boross 1979; Jensen, Christiansen, Rødbro 1985; McNair et al. 1980; Mellström et al. 1982; Rundgren and Mellström 1984; Sparrow et al. 1982; Suominen et al. 1984; Slemenda et al. 1989), and the difference was statistically significant in all but one of these nine studies (Suominen et al. 1984). The population-based studies by Mellström and associates (1982) and Rundgren and Mellström (1984) are noteworthy because they controlled for potentially confounding variables. In both studies, bone mass was measured by dual photon densitometry of the heel. Mellström and colleagues (1982) reported that bone mass of the heel was significantly lower in smokers than in nonsmokers. Rundgren and Mellström (1984) reported 10 to 20 percent lower bone mass in male smokers and 15 to 30 percent lower bone mass in female smokers.

**TABLE 5.—Summary of studies of smoking and bone mass**

| Reference | Population | Bone measurement | Findings | Comments |
|---|---|---|---|---|
| Daniell (1976) | 103 women aged 40–49<br>208 women aged 60–69 | PCA from x ray of the right 2nd metacarpal | Women aged 40–49 yr: no association of smoking ≥10 cig/day for ≥5 yr and PCA; women aged 60–69 yr: smokers had lower PCA than nonsmokers[a] | Using the 40–49-year-old women as baseline, the 60–69-year-old smokers lost more PCA/yr since menopause than nonsmokers, but this finding was statistically significant only among nonobese women; no control for confounding |
| Holló, Gergely Boross (1979) | 95 men aged 61–75<br>49 men aged 76–90<br>66 women aged 61–75 | BM by SPA of radius of the nondominant forearm | BM was significantly less in heavy smokers (≥20 cig/day) compared to never smokers in each age, sex strata[a] | Controlled for age and sex only |
| McNair et al. (1980) | 163 insulin-dependent diabetics aged 21–70 | BM by SPA at 6 forearm sites | Mean BM compared to normal nondiabetics:<br>Smoker<br><11 cig/day 9.3% less<br>11–15 cig/day 10.1% less<br>>15 cig/day 12.7% less<br>Nonsmoker 5.4% less<br>Mean BM in smokers significantly less than mean BM in nonsmokers | All subjects were diabetic, and findings may not generalize to all smokers; no control for confounders |
| Lindquist et al. (1981) | 130 women in a population-based study in Sweden | BM by DPA at 3rd lumbar vertebrae | Stratifying by age and menopausal status, no difference in BM between smokers and nonsmokers | Controlled for age, race, sex, menopausal status |
| Lindergård (1981) | 136 healthy volunteers aged 20–69 | BM by SPA of midshaft of forearm | No association of smoking and BM | No control for confounders |

**TABLE 5.—Continued**

| Reference | Population | Bone measurement | Findings | Comments |
|---|---|---|---|---|
| Mellström et al. (1982) | 357 men in a population-based study in Sweden | BM by DPA at heel | BM lower in smokers vs. nonsmokers[a] | No control for confounders |
| Lindquist (1982) | 1,462 women in a population-based study in Sweden | BM by DPA at 3rd lumbar vertebrae | Stratifying by age and menopausal status, no difference in BM between smokers and nonsmokers | Controlled for age, race, sex, menopausal status; data may include that reported in Lindquist (1981) |
| Sparrow et al. (1982) | 341 men aged 40–80 followed for 3–5 yr | PCA x ray of right 2nd metacarpal performed at baseline and 3–5 yr later | At baseline, no difference between PCA in smokers and nonsmokers; over the 3–5-yr period, smokers lost more PCA than nonsmokers[a] (B=–0.148, p=0.03) | Controlled only for age |
| Rundgren and Mellström (1984) | 409 men and 559 women born in 1901–02 or 1906–07 from a population-based study in Sweden | BM by DPA at heel | BM in women was 15–30% lower in smokers vs. nonsmokers[a] and in men 10–20% lower in smokers vs. nonsmokers[a]; no difference between ex-smokers and smokers | Controlled for age, race, sex, weight, but not for menopausal status or estrogen use |
| Suominen et al. (1984) | 142 men aged 31–75 | BM by γ ray attenuation in the calcaneums | BM in smokers lower than that in nonsmokers, but not statistically significant | Multiple tests performed; controlled for age only |
| Johnell and Nilsson (1984) | 395 49-yr-old white women randomly selected from participants in a population-based study in Sweden | BM by γ absorptiometry at the radius 1 cm and 6 cm proximal to the ulnar styloid | No association of smoking and BM in univariate or multivariate analysis | Controlled for age, race (white), sex, height, weight, age at menarche, menopausal status, number of children breast feeding, oral contraceptive use, physical activity, and calcium intake |

**TABLE 5.—Continued**

| Reference | Population | Bone measurement | Findings | Comments |
|---|---|---|---|---|
| Jensen, Christiansen, Rodbro (1985) | 136 postmenopausal women volunteers from Sweden randomly assigned to different estrogen doses and followed for 1 yr | BM by SPA at distal radius performed at baseline and after 1 yr of estrogen treatment | At baseline, no difference in BM between smokers (smoked in prior 6 mo) and nonsmokers (no smoking in prior 6 mo); in 28 smokers treated with high doses estrogen, the mean % increase in BM was less than the mean % increase in 28 treated nonsmokers[a] | No control for confounders |
| Sowers, Wallace, Lemke (1985) | 86 women volunteers from 2 rural communities in Iowa | BM by SPA at distal radius | No association of smoking and BM | Small study with poor power; subjects were young, limiting generalizability; no control for confounders |
| Cauley et al. (1986) | 78 white postmenopausal women not on estrogen therapy | BM CT scan of the dominant radius at 30% of distance from wrist to elbow | No association of smoking and BM in univariate analysis | Small study with poor power; no control of confounders |
| Slemenda et al. (1987) | 84 peri- and postmenopausal women evaluated every 4 mo for 3 yr; none on estrogen therapy | BM SPA at midshaft and distal radius | No association of smoking and BM overall in peri- and postmenopausal groups | Small study with poor power; no control of confounders |
| McDermott and Witte (1988) | 35 smokers (≥1 ppd for ≥14 yr and currently smoking) 35 nonsmokers (never smoked); matched for age, sex, weight, height, calcium intake, menopausal status, and estrogen use | BM SPA of midradius | No association of smoking and BM | Authors state that power to detect a 5% difference between groups at $\alpha = 0.05$ was >80% in both men and women; confounding controlled by matching |

**TABLE 5.—Continued**

| Reference | Population | Bone measurement | Findings | Comments |
|---|---|---|---|---|
| Aloia et al. (1988) | 26 menstruating white women volunteers | BM SPA of the radius and DPA of the spine | Smoking was associated with lower BM in the radius ($p<0.01$) and of the spine ($p<0.03$) | Controlled for physical activity and height only |
| Picard et al. (1988) | 183 healthy French-Canadian women aged 40–50 | BM by DPA of 2nd–4th lumbar vertebrae and by SPA of the distal radius | No association of smoking with either BM of the lumbar vertebrae or distal radius | No control for confounders |
| Bilbrey, Weix, Kaplan (1988) | 1,069 women referred for osteoporosis screening to 18 centers in 11 States | BM by SPA of distal and midradius | No association of smoking with BM of radius | |
| Stevenson et al. (1989) | 284 healthy women (112 premenopausal, 172 postmenopausal) volunteers aged 21–68 | BM by DPA of femoral neck, Wards triangle, trochanteric region and 2nd–4th lumbar vertebrae | In premenopausal women, correlation of ppd smoked and BM of vertebrae=–0.24[a]; no association at other sites; in postmenopausal women, no association of ppd smoked and BM at any site | Controlled for menopausal status only |
| Slemenda et al. (1989) | 84 peri- and postmenopausal women | BM by SPA of distal and midradius, DPA of lumbar spine | Significantly low BM in heavy smokers compared with nonsmokers, no difference in rates of change in BM between smokers and nonsmokers | Controlled for menopausal status (by design) and adjusted for age and body mass index |

NOTE: PCA=percent cortical area; BM=bone mass; SPA=single photon absorptiometry; DPA=dual photon absorptiometry; ppd= packs/day.

[a] $p<0.05$.

Eleven other published studies reported no association between smoking and bone mineral content (Bilbrey, Weix, Kaplan 1988; Cauley et al. 1986; Johnell and Nilsson 1984; Lindergård 1981; Lindquist 1982; Lindquist et al. 1981; McDermott and Witte 1988; Picard et al. 1988; Slemenda et al. 1987; Sowers, Wallace, Lemke 1985; Stevenson et al. 1989). In addition, one study that found differences in bone mass between heavy smokers and nonsmokers reported no differences in longitudinally measured rates of bone loss (Slemenda et al. 1989). Some of these studies were small, and the findings of no association may be due to type II statistical errors, that is, the failure to find a true association (Cauley et al. 1986; Slemenda et al. 1987; Sowers, Wallace, Lemke 1985); other studies were large and had excellent statistical power (Bilbrey, Weix, Kaplan 1988; Johnell and Nilsson 1984; Lindquist 1982; McDermott and Witte 1988).

One study evaluated the effect of smoking on bone mass among women taking estrogen (Jensen, Christiansen, Rødbro 1985). Among 56 postmenopausal women who underwent replacement therapy with high doses of estrogen for 1 year, the mean percentage increase in bone mass of the distal radius was 1.01 in 28 smokers compared with 2.58 in nonsmokers. This difference was statistically significant.

### Smoking as a Risk Factor for Osteoporotic Fractures

Daniell (1976) reported that 76 percent of women with osteoporotic vertebral fractures smoked 10 cigarettes or more per day for 5 years or more, compared with 43 percent of controls with no vertebral fracture. Smoking is strongly associated with age, alcohol use, and, among some populations, use of exogenous estrogens. These are potentially strong confounders of the relationship between smoking and vertebral fracture, but Daniell's comparison between cases and controls did not consider them.

Since Daniell's 1976 study, seven other case–control studies have examined the association between smoking and fracture of the hip or vertebrae (Table 6). Five of the seven case–control studies reported an increased risk of these osteoporotic fractures among smokers (Aloia et al. 1985; Cooper, Barker, Wickham 1988; Paganini-Hill et al. 1981; Seeman et al. 1983; Williams et al. 1982), and this association was statistically significant in three of the studies (Aloia et al. 1985; Cooper, Barker, Wickham 1988; Williams et al. 1982). In the study by Williams and coworkers (1982), smokers were compared with obese nonsmokers, making it difficult to assess the independent association of smoking with the risk of osteoporotic fractures. A second analysis of smoking and the risk of hip or forearm fracture among the same subjects who were studied by Williams and colleagues (1982) showed no overall association of smoking and fractures (Alderman et al. 1986). In only two case–control studies were statistical adjustments made for age and exogenous estrogen use, which are potentially strong confounding variables; in both of these studies, there was no statistically significant association of smoking and fracture risk (Paganini-Hill et al. 1981; Kreiger et al. 1982; Kreiger and Hilditch 1986).

In five cohort studies (Table 7), there was no increase in the risk of fracture among smokers (Farmer et al. 1989; Felson et al. 1988; Hemenway et al. 1988; Holbrook, Barrett-Connor, Wingard 1988; Jensen 1986). Three of these reports were based on

**TABLE 6.—Summary of case–control studies of smoking and fractures**

| Reference | Population | Vertebral fractures | | |
|---|---|---|---|---|
| | | Comparison | Estimated relative risk | Comments |
| Daniell (1976) | Cases: 38 women aged 40–69 with acute symptomatic vertebral fractures after minimal trauma<br>Controls: 572 women outpatient volunteers aged 50–69 | ≥10 cig/day for ≥5 yr vs. less | 4.2[a, b] | No control for confounders; no statistical analysis |
| Seeman et al. (1983) | Cases: 105 men aged 44–84 with vertebral fractures<br>Controls: 105 men aged 44–83 with Paget's disease matched for age and length of followup | Nonobese, nondrinking, nonsmokers vs. nonobese, nondrinking smokers with no underlying disease:<br>aged <60<br>aged 60–69<br>aged ≥70 | <br>0.8<br>1.6<br>3.1 | One-third of the cases had a medical condition associated with bone loss; controls with Paget's disease may not be representative of men without vertebral fractures; design controls for age, obesity, and alcohol use |
| Aloia et al. (1985) | Cases: 58 white women (mean age 64.5) volunteers with vertebral fractures<br>Controls: 58 white women volunteers matched for age | Smokers vs. nonsmokers | 3.2[a, b] | Controlled for age only; multiple other risk factors examined using univariate tests |