Smoking Lower Yield Cigarettes and Disease Risks

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INTRODUCTION This chapter examines whether the disease risks of smoking have changed as a result of the changes in cigarette design over the last 50 years. Cigarette design and manufacture have changed substantially over the last half century, and the relationship of these changes to altered disease risks is an important scientific and public health issue. No cigarette currently manufactured and sold can be considered safe, and the principal recommendation for any smoker interested in reducing future disease risks is to quit smoking. However, approximately 47 million individuals remain cigarette smokers in the United States (CDC, 2000a), and many of these smokers have tried to quit and failed. If these continuing cigarette smokers could alter their risk by choosing cigarettes that differ in machine-measured tar and nicotine yields or other characteristics, and if this choice did not interfere with their likelihood of cessation, then advice to switch brands might be one component of a comprehensive strategy to reduce the disease consequences of tobacco use. Alternatively, if these lower yield products do not reduce risks and if smokers switch brands instead of quitting, then the changes in cigarettes and their marketing as reduced-risk products represent a cruel deception of current smokers. For those smokers who delay cessation, the increased duration of smoking that results from delayed cessation is likely to be a more powerful determinant of disease risk than a small, or nonexistent, reduction in tar exposure from use of these cigarettes.

Prior reviews (U.S. DHHS, 1981; NCI, 1996) of changes in disease risk with switching from unfiltered or higher yield to filtered or lower yield cigarettes concluded that switching probably reduced lung cancer risk somewhat, but only if smokers did not increase the number of cigarettes that they smoked per day when they switched to lower yield cigarettes. Ninety-seven percent of the cigarettes sold in the United States currently have filters and the sales-weighted tar yield of cigarettes has declined by more than 60 percent since the 1950s.

Assessing the consequences of changes in cigarette design and manufacturing is made difficult by the lengthy time period over which these changes have been made, the difficulty of tracking changes in smoking behavior over time, and the lack of validity of the FTC yield data as indicators of doses of toxic compounds of cigarette smoke. Nevertheless, epidemiological evidence has provided some insights concerning the consequences of changes in cigarettes over the last fifty years. The data have three sources: (1) observations of national rates of lung cancer by age in relation to age-specific smoking patterns; (2) case-control and cohort studies that have compared lung cancer risks in smokers of different types of products at particular points and times; and (3) comparisons of lung cancer in smok-

ers over time, coming from either a single cohort with lengthy follow-up (the British Physicians Study) or repeated cohort observations (the two CPS studies of the American Cancer Society).

Each of these sources of data has strengths and limitations when used to assess the effect of changes in cigarette design on disease risks. Changes in age-specific national lung cancer death rates over time measure the actual population burden of disease, and these rates must change if there has been any substantive benefit resulting from changes in cigarette design. They also offer the opportunity to examine change in disease rates over periods of time long enough to allow full expression of the cumulative effects of all of the changes in cigarette design, which have also occurred over multiple decades. One major limitation of these data is the absence of information on smoking status and type of cigarette smoked in national death registry data. This absence requires comparison of the lung cancer death rate data with information derived from population surveys on smoking behavior and market data on type of cigarette sold. It limits the examination of these data sets to ecological analyses and comparisons of trends over time in population measures of smoking behaviors and disease rates.

Epidemiological studies have the strength of being able to collect detailed information on smoking behaviors, type of cigarette smoked and other variables of interest that allow differences in these factors to be examined in detail, and controlled, in the analysis of disease risk. However, these studies are limited by confining their observations to relatively short slices of time or fixed cohorts of individuals. The cross-sectional nature of case-control studies requires extrapolation from differences observed across individuals who smoke different types of cigarettes at one slice of time, with the presumption that those cross-sectional differences in type of cigarette smoked reflect the longitudinal changes in cigarette design that preceded them. For example, the difference in dose of smoke received by a filter cigarette smoker compared to a non-filter cigarette smoker in 1980 may or may not correspond to the differences in smoke dose received by smokers in the 1950s (almost entirely non-filtered cigarette smokers) compared to the dose of smoke received by filtered cigarette smokers in the 1980s. A more important limitation of these studies of changing cigarette design is the possibility that the characteristic of the cigarette being studied (machine-measured yield) may directly influence smoking behavior, including the number of cigarettes smoked per day. This linkage between the characteristic being studied and the measures used to control for differences between populations of smokers in the dose of smoke received makes control for intensity of smoking problematic. In addition, the reasons for choosing the brand smoked may be linked to other demographic or behavioral characteristics which may also influence disease outcome (level of addiction, interest in cutting down or quitting, differences in other health related behaviors, etc.).

Examination of cohorts with long durations of follow-up (the British Physicians Study), or comparing similar cohorts separated by a long interval (the two CPS studies of the American Cancer Society), offer the strengths of long periods of observation and the availability of individual level data on

smoking behaviors and other characteristics. Limitations of following a single cohort for long periods of follow-up include the fact that the cohort becomes less and less representative of the entire population over time; and, in particular, it is limited in its ability to examine the effects of changing cigarette design on smokers who initiate with those products rather than switch to them. Comparison of similar cohorts separated by more than 20 years allows inclusion of younger generations of smokers, but is limited by the possibility that the smokers in the two cohorts are likely to be of different composition in demographic characteristics and may differ in other characteristics as well. These differences may occur because the later cohort of smokers from the 1980s is composed of those who have been unable or unwilling to quit smoking; and therefore, it may not be directly comparable to the earlier cohort from the 1960s when the percentage of former smokers was lower.

Each of these sources of epidemiological data can expand our understanding of the disease burden that results from changing cigarette design, and together they complement each other to counter the limitations present when any one data source is examined in isolation. The question addressed in this chapter is whether cigarette smoking in the year 2000, with all of the changes in cigarette design and all of the compensatory changes in smoking behavior, is more or less hazardous than it was in 1950. The disease consequences of changes in cigarette design and the consequences of switching type of cigarette smoked can be approached from two perspectives. First, has the risk of disease per cigarette smoked changed; and second, has the risk of disease for smokers compared to nonsmokers changed. From the public health perspective, the latter is the more relevant question.

The body of existing published literature was examined to answer this question, and new analyses of data sets from the American Cancer Society and the California Tobacco Survey are provided to explore and clarify the differences between epidemiological evaluations and the national trends in lung cancer death rates.

The chapter begins with a discussion of the historical development of cigarettes that have produced ever lower machine-measured tar and nicotine yields using the Federal Trade Commission (FTC) protocol[1] (Pillsbury, 1996). It then discusses the complexity of epidemiological examination of the self-selected behavior of smoking lower yield cigarettes and outlines the potential sources of confounding likely to occur in epidemiological studies. Next, various epidemiological studies that have assessed the risks of low-yield cigarettes in relation to lung cancer and cardiovascular and chronic respiratory diseases are examined. The chapter considers the evidence on compensatory smoking, those changes in smoking behavior that allow smokers to maintain their customary nicotine intake when they switch to a cigarette with a lower machine-measured nicotine yield. It discusses two

[1] The machine smokes the cigarette with 2-second, 35-ml puffs and a 58-second inter-puff interval until a 23-mm butt length or 3 mm from the filter overwrap is reached.

new epidemiological analyses that find higher daily cigarette consumption among smokers of lower yield cigarettes. Finally, the chapter considers cohort- and population-based studies that have examined temporal trends in lung cancer incidence or mortality in relation to changes in cigarette design and/or smoking behavior.

Greater weight was placed on evidence derived from trends in populations over time than on evidence from cross-sectional epidemiological studies since reductions in general population death rates are the ultimate outcome measure for the effect of changing cigarette design over the last 50 years. If the changes in cigarette design are of public health significance, they must impact the rates of disease actually occurring in the population of smokers who use these cigarettes. The true effect of changing cigarette design requires integration of the information from epidemiological studies and the population trends in disease rates. If a substantive reduction in disease risk is expected from the epidemiological studies, it should be evident as a change in population disease rates. If the effect is not evident in the population data, then one should reconsider the potential for self-selection and compensatory smoking to bias the epidemiological results or confuse their interpretation.

While the emphasis in the discussion and analyses presented in this chapter is on the tar and nicotine yields measured by the FTC protocol, the question being asked is really whether all of the changes in cigarette design and manufacture over the last half century have altered the disease risks of smoking cigarettes. Part of this focus on FTC yields comes from their use, appropriately, as exposure variables in epidemiological studies. Machine-made measurements of tar and nicotine are used in the discussion simply as convenient surrogates for the cumulative effect of all of the changes that have occurred. Arguments can be made to support differences in risk that might result from individual engineering changes in cigarette manufacturing using evidence based on changes in tobacco smoke chemistry or biological exposure studies, but ultimately, the issue of concern is the net effect of these cigarette design changes on the total disease burden in human smokers as the cigarettes are smoked by the general public. This chapter is focused on answering the question: "Have changes in cigarette manufacture and design over the last 50 years resulted in a meaningful public health benefit to human smokers?" This overall question has two related but distinct research questions. First, has the risk per cigarette smoked been changed by these product modifications; and second have the net adverse consequences of smoking for the population been changed by these product modifications.

Other chapters in this volume describe the marketing and behavioral issues of cigarettes with low machine-measured yields.

HISTORICAL DEVELOPMENT OF THE LOWER YIELD CIGARETTE ISSUE

Cigarette smoking was definitively linked to increased lung cancer risk in the 1950s (Wynder and Graham, 1950; Doll and Hill, 1952, 1954; Hammond and Horn, 1958). It was almost simultaneously discovered that painting cigarette smoke condensate on the skin of animals produced

tumors (Wynder *et al.*, 1953). A logical extrapolation of these observations was that reducing exposure of smokers to the total particulate matter in cigarette smoke should reduce the risk of developing lung cancer. Independent scientists and public health authorities recommended that cigarettes which reduced tobacco smoke delivery to the smoker be developed and marketed by tobacco companies (U.S. Congress, 1967). The tobacco industry initially responded by adding filters to cigarettes and then by offering cigarettes that delivered less tar (the total particulate matter in smoke minus the water and nicotine) in measurements made by machine smoking of cigarettes using a fixed pattern of smoking (U.S. DHHS, 1981; NCI, 1996; Warner, 1985). A variety of approaches to tar reduction were utilized, including 'puffing' the tobacco to reduce the weight of tobacco in a cigarette, altering the blends of tobacco used and porosity of the paper wrapper, changing the density of the tobacco rod, using tobacco stems and reconstituted tobacco sheet, and using a wide variety of filter materials. These changes are detailed more completely in Chapters 2 and 5. Ultimately, this effort to reduce machine-measured tar yields led to the introduction of cigarettes with ventilation holes around the filter. These ventilated filters reduced the tar measured by machine using the FTC method by diluting the smoke with entrained air. Ventilation is the principal method by which the very low levels of machine-measured tar yields of most current light and ultralight cigarettes are produced (see Chapter 2).

Both the smoke exposure and the disease risks resulting from smoking lower yield cigarettes depend on how these cigarettes are used by smokers. Machine-measured yields are only informative for the smoker to the extent that they reflect the smoker's exposure and disease risk either directly or in relation to other brands of cigarettes. Internal tobacco industry documents from the 1960s and 1970s, when filtered and lower yield cigarettes were first heavily marketed to assuage health concerns of smokers, recognized that these changes in cigarette design might not actually result in delivery of less tar to smokers. Since smokers were smoking to derive a sufficient dose of nicotine, they could compensate for reductions in nicotine delivery by changing the way that they smoked these cigarettes in order to preserve their nicotine intake. Tar yield is closely correlated with nicotine yield, and so compensation to preserve nicotine intake preserves tar intake as well.

A Philip Morris company memo (Wakeham, 1961) expressed concern about smokers' likely response to the new highly filtered cigarettes: "As we know, all too often the smoker who switches to a hi-fi cigarette winds up smoking more units in order to provide himself with the same delivery which he had before. In short, I don't believe the smoking pattern has changed much, even with the cancer scares and filter cigarettes."

A research planning memo by Claude Teague (Teague, 1972) was even more explicit: "Given a cigarette that delivers less nicotine than he desires, the smoker will subconsciously adjust his puff volume and frequency, and smoking frequency, so as to obtain and maintain his per hour and per day requirement for nicotine . . ." A Brown & Williamson Tobacco Company memo (Pepples, 1976) commented, "The new filter brands vying for a piece of the growing filter market made extraordinary claims . . . In most cases,

however, the smoker of a filter cigarette was getting as much or more nicotine and tar as he would have gotten from a regular cigarette. He abandoned the regular cigarette, however, on the ground of reduced risk to health." Because tar is delivered in a relatively fixed ratio to nicotine for most conventional cigarettes (see Chapters 2 and 3), compensation to preserve nicotine intake would also preserve tar exposure, minimizing any reduction in a smoker's lung cancer risk from switching to these cigarettes. There has been a reduction in machine-measured tar-to-nicotine ratios in ultralow cigarettes when measured by the FTC method, but these same ratios in ultralow cigarettes increase when smoked under conditions that mimic those of human smokers (see Chapters 2 and 3).

The tobacco industry's response to health concerns about smoking raised by the public health community was to develop cigarettes with lower yields of tar and nicotine as measured by the FTC method. The reductions in tar were marketed as a surrogate for reductions in risk (see Chapter 7). There is no current evidence that the tobacco companies conducted any biological or animal testing to test this hypothesis of reduction in risk. Again, internal tobacco industry documents illuminated the goals and design directions taken by the industry in this effort. A report on a tobacco research conference (Green, 1968) noted, "Research staff should lay down guide lines against which alternative products can be chosen in everyday operations. Although there may, on occasions, be conflict between saleability and minimal biological activity, two types of products should be clearly distinguished, viz:

a) A Health-image (health reassurance) cigarette.

b) A Health-oriented (minimal biological activity) cigarette, to be kept on the market for those consumers choosing it."

Conversion of this line of thinking into cigarette design modifications was further specified in an undated British American Tobacco Company memo: "What would seem very much more sensible, is to produce a cigarette which can be machine smoked at a certain tar band, but which, in human hands, can exceed this tar banding . . ." (BATCO, undated). This concept is described as "elasticity of delivery," which has two definitions as used in this chapter and in tobacco industry documents. First, elasticity is used to describe the phenomenon of a smoker being able to derive markedly different amounts of tar and nicotine from a cigarette by changing the way that it is smoked. Inherent in this concept is the understanding that the elastic cigarette will provide whatever dose of nicotine the smoker wants if the smoker adjusts his or her pattern of smoking appropriately. A second, more technical definition was provided in an Imperial Tobacco of Canada document, which stated, "If the tar delivery increases in direct proportion to the increase in puff volume, the product is inelastic (*i.e.*, elasticity = 1), while if tar delivery increases faster than puff volume, elasticity > 1." (See Imperial Tobacco Limited, 1993.)

The importance of ventilation from perforated filters in achieving this elasticity was clarified by a 1982 Philip Morris memo that described tests on machine yields of cigarettes with ventilated filters when the holes in the fil-

ters were covered and uncovered, using different puff volumes to simulate smoker compensation (Goodman, 1982). The conclusion reached by Goodman stated, "The decrease in dilution from covering a portion of the perforated area can result in an increased delivery to the smoker of highly-diluted cigarettes even though the puff parameters decrease." Implications of the elasticity of delivery design for actual delivery to the smoker had been defined in a prior memo by the same individual (Goodman, 1975) that described a study which examined yields of Marlboro Light® and Marlboro 85® cigarettes when smoked by smokers who had been switched to these brands from their regular choice. The smoking puff profile for these smokers was recorded and then replicated to make measurements on a smoking machine. The conclusion reached by Goodman (1975) stated: "In effect, the Marlboro 85 smokers in this study did not achieve any reduction in smoke intake by smoking a cigarette (Marlboro Lights) normally considered lower in delivery."

These internal tobacco company documents suggest that the effort to develop low-yield cigarettes was conducted with a clear appreciation of the compensation to preserve nicotine intake that was likely to occur in smokers. Cigarettes were designed with elasticity of delivery in an effort to provide low machine yields, allowing marketing of the product as a "health-reassurance" cigarette while continuing to deliver high levels of nicotine to satisfy the addictive demands of the smokers of these cigarettes.

However, even though the impact of changes in cigarette design on actual smoke delivery to smokers was questionable, early studies of the disease risks among smokers of low-yield cigarettes were encouraging. They demonstrated a somewhat lower lung cancer risk among populations of individuals who used filtered and low-yield products, albeit a much smaller reduction in lung cancer risk than the extent of reduction in machine-measured tar. These studies led to considerable optimism about the likely public health benefits of changes that had occurred in cigarette design (U.S. Congress, 1967; U.S. DHEW, 1971, 1979). The early data were particularly encouraging because the reductions in lung cancer risks were demonstrable in populations observed during the mid to late 1960s when filtered cigarettes had only been available for a short period of time (Bross, 1968; Bross and Gibson, 1968; Hammond *et al.*, 1976, 1977). Widespread use of filtered and lower yield products began in the mid 1950s. Since the reduction in excess lung cancer risk with cessation continues to increase for 15-20 years following cessation (U.S. DHHS, 1990; Burns *et al.*, 1997b), it was expected that these modest changes in risk demonstrable with short-term use of reduced-tar products would have a growing impact on lung cancer death rates as more smokers used these products for longer periods of time (Wynder and Stellman, 1979).

Over the last 50 years, machine-measured, sales-weighted tar yields for U.S. cigarettes have declined by over 60 percent. Several careful reviews of the available scientific data (U.S. DHHS, 1981; NCI, 1996) have suggested that there is a reduction in lung cancer risk for populations of smokers who use lower yield cigarettes if they did not increase the number of cigarettes that they smoked as they decreased the yield of the cigarette that they

smoked. These reviews did not identify reductions in heart or lung disease risks associated with reductions in tar and nicotine yield of the cigarette smoked. The lung cancer risk reductions offered the promise of a substantial reduction in U.S. lung cancer death rates.

A reduction in U.S. lung cancer death rates of the magnitude expected from the differences in risk found in epidemiological studies of lower yield cigarettes (15-40%) has not been realized. Lung cancer death rates have continued to rise among women, and the modest decline in lung cancer death rates observed among men is generally consistent with the temporal trends of reduced initiation and increased cessation among males. (Tolley *et al.*, 1991; Mannino *et al.*, 2001). In addition, two studies performed by the American Cancer Society 20 years apart (1960s vs. 1980s) have shown an increase in lung cancer risk among current smokers (Thun and Heath, 1997; Thun *et al.*, 1997a & b). In these studies, there was no evidence for any decline in lung cancer risk, even when the subjects were compared controlling for number of cigarettes smoked per day, duration of smoking, and age. This increase in lung cancer risk over time was confirmed by the results of the British Physicians Study (Doll *et al.*, 1994) which demonstrated an increase in lung cancer risk among continuing cigarette smokers during the last 20 years of the 40 years of follow-up (1951-1991) when compared to the first 20 years of follow-up, despite a substantial fall in machine-measured tar yield of British cigarettes over this same period.

The discrepancies between epidemiological studies demonstrating reductions in risk with the use of low-yield and filtered cigarettes and the absence of population-based reductions in the hazards of smoking led to a reexamination of the question: Does the use of lower yield cigarettes result in meaningful reductions in disease risks compared to use of higher yield cigarettes? The authors integrated what is known from published epidemiological studies of smokers of low-yield cigarettes with what is known about compensatory smoking behavior and the characteristics that lead smokers to choose low-yield products. In addition, a series of new analyses are presented in an effort to resolve the apparent differences between published epidemiological evaluations and the mortality experience in the United States.

LIMITATIONS OF EPIDEMIOLOGICAL STUDIES IN EXAMINING THE RISKS OF LOW-YIELD CIGARETTE USE

Examination of changes in disease risks that result from changes in cigarette design raises a set of formidable challenges in human epidemiological studies. These changes come from the temporally dynamic nature of smoking over the last fifty years. The changes include changes in the product, changes in the age of smoking initiation, and changes in cessation. Related methodological challenges stem from the changing demographic distribution of tobacco use; the relationship of duration of smoking and age to disease risks; the cross-sectional slice of the population experience that is inherent in either retrospective or prospective epidemiological evaluations; the complexity and wide variety of changes that have occurred in cigarette design over the last 50 years; the changes in measures of smoking intensity that result from switching to lower yield cigarettes; the linkage between reasons for choosing lower yield

cigarette brands and other behaviors intended to reduce risks (including cessation); and the limited availability of information on what changes were made to which cigarettes, over what periods of time, and their potential impacts on smoking behaviors. The tools used by epidemiologists for approaching these challenges are rather blunt; obtaining smoking histories that cover products smoked, age started smoking, and number of cigarettes smoked per day. FTC yield measurements have been used in some studies as a surrogate for changes in exposure, in spite of the well-recognized limitations of its use for this purpose (see Chapters 2 and 3).

Cigarette smoking prevalence varies with age, gender, education, race/ethnicity, and most other demographic characteristics relevant to population risks (U.S. DHHS, 1998). The distribution of smoking prevalence within demographic characteristic has also varied with calendar year over the last 50-100 years in ways that influence current differences in disease rates (Burns *et al.*, 1997a & b; Thun *et al.*, 1997b). For example, women first began to smoke in large numbers in the late 1930s and 1940s, but during those years, women initiated smoking across a wide age range (Burns *et al.*, 1997a). As a result, female smokers who are currently old enough to have high risks of lung cancer have, on average, shorter durations of smoking than males of the same age. This difference explains much of the male/female differences in U.S. lung cancer mortality rates (Mannino *et al.*, 2001). Demographic and temporal variation in smoking behaviors is also evident in patterns of smoking cessation (Burns *et al.*, 1997a).

Superimposed on this complex variation in smoking behaviors are an equally complex demographic and temporal variations in use of filtered and lower yield cigarettes, and these patterns do not always parallel those of smoking prevalence. For example, current survey data show that smoking prevalence declines with age among adults, but use of low-yield cigarette increases with age. In addition, older females, who have lower rates of smoking prevalence than their age-matched male contemporaries, are more likely to have used filtered and lower yield cigarettes and to have used them for much more of their smoking histories.

Some of these differences would be less important if smoking caused disease instantaneously, or if recent smoking was the principal determinant of disease risk. However, most diseases caused by smoking are the result of long periods of cumulative damage to the smoker and are heavily influenced by smoking that occurred 10, 20, or even 30 years or more in the past. Traditional measures of smoking intensity, such as number of cigarettes smoked per day, are recorded at entry into an epidemiological study. They have been useful approximations of lifetime smoking intensity in these studies because of the relative stability of this measure in smokers over their smoking lifetime. The same stability cannot be assumed when the smoker switches to a new type of cigarette, particularly when that new cigarette delivers less nicotine than the smoker is trying to obtain by smoking. What is often measured in epidemiological studies is the number of cigarettes currently smoked with the current type of cigarette. If the type of cigarette influences the number of cigarettes, then the current number of cigarettes smoked per day is not necessarily a valid measure of intensity of

smoking in the past with other types of cigarettes. Similarly, it is also not a valid measure when comparing current smoking intensities among individuals who smoke different types of cigarettes. Thus, one of the most common measures used to control for smoking intensity in epidemiological studies may be linked to, and perhaps partly determined by, the characteristics of the cigarette that the epidemiological study is attempting to examine.

Epidemiological studies examine events during follow-up over defined slices of time in fixed populations. From these data, investigators attempt to separate the effects related to age, intensity and duration of smoking from differences in cigarette design on disease risks produced by smoking. Even prospective epidemiological studies start with a fixed population defined at a fixed point in time and follow that population forward in time. These populations define a temporally specific set of smoking experiences with a specific set of cigarette products, and these limitations restrict the range of product changes that can be observed. In other words, any study addresses only a specific time period and the products used by the smokers observed in the study. The generalizability of the findings to other time periods and other products is uncertain.

Extrapolating effects beyond the range for which one has observations is always problematic. Generalizability is a particular problem in examining changing cigarette designs because many design changes occurred simultaneously, and some of them may have influenced cigarette yields in ways that are contrary to that expected by investigators. For example, some of the filtered cigarettes introduced in the 1950s and 1960s actually had higher tar deliveries than their nonfiltered brands in the same brand family (see Chapter 7), making the use of filter cigarette smoking as a measure of lower tar exposure uncertain.

Smokers of low-yield cigarettes may differ from smokers of high-yield cigarettes in important characteristics other than the cigarette smoked. These differences need to be carefully considered in epidemiological studies in order to prevent these other characteristics from introducing confounding facts that may bias the results of these studies. If low-yield cigarette smokers have lower intensities of smoking, are more likely to quit smoking, or have other characteristics that lower their disease risks, then differences in disease risks demonstrated between populations of high- and low-yield cigarette smokers may not be due to the differences in the cigarette that they smoke. These differences can be considered as confounding, as they relate to differences between high- and low-yield cigarette smokers reflecting the differences between those selecting and not selecting the product.

The principal determinant of the chronic disease risks associated with smoking is the amount of tobacco smoke to which an individual is exposed as measured by the intensity and duration of smoking. Smoking intensity is correlated with nicotine levels in the blood (Benowitz *et al.*, 1983; Benowitz, 1996) and with the need to maintain those levels (U.S. DHHS, 1988). As discussed elsewhere in this monograph (see Chapters 2 and 3), clinical and pharmacological studies demonstrate that smokers who switch

to cigarettes with low-nicotine yield modify their smoking behavior to maintain their accustomed nicotine intake. Compensatory behaviors may include: 1) taking more frequent puffs per cigarette; 2) taking larger puff volumes and inhaling more deeply; 3) obstructing the ventilation holes that would otherwise dilute the mainstream smoke; and 4) smoking more cigarettes per day. Thus, the FTC tar and nicotine ratings do not accurately reflect the exposure of an individual smoker to the carcinogens in tobacco smoke, as they do not take account of any of these compensatory behaviors.

The nicotine yield of the cigarette smoked may be a determinant of the measure of smoking intensity (number of cigarettes smoked per day) most commonly used as a control variable in epidemiological studies. If smokers who switch to lower yield cigarettes increase the number of cigarettes smoked per day to preserve a constant nicotine intake, then accounting for the number of cigarettes smoked per day in an analysis misrepresents the net consequences of changing cigarette type for dose of smoke exposure and risk. This widely employed strategy addresses the risk of different products conditional on the number of cigarettes smoked per day. For example, a smoker who smokes 10 high-nicotine cigarettes, and who switches to a low-nicotine variety, may compensate by smoking 20 low- nicotine cigarettes to maintain exactly the same level of nicotine intake. Measures of nicotine intake are good measures of total smoke dose; and, if smokers preserve the same nicotine intake, one would expect them to preserve their total smoke dose and disease risk as well. However, if the number of cigarettes smoked per day is used as a measure of smoke dose, then the smoker in this example would appear to have doubled his or her smoke dose on switching to the low-nicotine cigarette, when in reality the smoking intensity or total smoke dose had not changed at all.

Comparing Populations of High- and Low-Yield Cigarette Smokers in Epidemiological Studies—Population Differences

Over the last several decades, there is substantial evidence showing that smokers of low yield cigarettes differ from smokers of high yield cigarettes. Some of these differences involve other risk factors for cigarette caused diseases, raising the possibility of confounding. Attribution of differences in risks between the populations to the less hazardous character of the cigarettes that they smoke requires examination of differences between these two populations of smokers in their use of cigarettes, extent of compensation, reasons for choosing these products, and other behaviors related to disease risks.

In the United States, the majority of adolescents begin smoking Marlboro®, Camel®, or Newport® cigarettes (CDC, 2000b), brands that are mid-range yield. Thus, it is brand shifting, and the decline in tar and nicotine yields of the same brands over time, rather than brand initiation that leads to the use of low machine-measured yield cigarettes among adults. Figure 4-1 presents data from the 1996 California Tobacco Survey for the fraction of adult smokers with different demographic characteristics who reported that the brand they smoke is low in tar and nicotine. Similar dif-

ferences across type of cigarette smoked were evident in a national sample of smokers (Giovino *et al.*, 1996). The fraction of smokers reporting use of low-tar products increases dramatically with age, education, and income, and is higher among females than among males. These demographic differences might be expected from the marketing of these products as lower risk products.

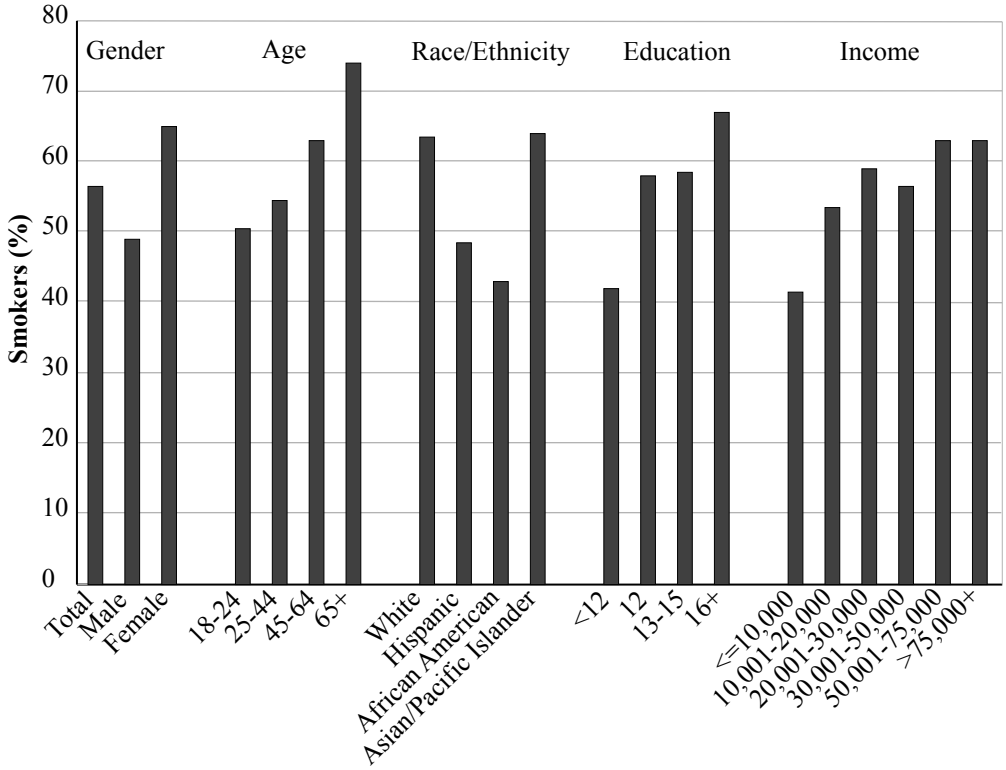
Low-yield cigarettes have been marketed as delivering less tar, and this is commonly understood by smokers as resulting in less risk (see Chapters 6 and 7). It is, therefore, not surprising that a substantial fraction of those who switch from higher to lower yield cigarettes do so in an effort to reduce their disease risks (Cohen, 1996a & b; see Chapters 6 and 7). In addition, some smokers switch to these products hoping to quit or substantially reduce their smoking (Giovino *et al.*, 1996; see Chapters 6 and 7). Other smokers, after a failed cessation attempt, relapse to using low-yield products in an effort to mitigate the risk from resumption of smoking. Because of these health concerns, and an ongoing interest in cessation, these same low-yield cigarette smokers may also have higher rates of successful long-term smoking cessation or may voluntarily reduce the amount that they smoke for health reasons. Risk reductions that accompany cessation or lowered smoking intensity may appear to be related to the tar level of the cigarette smoked while actually resulting, at least in part, from other factors. Cohort studies following a population longitudinally for assessment of disease risk without repeated follow-up assessment of smoking status may be particularly vulnerable to this bias.

Hammond (1980) examined the American Cancer Society's first Cancer Prevention Study (CPS-I) data to look for this association between use of low-yield cigarettes and smoking cessation. Smokers of low-tar (17.6 mg or less) cigarettes midway through the study in 1965 were more likely to be former smokers than medium- or high-tar cigarette smokers at the last follow-up in 1972.

The higher educational and socioeconomic status of low-yield cigarette smokers are likely to be correlated with other positive health behaviors (diet, exercise, etc.) that may lower disease risks for reasons independent of choice of cigarette type. Giovino and colleagues (1996) showed that smokers of low-yield products have higher levels of formal education than persons who smoke higher yield products. Haddock and associates (1999) found that Air Force recruits who had switched in the previous year to lower tar and nicotine brands in order to reduce their health risks were also more likely to have more nutritious diets.

The rising level of health concerns that occur in middle age may lead individuals to a variety of changes in their behavior that are intended to improve their health, including smoking cessation. It would not be surprising to learn that these same individuals, should they relapse to smoking following a cessation attempt that is part of their efforts to change future disease risks, are more likely to smoke lower yield cigarettes. Any successful change in their diet, level of exercise, reductions in alcohol or tobacco, as well as the reductions in disease risks that result from these changes, would be linked to the use of lower yield cigarettes.

Figure 4-1
Percentage of Smokers Over Age 18 Reporting That Their Brand is Low in Tar and Nicotine, 1996 California Tobacco Survey



Conversely, smokers with newly diagnosed disease who are unable to quit may switch to low-yield cigarettes in the belief that there is less risk associated with their use. This would have the effect of increasing disease rates in populations of low-yield cigarette smokers.

It is also possible that less-intense and less-addicted smokers may either use, or be more likely to successfully switch to, low-yield cigarettes. Their demand for nicotine is less, and it may be more easily satisfied by cigarettes that deliver less nicotine. In contrast, heavy smokers and those who are strongly dependent may not be able to extract sufficient nicotine from these lower yield products to satisfy their addiction, so they may preferentially choose higher yield cigarettes.

These differential characteristics of smokers of different types of cigarettes may affect case-control and cohort studies in different ways. In case-control studies of lung cancer, filter or lower yield cigarette smokers are likely to be better educated, have higher incomes, and have better dietary habits than will unfiltered or higher tar cigarette smokers. The former may also be more likely to be less-intense and less-dependent smokers than the latter. These characteristics may influence the rates of lung cancer occurrence independent of any effect of cigarette type smoked; but unless they are carefully controlled in the analysis, they may bias toward finding a lower lung cancer risk among filtered or lower yield cigarette smokers.

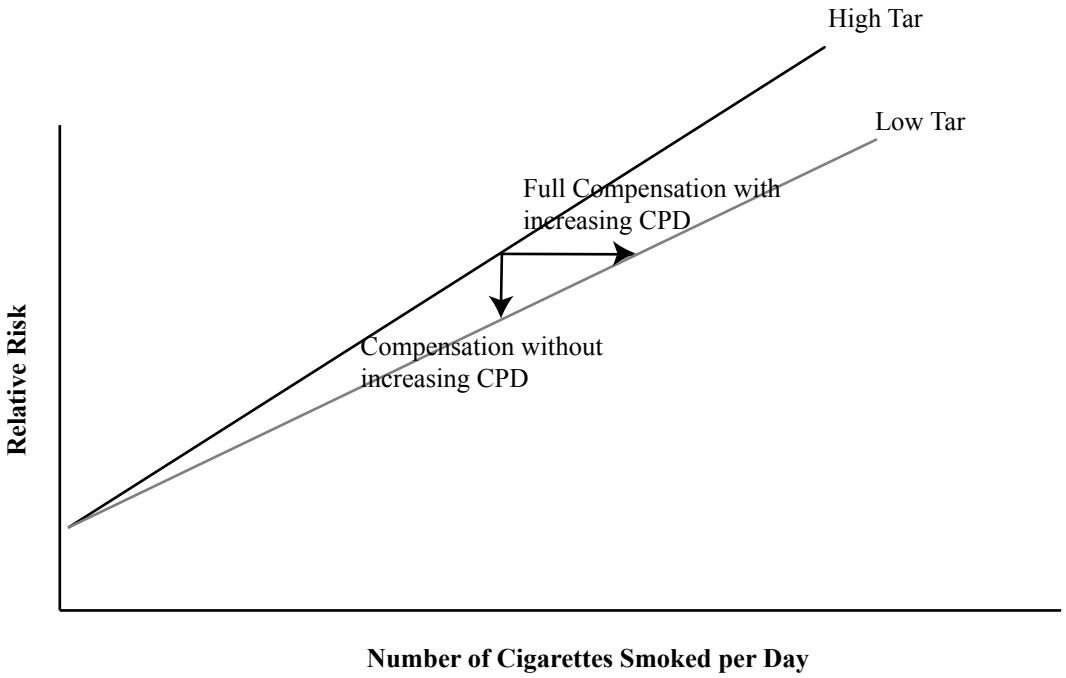
Prospective cohort studies of lung cancer risk in relation to the type of cigarette smoked follow smokers forward in time to observe lung cancer risks. If lower yield cigarette smokers are more likely to quit successfully or adopt other healthy behaviors, and subjects are not tracked repetitively during the follow-up period, then trends toward lower risk smoking behaviors, cessation and other healthy behaviors may occur with a higher frequency in the lower yield cigarette group. A reduced rate of disease in lower yield cigarette smokers may be due to changes in their risk-related behaviors after the initial entry into the study, rather than to the type of cigarette they smoked. Many cohort studies have followed populations for a decade or more, sufficient time for differences to arise in characteristics of smokers of different types of cigarettes.

Using Number of Cigarette Per Day to Control for Intensity of Smoking in Epidemiological Studies

The principal method utilized to control for differences in the intensity of smoking among different populations of smokers is to use the number of cigarettes smoked per day as a measure of smoking intensity or dose of smoke received. The validity of this approach is supported by the demonstration of higher blood levels of cotinine (the major metabolite of nicotine) among smokers of larger numbers of cigarettes per day (Jarvis *et al.*, 2001; Benowitz *et al.*, 1983). Current understanding of the compensatory changes in smoking behavior that occur with the use of low yield cigarettes suggests that the bulk of compensation occurs by adjusting the topography of smoking for each individual cigarette (see Chapters 2 and 3). Smokers take larger puffs, inhale more deeply, and change their smoking pattern in other ways to extract the same amount of nicotine from cigarettes with vastly different nicotine yields by the FTC method. Smokers may also compensate by increasing the number of cigarettes smoked per day when they switch to low yield cigarettes.

Many published epidemiological studies of low-yield cigarettes have adjusted for the number of cigarettes smoked per day because it is the most readily available quantitative measure of smoke dose. It is possible for smokers who switch to lower yield cigarettes to fully preserve the daily dose of nicotine and smoke they receive from smoking (see Chapters 2 and 3). The preservation of a constant daily dose of smoke when shifting to a cigarette with a lower machine-measured yield may occur through changes in the way the cigarette is smoked, through an increase in number of cigarettes smoked per day, or through a combination of both methods. A smoker who fully compensates, and who increases the number of cigarettes smoked per day when he or she switches to a lower yield cigarette to achieve that compensation, will receive the same daily dose of smoke exposure with high and low yield cigarette smoking; but they will report different numbers of cigarettes smoked per day when smoking high and low yield cigarettes for that same daily dose of smoke. If cigarettes smoked per day is used in an epidemiological study to estimate the biologic dose of toxin or carcinogen that this smoker is receiving, then it will appear that the dose increased when the smoker switched to lower yield cigarettes; and the true dose of smoke exposure will be overestimated when smoking lower yield cigarettes as compared to higher yield cigarettes. If a substantial frac-

Figure 4-2
Effect of Increasing the Number of Cigarettes Smoked per Day When Switching to Low-Yield Cigarettes on the Measurement of Relative Risk in Epidemiological Studies Which Control for Number of Cigarettes Smoked per Day



Source: Hypothetical.

tion of lower yield cigarette smokers are compensating by increasing the number of cigarettes smoked per day, then epidemiological studies which use CPD to control for differences in daily dose will overestimate the dose received by lower yield cigarette smokers relative to higher yield cigarette smokers. This overestimation, if present, will bias the risk estimates in favor of finding lower risks among lower yield cigarette smokers when high and low yield cigarette smokers are compared in analyses that use CPD to control for daily dose of smoke received by smokers. Even slight compensation through increasing CPD can substantially bias the risk estimate.

This potential interaction between number of cigarettes smoked per day and type of cigarette smoked is illustrated in Figure 4-2 which presents theoretical relationships between disease relative risks and increasing number of cigarettes smoked per day for high and low yield cigarettes. In theory, a smoker who compensates fully could do so by either exclusively changing the pattern of smoking or by increasing the number of cigarettes smoked per day as part of that compensation. If a smoker compensates entirely by changing the pattern of smoking and does not increase the number of cigarettes smoked per day, the smoker will drop vertically from the high tar line to the low tar line. If the level of compensation is only partial, this smoker would experience a reduction in the daily smoke dose received, and one would expect a population of smokers who had this form of partial com-

pensation to have lower lung cancer rates. Their lung cancer risk in relation to CPD would generate a line similar to that presented as the low tar line in Figure 4-2, that is a lower risk at any given number of cigarettes smoked per day. However, if the compensation is complete, one would expect no reduction in daily dose of smoke or in lung cancer risk; and the line representing their lung cancer risk in relation to CPD would superimpose on that for high tar cigarette smokers.

However, a smoker of high-yield cigarettes may also increase the number of cigarettes smoked per day as part of the compensatory changes in smoking behavior that occur in order to preserve nicotine intake when he or she switches to low-yield cigarettes. This pattern of complete compensation is represented as a horizontal shift between the two lines in Figure 4-2; it combines the compensation that occurs due to changes in the pattern of smoking each individual cigarette with the compensation that occurs through increasing the number of cigarettes smoked per day. With complete compensation to preserve the same dose of toxic and carcinogenic intake in this pattern, no change in smoke intake or disease risk would occur; but when disease risk is plotted against number of cigarettes smoked per day, the disease risk lines would not superimpose. Instead, they would look like the two lines in Figure 4-2. The difference between these risk lines would correctly suggest that a difference in disease risk per cigarette smoked exists, when there is actually no change in disease risk for individual smokers resulting from switching to the lower yield brand of cigarettes due to the increase in number of cigarettes smoked.

Using the number of cigarettes smoked per day to control for the biological dose of smoke intake by the smoker can thus produce an artifactual difference in disease risk if the question being asked is whether risk declines when smokers switch to low yield cigarettes rather than if the risk per cigarette smoked declines. If compensatory changes include an increase in number of cigarettes smoked per day, analyses that control for intensity of smoking using CPD produce a risk estimate per cigarette smoked per day, when in reality what is needed is a risk estimate for the total smoking behavior of the smoker as he or she switches brands of cigarettes. The risk should be expressed per smoker rather than per cigarette. For example, a smoker of 20 high-tar cigarettes per day who switches to a low-tar product, and who increases his or her number of cigarettes smoked to 25 per day to fully preserve tar and nicotine intake, would also preserve the same disease risk. However, he or she would appear to have a risk on a per-cigarette-smoked basis that was 80 percent (20 divided by 25) of the risk of smoking high-tar cigarettes.

While it is possible to argue the legitimacy of expressing risk on a per-cigarette basis by suggesting that smokers should be educated not to increase the number of cigarettes smoked per day when they change brands, a public health benefit from use of low-yield cigarettes can only accrue if there is a difference in disease risks across individuals as they actually use these low-yield cigarettes. If a cigarette produces a 20-percent decrease in risk per cigarette, but its use by smokers results in 20 percent more cigarettes being smoked per day, the net result will likely be no change in disease risk for the individual or within the population.

The potential for smokers to increase the number of cigarettes that they smoke per day when they switch to lower yield cigarettes can complicate analyses of disease risks among smokers of different types of cigarettes in both case-control and prospective epidemiological evaluations. Data are presented later in this chapter to show that smokers who switched to low-yield cigarettes in the CPS-I study increased the number of cigarettes that they smoked per day, and that smokers of ultralow nicotine-yield cigarettes smoked more cigarettes per day in recent California Tobacco Surveys.

Even this limited discussion should make it apparent that epidemiological studies which simply compare the disease risks of high- and low-yield cigarette smokers must be interpreted with great caution when addressing the question of whether the cigarettes used are themselves the source of the differences in risks. Some of the published epidemiological studies have recognized this concern, and the studies cited in Tables 4-1 to 4-3 used a variety of design and statistical approaches to adjust for differences in age, duration of smoking, and intensity of smoking, as well as other characteristics of the populations.

In summary, a number of cautions are appropriate when examining epidemiological data on disease risks among those who smoke cigarettes with different machine-measured tar and nicotine yields. Comparisons of populations without controlling for differences in intensity of smoking likely to exist between high- and low-yield smokers can only define the populations as different, and these comparisons have limited ability to link the differences in risks observed to differences in the product used. However, control for intensity of smoking across populations using number of cigarettes smoked per day as the measure of dose may result in model misspecification if smokers who switch to low-yield cigarettes compensate by increasing the number of cigarettes that they smoke per day.

PUBLISHED EPIDEMIOLOGICAL STUDIES OF HEALTH ENDPOINTS

Tables 4-1 to 4-3 present epidemiological evaluations of smokers who used cigarettes with filters or different levels of machine-measured tar yield. An effort was made to include all of the published studies that evaluated individual smokers and presented numerical risks of disease associated with lower yield cigarettes. Studies were excluded if they used national consumption data as the measure of smoking, examined black versus blond tobacco, bidis, small cigars, hand-rolled cigarettes, cigarettes limited predominantly to other countries, clove cigarettes and other smoking products, Asian-Indian smoking behaviors, or other forms of tobacco use besides cigarettes.

Lung Cancer

Table 4-1 shows the studies that have examined lung cancer risks with low-yield products. While a few studies have not found a relationship, and several of the relationships identified were not statistically significant, the clear impression from these studies taken as a whole is that there is a lower risk of lung cancer among populations of smokers who use lower yield products. This relationship is evident in case-control studies as well as in prospective mortality studies (see Table 4-1). The vast majority of these studies controlled for intensity of smoking using the number of cigarettes

Table 4-1

Epidemiological Studies of Low-Yield Cigarettes and Lung Cancer

Citation	Population	Time Period	Cigarette Type	Relative Risk	Comments
Bross, I.D., Gibson, R. Risks of lung cancer in smokers who switch to filter cigarettes. *Am. J. Public Health* 58(8): 1396-1403, 1968.	Case-control study of 974 White male lung cancer patients and hospital controls.	1960-1966	Filter/Regular	0.59	Stratified by duration of smoking and number of cigarettes/day. Risk for regular is 6.48 and for filtered is 3.83. Filtered smokers were more likely to smoke more than one pack per day, 38% to 35%. Many had been smoking filtered cigarettes for leass than 3 years.
Bross, I.D. Effect of filter cigarettes on lung cancer risk. National Cancer Institute Monograph No. 28, *Toward a Less Harmful Cigarette.* U.S. DHEW, NCI, 1968.	Case-control study of 974 White male lung cancer patients and hospital controls.	1960–1966	Filter/ Regular	0.59	Stratified by duration of smoking and number of cigarettes/day. Risk for regular is 6.59 and for filtered is 3.9. Filtered cigarette smokers were more likely to smoke more than one pack per day, 38% to 35%. Many had been smoking filtered cigarettes for less than 3 years.
Hammond, E.C. *et al*. Some recent findings concerning cigarettes smoking. Cold Springs Harbor Conferences on Cell Proliferation, Volume 4. *Origins of Human Cancer*, Book A, *Incidence of Cancer in Humans*. pp. 101-112, 1977.	12-year follow-up of CPS-I. A prospective mortality study of over 1 million men and women.	1960-1972	Tar yield	Male low-tar RR= 0.93 for 1960-1966, 0.82 for 1966-1972; female RR=0.81 for 1960-1966, 0.81 for 1966-1972.	
Hammond, E.C. *et al*. "Tar" and nicotine content of cigarette smoke in relation to death rates. *Environ. Res*. 12:263-274, 1976.	12-year follow up of CPS-I. A prospective mortality study of over 1 million men and women.	1960-1972	Tar yield	Male low-tar RR= 0.93 for 1960-1966, 0.82 for 1966-1972; female RR=p.81 for 1960-1966, 0.81 for 1966-1973.	

Table 4-1 (continued)

Citation	Population	Time Period	Cigarette Type	Relative Risk	Comments
Lee, P.N., Garfinkel, L. Mortality and type of cigarette smoked. *J. of Epidemiol. Community Health* 35:16-22, 1981.	12-year follow-up of CPS-I. A prospective mortality study of over 1 million men and women.	1960-1972	Tar yield; low/high	Male=0.82; female=0.60	CHD risks are significantly different, but emphysema risks are not.
Higenbottam, T. *et al*. Cigarettes, lung cancer, and coronary heart disease: The effects of inhalation and tar yield. J. *Epidemiol. Communty Health* 36:113-117, 1982.	10-year follow-up of 17, 475 male civil servants, aged 40-54, and a sample of male British residents.	1965-1975	Tar yield	There was a small nonsignificant difference in lung cancer mortality by tar yield that was more evident among noninhalers.	
Hawthorne, V.M., Fry, J.S. Smoking and health: The association between smoking behavior, total mortality, and cardiorespiratory disease in West Central Scotland. *J. Epidemiol. Community Health* 32:260-266, 1978.	Prospective follow-up of 18,786 people attending a multiphasic screening examination.	1965-1977	Filter/Regular	0.83	No significant difference in mortality rates for filter users for lung cancer or cardiovascular disease. Smokers of plain cigarettes had lower rates of respiratory symptoms than filter smokers.
Todd, G.F. *et al*. Four cardiorespiratory symptoms as predictors of mortality. *J. Epidemiol. Community Health* 32:267-274, 1978.	12.4-year prospective follow-up of 10,063 subjects aged 35-69 from a random sample of the population in Great Britain.	1965-1977	Filter/Regular	1.40	The increase in lung cancer mortality with filter use was not statistically significant; there was a statistically significant decrease in all-cause mortality and male CHD mortality with filter use (stan dardized for number of ciga rettes/day).
Engeland, A. *et al.* The impact of smoking habits on lung cancer risk: 28 years' observation of 26,000	A prospective study of 26,126 Norwegian men and women drawn from a population sample.	1966-1993	Filter/Regular	Male=0.67; female=0.91	Controlled for age, number of cigarettes/day, and age at initiation.

Table 4-1 (continued)

Citation	Population	Time Period	Cigarette Type	Relative Risk	Comments
Norwegian men and women. *Cancer Causes and Control* 7:366-376, 1996.					
Borland, C. *et al*. Carbon monoxide yield of cigarettes and its relation to cardiorespiratory disease. *BMJ* 287:1583-1586, 1983.	Prospective 10-year follow-up of the Whitehall study where 4,910 men had known CO yields of the cigarettes that they smoked.	1967-1979	CO yield	0.67	Controlled for age, grade of employment, cigarettes/day, and tar yield. Those who smoked high CO-yield cigarettes (>20 mg) tended to smoke fewer cigarettes/day.
Tang, J.L. *et al.* Mortality in relation to tar yield of cigarettes: a prospective study of four cohorts. *BMJ* 311:1530-1533, 1995.	Four prospective mortality studies from the United Kingdom.	1967-1982	Filter/Non-filter and tar level	Tar 0.94 (0.75-1.18)	Relative risks for all tobacco-related diseases combined were statistically significant. RR are adjusted for age, study, and number of cigarettes/day.
Wynder, E.L. *et al*. The epidemiology of lung cancer: recent trends. *JAMA* 213:2221-2228, 1970.	Case-control study of 350 lung cancer patients and approximately 700 hospital controls.	1968-1969	Filter for at least 10 years/Non-filter		Decreased risk in smokers of filter cigarettes for 10 or more years controlled and stratified by number of cigarettes/day.
Wynder, E.L., Stellman, S.D. Impact of long-term filter cigarette usage on lung and larynx cancer risk: A case-control study. *JNCLI* 62:471-477, 1979.	Case-control study of 684 lung cancer patients and 350 larynx cancer patients.	1969-1976	Filter for at least 10 years/Non-filter	RR for 1-10 cigarettes/day= 0.61 (M), 0.38 (F); 11-20 cigarettes/day =0.71 (M), 0.79 (F); 31-40 cigarettes/day=0.66 (M); 30+ cigarettes/day=1.03 (F); 41+ cigarettes/day=0.86 (M).	
Augustine, A. *et al*. Compensation as a risk factor	Case-control study of 1,242 lung cancer cases	1969-1984	Filter/Non-filter	Compared to those who did not increase	

Table 4-1 (continued)

Citation	Population	Time Period	Cigarette Type	Relative Risk	Comments
for lung cancer in smokers who switch from nonfilter to filter cigarettes. *AJPH* 79:188-191, 1989a	and 2,300 sex- and age-matched hospital controls.			their cigarette/day when they switched to filtered cigarettes, the odds ratios for those increased 1-10 cigarettes/day wer M=1.19, F= 1.66, for those increased 11-20 cigarettes/day, the odds ratios were M=1.75, F=2.97, and for those who increased more than 20 cigarettes/day, the odds ratios were M=2.37, F=3.89.	Mean changes in cigarettes/day after switching for cases and controls were adjusted by linear regression for age at switching and duration of non-filter smoking utilizing analysis of covariance.
Kabat, G.C. Aspects of the epidemiology of lung cancer in smokers and nonsmokers in the United States. *Lung Cancer* 15:1-20, 1996.	Case-control study of 7,553 lung cancer cases and 19,992 hospital controls.	1969-1991	Filter/Non-filter	Non-filter/filter only 0.7 (0.4-1.3);non-filter/switchers of 10+ years 0.7 (0.5-0.9).	Reduction in male filter smokers for Kreyberg I, but not Kreyberg II; effect in women not significant; odds ratios adjusted for number of cigarettes/day.
Rimington, J. The effect of filters on the incidence of lung cancer in cigarette smokers. *Environ. Res.* 24:162-166, 1981.	Follow-up study of 2,393 non-filter and 3,045 filter cigarette smokers from a sample of mass radiography volunteers aged 40 or more in England.	1970-1976	Filter/Non-filter	0.65	Age standardized.
Kuller, L.H. *et al*. Cigarette smoking and mortality MRFIT Research Group. *Preventive Med*. 20:638-654, 1991.	10.5-year follow-up of the MRFIT participants.	1972-1985	Tar level, nicotine level	Nicotine RR=1.0 for nicotine level≤1 mg; 0.97 (0.62-1.52) for	Adjusted for age, serum cholesterol, diastolic blood pressure, and cigarettes/day. Low-tar and low-nicotine cigarette smokers tended to smoke more cigarettes/day.

Table 4-1 (continued)

Citation	Population	Time Period	Cigarette Type	Relative Risk	Comments
Lubin, J.H. *et al*. Patterns of lung cancer risk according to type of cigarettes smoked. *Int. J. Cancer* 33:569-576, 1984.	A case-control study of 7,804 cases and 15,207 hospital-based controls in seven Western European locations.	1976-1980	Filter/Non-filter	Male=0.59; female=0.50	Adjusted for years of cigarette use, number of cigarettes/day, and years since cessation.
Lubin, J.H. Modifying risk of developing lung cancer by changing habits of cigarette smoking. *Brit. Med. J.* 288:1953-1956, 1984a; *Brit. Med. J.* 289: 921, 1984b (letter-response).	Case-control study of 7,181 lung cancer patients and 11,006 hospital controls in five Western European countries.	1976-1980	Filter/Non-filter	0.54	Risks adjusted for duration of use in years.
Benhamou, S. *et al.* Lung cancer and use of cigarettes: A French case-control study. *JNCI* 74:1169-1175, 1985.	Case-control study of 1,625 lung cancer patients and 3,091 hospital controls.	1976-1980	Filter/Non-filter	0.60	
Buffler, P.A. *et al.* Environmental associations with lung cancer in Texas coastal counties. *Annual Clinical Conference on Cancer* 28:27-34, 1986.	Case-control study of 476 cases and 466 population-based controls.	1976-1980	13-14 mg/cigarette (middle)	0.91	No significant difference for filters.
Benhamou, E. *et al*. Lung cancer and women: Results of a French case-control study. *Brit. J. Cancer* 55:91-95, 1987.	Case-control study of 96 women with lung cancer and 192 matched hospital controls.	1976-1980	Filter/Non-filter	100% non-filter; RR=0/28 (0.05-1.47)	Controlled for number of cigarettes/day duration and inhalation.
Benhamou, E.,*et al*. Changes in patterns of	Case-control study of 1,057 cases and 1,503	1976-1980	Filter/Non-filter	0.7 (0.5-0.9)	Adjusted for age and duration of cigarette smoking and number of cigarettes/day.

Table 4-1 (continued)

Citation	Population	Time Period	Cigarette Type	Relative Risk	Comments
cigarette smoking and lung cancer risk: Results of a case-control study. *Br. J. Cancer* 60:601-604, 1989.	matched hospital controls in France.				
Benhamou, S. *et al.* Differential effects of tar content, type of tobacco and use of a filter on lung cancer risk in male cigarette smokers. *Int. J. Epidemiology* 24:437-443, 1994.	Case-control study of 1,114 lung cancer patients and 1,466 hospital controls.	1976-1980	Filter/Non-filter	0.63	Risk adjusted only by age is 0.38 for filter smokers only compared to non-filtered and mixed smokers. Multivariate analysis shows slight nonsignificant increase with percentage time smoking high-tar cigarettes.
Vutuc, C., Kunze, M. Lung cancer risk in women in relation to tar yields of cigarettes. *Preventive Med.* 11: 713-716, 1982.	Case-control study of 297 female lung cancers and neighborhood controls from 15 lung cancer centers in Austria.	1976-1980	Tar level	Tar level <15, odds ratio=0.29; tar level 15-24, odds ratio= 0.49; tar level > 24, odds ratio=1.0	Adjusted for age, duration, and number of cigarettes/day.
Vutuc, C., Kunze, V. Tar yields of cigarettes and male lung cancer risk. *JNCI* 71: 435-437, 1983.	Case-control study of 252 male lung cancers and hospital/neighborhood controls from 15 lung cancer centers in Austria.	1976-1980	Tar level	Tar level <15, odds ratio=0.30; tar 15-24, odds ratio=0.56, tar level >24, odds ratio=1.0	Adjusted for age, duration, and number of cigarettes/day.
Benhamou, E., Benhamou, S. Black (air-cured) and blond (flue-cured) tobacco and cancer risk. VI: Lung cancer. *Eur. J. Cancer* 29A(12): 1778-1780, 1993.	Combination of four case-control studies in Cuba, France, Uruguay, an Italy.	1976-1988	Filter/Non-filter	0.91	Adjusted for age, duration, cigarettes/day, current smoking, and residence.

Table 4-1 (continued)

Citation	Population	Time Period	Cigarette Type	Relative Risk	Comments
Lange, P. *et al*. Relationship of the type of tobacco and inhalation pattern to pulmonary and total mortality. *Eur. Respir. J*. 5:1111-1117, 1992.	6,511 men and 7,703 women selected randomly after age stratification from the general population in Copenhagen, followed for 13 years.	1976-1989	Filter/Non-filter	Male=0.82; Female=0.61	
Gillis, C.R. *et al*. Cigarette smoking and male lung cancer in an area of very high incidence. I: Report of a case-control study in the West of Scotland. *J. Epidemiol. and Community Health* 42:38-43, 1988.	Case-control study of 656 male lung cancer patients and 1,312 age-matched hospital controls.	1977-1981	Low-, medium-, and high-tar yield	Relative risks did not change significantly with tar yield for smokers of 25+ cigarettes/day. For smokers of 15-24 cigarettes/day, risks fell with tar yield, but it was not statistically significant. Smokers of 1-14 cigarettes/day had a significant fall with tar yield.	
Alderson, M.R. *et al.* Risks of lung cancer, chronic bronchitis, ischaemic heart disease, and stroke in relation to type of cigarette smoked. *J. Epidemiol. and Community Health* 39:286-293, 1985.	Case-control study of 12,693 in-patients.	1977-1982	Always flter/non-filter	Male 1.48, female 0.85	Adjusted for number of cigarettes/day.
Wynder, E.L., Kabat, G.C. The effect of low-yield ciga-	Case-control study of 1,278 Kreyberg I	1977-1984	Filter/Non-filter	Male Kreyberg I, filter-only smokers,	Adjusted for cigarettes/day, age, inhalation, and years of education.

Table 4-1 (continued)

Citation	Population	Time Period	Cigarette Type	Relative Risk	Comments
rette smoking on lung cancer risk. *Cancer* 62:1223-1230, 1988.	patients and 2,408 hospital controls and 807 Kreyberg II partients and 1,543 matched controls.			0.69 (0.37-1.27); male Kreyberg II, 0.87 (0.43-1.54)	
Stellman, S.D. *et al*. Risk of squamous cell carcinoma and adenocarcinoma of the lung in relation to lifetime filter cigarette smoking. *Cancer* 80(3):382-388, 1997.	Case-control study of 1,442 male and 850 female lung cancers from 1977 to 1995 and hospital control.	1977-1995	Filter/Non-filter	Lifetime filter/non-filter: 0.4 (0.2-0.8)	Reduction in risk for squamous cell carcinoma in female lifetime filter smokers compared to lifetime non-filter smokers controlling for number of cigarettes/day, no differences for males or for adenocarcinoma.
Petitti, D.B., Friedman, G.D. Cardiovascular and other diseases in smokers of low yield cigarettes. *J. Chron. Dis.* 38:581-588, 1985.	4-year prospective follow-up of 16,270 current regular smokers and 42,113 subjects who never used any form of tobacco.	1979-1982	Tar level and high- and low- (<15 mg tar and 1 mg nicotine) yield determined at the start of the study.	0.87 (0.68-1.11) for a 5-mg increase in tar	Controlled for age, sex, race, and number od cigarettes/day.
Sidney, S. *et al*. A prospective study of cigarette tar yield and lung cancer. *Cancer Causes and Control* 4:3-10, 1993.	Prospective follow-up of 79,946 Kaiser Permanente Medical Care group members for an average of 5.6 years.	1979-1985	Tar yield	1.02 (0.98-1.05) in men; 0.99 (0.96-1.03) in women	Long-term (20+ years) filter use was associated with a reduced lung cancer risk in women, RR= 0.36 (0.18-0.75), but not in men.
Wilcox, H.B. *et al*. Smoking and lung cancer: Risk as a function of cigarette tar content. *Preventive Med.* 17:263-272, 1988.	Case-control study of all incidence cases of lung cancer (763) in six areas of New Jersey compared to population-based controls.	1980-1981	Tar level	Tar level 21.1-28.0, odds ratio= 1.0; tar level 17.6-21.0, odds ratio= 1.21 (0.75-1.96); tar level	Adjusted by intensity and duration of smoking. There was an increasing intensity of smoking with decreasing level of tar among the cases when consumption in two time periods were compared.
Pathak, D.R. *et al.* Determinants of lung can-	Case-control study of 521 lung cancers and 769 con-	1980-1982	Lifelong filter/ non-filter	0.80	Odds ratio was much lower

Table 4-1 (continued)

Citation	Population	Time Period	Cigarette Type	Relative Risk	Comments
cer risk in cigarette smokers in New Mexico. *JNCI* 76:597-604, 1986.	trols matched for age, sex, and ethnicity.	1980-1982	Lifelong filter/ Non-filter	0.80	among Hispanics (0.04).
Kaufman, D. W. *et al.* Tar content of cigarettes in relation to lung cancer. *Am. J. Epidemiol.* 129:703-711, 1989.	Case-control study of 881 lung cancers and 2,570 hospital controls.	1981-1986	Tar yield: <22, 22-28, 29+	1, 1.9 (1.0-3.7), 3.1 (1.3-7.1)	Logistic regression controlled for age, sex, ethnicity, geographic region, years of education, year of interview, cigarettes/day, and year smoking started.
Khuder, S.A. *et al*. Effect of cigarettes smoking on major histological types of lung cancer in men. *Lung Cancer* 22:15-21, 1998.	Case-control study of 482 male lung cancer cases and neighborhood controls.	1985-1987	Filter/Non-filter	0.46	Adjusted for number of cigarettes/ day and the confidence intervals overlap.
Armadans-Gil, L. *et al*. Cigarette smoking and male lung cancer risk with special regard to type of tobacco. *Int. J. Epidemiol.* 28:614-619, 1999.	Case-control study of 325 male lung cancer patients and age-matched hospital controls.	1986-1990	Filter/Non-filter	0.40	Adjusted for age and cumulative cigarette consumption.
Pezzotto, S.M. *et al.* Variation in smoking-related lung cancer risk factors by cell type among men in Argentina: A case-control study. *Cancer Causes and Control* 4:231-237, 1993.	Case-control study of 215 lung cancers and 433 hospital controls.	1987-1991	Filter/Non-filter	0.29	Controlled for age, hospital of admission, and intensity and duration of smoking.

Table 4-1 (continued)

Citation	Population	Time Period	Cigarette Type	Relative Risk	Comments
De Stefani, E. Mate drinking and risk of lung cancer in males: A case-control study from Uruguay. *Cancer Epidemiology, Biomarkers, and Prevention* 5:515-519, 1996.	Case-control study of 497 cases and 497 hospital controls.	1988-1994	Filter/Non-filter	0.72	No significant difference for filters.
Agudo, A. *et al.* Lung cancer and cigarette smoking in women: A case-control study in Barcelona (Spain). *Int. J. Cancer* 59:165-169, 1994.	Case-control study of 101 women with lung cancer with two matched hospital controls.	1989-1992	Filter/Non-filter	0.22	
Matos, E. *et al*. Lung cancer and smoking: A case-control study in Buenos Aires, Argentina. *Lung Cancer* 21: 155-163, 1998.	Case-control study of 200 male lung cancer patients and 397 hospital controls	1994-1996	Filter/Non-filter	Filter 0.34 (CI: 1.09-0.11)	Filter cigarettes more risky in black vs. blond comparisons and in comparisons by cell type.
Jockel, K.H. *et al*. Occupational and environmental hazards associated with lung cancer. *Int. J. Epidemiol.* 21:202-213, 1992.	Case-control study of 194 lung cancer patients, 194 hospital controls, and 194 population controls in five German cities.	Not stated	Filter/Non-filter	0.41	

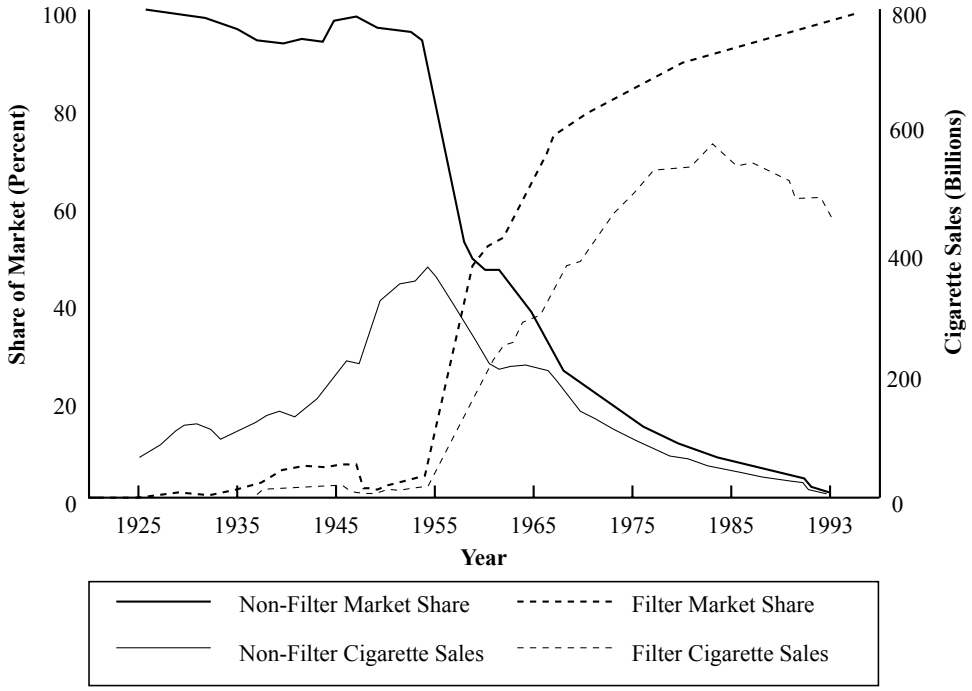
smoked per day. Measurement of cigarettes smoked per day was recorded in these studies at the same time that the brand of cigarettes smoked was recorded. As a result, the comparison in the studies is between smokers of equal numbers of different cigarettes smoked per day rather than between smokers when they are using different products. If smokers increase the number of cigarettes that they smoke per day when they switch from one type of cigarettes to another type, then comparing them on a risk per cigarette basis may result in the wrong conclusion if the question being asked is whether switching to lower yield cigarettes reduces the risk for the smoker.

One of the earliest studies (Bross and Gibson, 1968) was a case-control study of lung cancer patients diagnosed between 1960 and 1966. The study demonstrated a relative risk of 0.59 for filter smokers compared to nonfilter smokers in an analysis stratified by duration and number of cigarettes smoked per day. This analysis is of interest because it was conducted very soon following the introduction of filtered cigarettes. Figure 4-3 presents the number of filtered and nonfiltered cigarettes sold each year from 1925 to 1993, as well as their respective market shares. Essentially all cigarettes sold prior to 1955 were nonfiltered cigarettes, but the market share for filtered brands increased rapidly thereafter. Because lung cancer is often present for several years prior to its diagnosis, and 5-10 years of cessation are required to produce a 50-percent reduction in the excess risk of lung cancer, the presence of such a large reduction in relative risk following so rapidly after the introduction of filtered cigarettes raises questions concerning the biological plausibility of these results. Bross and Gibson raised these biological plausibility concerns, noting that many of the filter smokers had been using filtered cigarettes for less than 3 years. In addition, a table presented in their article demonstrated that 38 percent of the filter smokers smoked more than one pack per day in contrast to 35 percent of nonfilter smokers. This finding was in the opposite direction from the expectation that those who switched to filtered cigarettes were likely to be lighter smokers on average. It raises the likelihood that smokers who had switched to filtered cigarettes may have compensated for the decreased nicotine delivery of those cigarettes by increasing the number of cigarettes that they smoked per day, in effect biasing the analyses by moving less-intense filter smokers into strata where they were compared to more-intense nonfilter smokers.

Perhaps the most influential analyses have been those examining the 12-year follow-up of the American Cancer Society's CPS-I, which followed over 1 million men and women for up to 12 years between 1960 and 1972 (Hammond *et al.*, 1976, 1977; Lee and Garfinkel, 1981). These analyses were conducted using differences in machine-measured tar yields. Sales-weighted tar yields declined sharply during this period (see Chapter 5). Sales-weighted, machine-measured tar yields declined from 36 mg in 1954 to 19 mg in 1972. Figure 4-4 presents the market share of U.S. cigarettes by the level of machine-measured tar. Prior to 1967, most cigarettes yielded more than 20 mg of tar, but market shares of 16- to 19-mg tar cigarettes rose rapidly in the late 1960s and early 1970s.

The CPS-I compared smokers of high-tar cigarettes with more than 25.8 mg tar to smokers of mid-tar (17.6-25.8 mg) and low-tar (less than 17.6 mg)

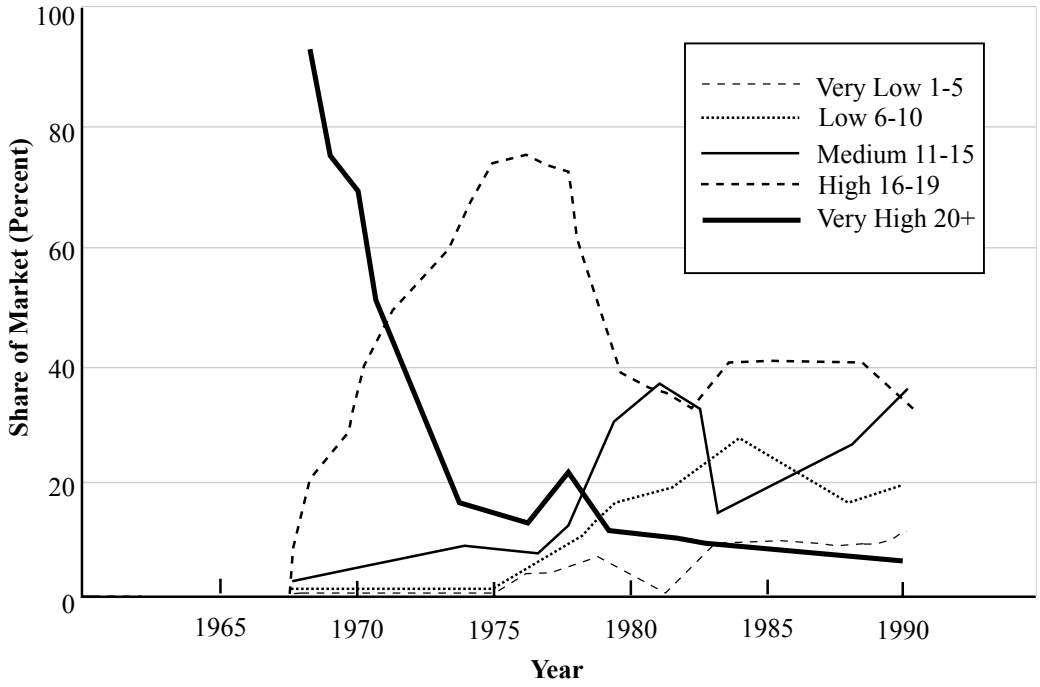
Figure 4-3
Market Share and Cigarette Sale of Filter and Non-Filter Cigarettes in the United States, 1925-1993



Source: Maxwell Report (Maxwell, 1994).

cigarettes. However, the 'high' group was defined as those who were in the high category from 1959 to 1960 and the high or mid category from 1965 to 1966; the low category consisted of those who were in the low category from 1959 to 1960 and either the low or medium category from 1965 to 1966. The comparison categorized smokers into groups with distinct levels of age, race, number of cigarettes smoked per day, age when smoking began, residence, occupation, education, and history of heart disease and cancer. A matched analysis of these groups was performed where the only difference between pairs was the tar level of the cigarette smoked. Measurement of the number of cigarettes smoked per day and tar levels of the cigarette smoked were at the same point in time in the follow-up, and control for number of cigarettes smoked per day was for the number smoked after switching to low-yield cigarettes. When smokers of low-yield cigarettes were compared to smokers of high-yield cigarettes in this matched analysis, the mortality ratios for lung cancer among males were 0.83 for the first 6 years of follow-up and 0.79 for the last 6 years of follow-up. Comparable ratios for females were 0.57 and 0.62, respectively. However, the researchers cautioned that the risk differences between smokers of different-yield cigarettes would disappear if smokers had increased their number of cigarettes smoked per day when they switched from high-tar to low-tar cigarettes. For example, the death rate for subjects who smoked 1-19 high-tar cigarettes per day was 75.8/100,000, but if individuals

Figure 4-4
U.S. Market Share of Cigarettes Sold by Tar Yield of the Brand, 1967-1990 (mg of Tar by FTC Method)



Source: Tar levels for given years are derived from FTC Reports (for years 1967-1990). Sales data by brand are from Maxwell Report (Maxwell, 1994). Brand-specific market shares are summed by tar level of the brand in the given year to generate the market share for cigarettes with given tar yields.

had increased to 20-39 cigarettes per day as they switched to low-yield cigarettes, the risk increased to 129.5/100,000.

This increase in lung cancer risk with compensation was examined more directly in a case-control study of lung cancer patients that examined the change in number of cigarettes smoked per day when smokers switched from nonfiltered to filtered cigarettes (Augustine *et al.*, 1989a & b). In detailed interviews with the lung cancer patients and hospital controls, the investigators constructed lifetime smoking histories by brand and number of cigarettes smoked per day for each brand. The mean number of cigarettes smoked when using nonfiltered brands was compared to the mean number of cigarettes smoked per day after switching to filtered brands. Among males, 45 percent of cases and 41 percent of controls increased the number of cigarettes that they smoked per day when they switched to filtered cigarettes. Among females, the percentages were even higher, with 59 percent of cases and 48 percent of controls increasing the number of cigarettes smoked per day. When compared to those who did not increase their cigarettes per day (CPD) when they switched to filtered cigarettes (odds ratio = 1), the lung cancer odds ratios rose with increasing compensation (the odds ratios for those who increased 1 to 10 CPD were 1.19 for males and 1.66 for females. The odds ratios for those who increased 11 to 20 CPD were 1.75

for males and 2.97 for females. The odds ratios for those who increased 21 or more CPD were 2.37 for males and 3.83 for females). The analyses were adjusted for cigarettes smoked per day with nonfiltered cigarette use (before switching), duration of nonfiltered cigarette use, age at switching, and duration of filtered cigarette use. These data demonstrated the importance of compensation with increasing number of cigarettes per day following the switch to filtered cigarettes in defining the change in lung cancer risks.

Other cohort studies have yielded mixed results. Some studies showed no significant reductions with low-yield products (Higenbottam *et al.*, 1982; Hawthorne and Fry, 1978; Todd *et al.*, 1978; Tang *et al.*, 1995; Kuller *et al.*, 1991; Petitti and Friedman, 1985; Sidney *et al.*, 1993), and others showed a decline in risk (Engeland *et al.*, 1996; Borland *et al.*, 1983; Rimington, 1981; Lange *et al.*, 1992). All of these studies controlled for intensity of smoking, using cigarettes smoked per day measured when the yield level of the brand of cigarettes smoked was entered into the analysis, and most studies controlled for a variety of other smoking (*e.g.*, duration) and demographic characteristics.

A large U.S. case-control study demonstrated significantly lower lung cancer odds ratios among filter cigarette smokers who had shifted to filtered cigarettes 10 or more years prior to diagnosis (Kabat, 1996) as well as for lifetime filter use (Stellman *et al.*, 1997). The odds ratios were adjusted for age, education, and number of cigarettes smoked per day. This study also noted that the risk decline was evident only for lung cancers in the Kreyberg I classification. Kreyberg II lung cancers showed no risk reduction with filter use. Kreyberg II lung cancers are predominantly adenocarcinoma, a form of lung cancer that has been increasing as a fraction of all lung cancers in recent decades.

Two reports from a large multicountry case-control study in Europe also reported reductions in lung cancer risk associated with lifetime filtered cigarette use (Lubin *et al.*, 1984; Lubin, 1984a & b). One study adjusted for cigarettes smoked per day at time of interview, duration of cessation, duration of smoking, and a variety of other demographic characteristics. The second study adjusted for duration of smoking, but did not adjust for CPD. There did not appear to be a systematic difference in the number of cigarettes smoked per day between filter and nonfilter smokers among the lung cancer patients. As would be expected, however, the lifetime filter smokers had substantially shorter durations of smoking. As is true of most studies of lifetime filtered cigarette users, the validity of self-reported lifetime use is in question since 63 percent of the lifetime filter smokers with lung cancer diagnoses between 1976 and 1980 in this study reported durations of filtered cigarette use of 30 or more years. Filtered cigarettes were not used in large numbers prior to the mid 1950s, making the likely maximum duration of filtered cigarette use approximately 25 years.

Epidemiological data on reduced risks of developing lung cancer among lower yield cigarette smokers are supported by a study of the histological changes in the airways of smokers (Auerbach *et al.*, 1979). The study was conducted on smokers who died of causes not associated with smoking dur-

ing two time periods (1955-1960 and 1970-1977). Sales-weighted average tar yield of cigarettes declined substantially between these two periods of time. The extent and severity of histological changes in the airways were significantly and substantially less during the second calendar-year period, controlling for number of cigarettes smoked per day. The histological changes included basal cell hyperplasia, loss of cilia, occurrence of cells with atypical nuclei, and presence of advanced changes defined as carcinoma *in situ*. Comparisons were confined to examination of the airways.

In summary, most case-control and prospective mortality studies conducted in different geographic locations demonstrated differences in lung cancer risks for filter and low-tar (machine-measured) smokers compared with nonfilter and high-tar smokers when controlled for cigarettes smoked per day. The question that remains is whether differences in lung cancer experience are due to differences in machine-measured tar yield of the cigarettes smoked, due to differences in other characteristics of the smokers who use these products, or due to differences introduced by model misspecification in these studies.

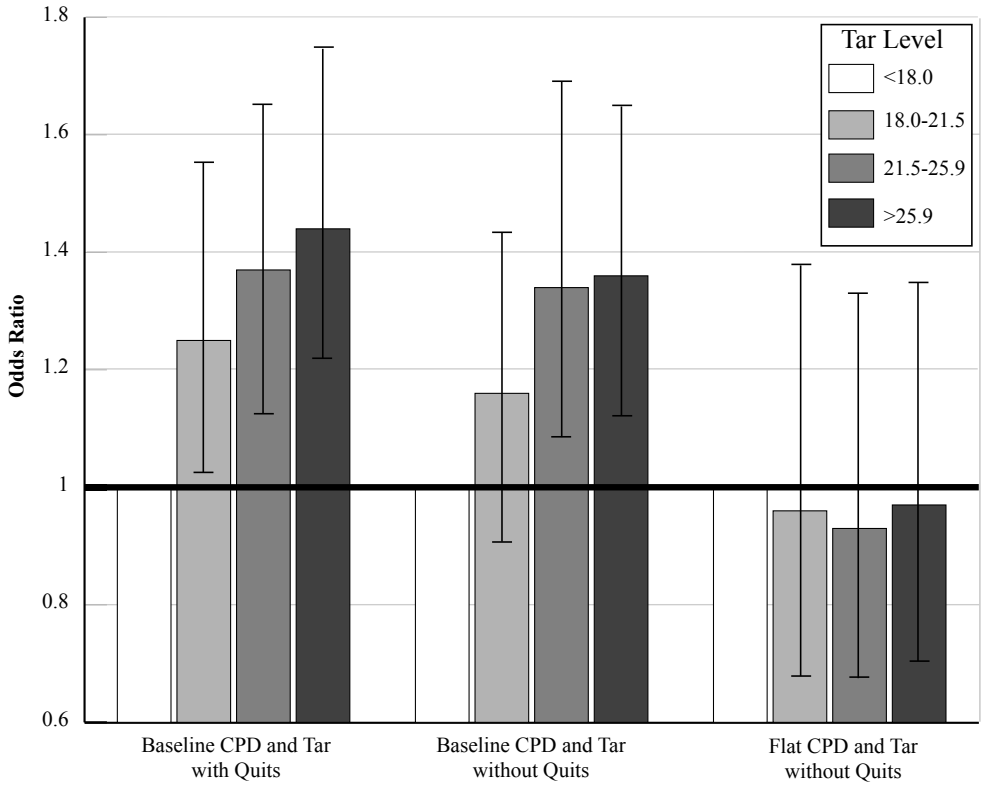
New Analyses of the American Cancer Society's Cancer Prevention Study I Data

A reexamination of the CPS-I data set (see Appendix) was inconclusive as to whether compensatory changes in the number of cigarettes smoked per day when smokers switch to a lower nicotine cigarette introduce a bias sufficient to explain the observed increased lung cancer risk among smokers of high-yield cigarettes. If a positive gradient in lung cancer risk with tar level was present in analyses that used the tar level and number of cigarettes smoked from the most recent follow-up, and that gradient disappeared when controlling for the number of cigarettes smoked per day at the start of the study (or before smokers changed brands), then one could postulate that the compensatory shift in number of cigarettes smoked per day might be biasing the results to show an effect of tar that was not real. A survival analysis examining lung cancer risks for smokers of different-yield cigarettes using the yield of the cigarette at the most recent follow-up was performed, but it did not show a significant effect of tar for lung cancer risk with either cigarettes smoked per day at baseline or at the most recent follow-up used to control for intensity of smoking. Since there was no effect of tar on lung cancer risk to examine, it was not possible to determine whether controlling for CPD using the number of cigarettes per day prior to switching brands reduced or eliminated the effect of tar on lung cancer risk.

A survival analysis of lung cancer risk by tar level of the cigarette smoked was also conducted among those who changed the brand of cigarettes that they smoked during the CPS-I study. No significant effect was detected when using either cigarettes smoked per day measured prior to switching or at the time of the most recent follow-up to control for intensity of smoking. However, the numbers of observed lung cancer deaths were much smaller than those for the analyses of the entire smoking population.

CPS-I recorded smoking behaviors at five points during the 12-year follow-up and, therefore, some examination of the interrelationships between

Figure 4-5
Relationship of Tar Level and Lung Cancer Risk for the American Cancer Society CPS-I Data



Source: American Cancer Society, CPS-I, White-male current cigarette-only smokers. Tar level interpolated from Reader's Digest *(Miller & Monahan, 1959, pp.40-41) and FTC (for years 1967-1973) data by brand and year. Tar levels as indicated. Odds ratios are results of SAS* lifereg *survival analysis with independent variables of duration, age, CPD, and an indicator variable for first v. second 6 years of follow-up.*

tar level, smoking cessation, and number of cigarettes smoked per day was possible. For the purposes of this monograph, this data set was reexamined using survival analyses that included age, number of cigarettes smoked per day, duration of smoking, and first or second 6-year period of follow-up as variables in the analyses. Three analyses of the CPS-I data set were examined in order to define the potential influences of excess cessation among low-tar smokers and the influence of shifting numbers of cigarettes smoked per day during follow-up. Figure 4-5 presents the odds ratios for four different tar levels in the three sets of survival analyses of the CPS-I data using different criteria to define which smokers are included in the analyses. The cigarettes smoked per day and tar levels of the cigarettes smoked were those recorded in the baseline survey for all of these analyses.

The first set of odds ratios was for the 12-year follow-up of smokers of cigarettes with different tar yields, with the tar level of the cigarette smoked and the number of cigarettes smoked per day derived from the baseline survey. These estimates corresponded to the approach utilized by most of the prospective mortality studies presented in Table 4-1. There was a clear and

statistically significant increase in risk with increasing tar level of the cigarette smoked, and there was a convincing dose-response relationship with tar level. Smokers who quit were censored in the analysis at the follow-up when they reported being former smokers. Since the last follow-up interval was from 1965-72, this analytic approach resulted in all of the smokers who were listed as current smokers in 1965 being considered current smokers until the end of the study follow-up, even if they reported being former smokers in the final follow-up survey in 1972.

The second set of analyses used the same population, but the analysis censored those smokers who reported being former smokers in the 1972 follow-up as of the date of the next to last follow-up (1965). Because cessation is known to influence lung cancer risk, removal of those who quit in long-term follow-up is necessary to avoid confounding by the association of choice of a low tar brand and subsequent cessation of smoking. Hammond (1980) examined the CPS I data and demonstrated that smokers who were smoking low-tar (17.6 mg or less) cigarettes in 1965 were more likely than medium or high tar cigarette smokers to have become former smokers by the end of the study in 1972. Removal of those who had quit by the last follow-up did not eliminate the effect of baseline level of tar on lung cancer risk, but the dose response relationship was less apparent.

The third set of analyses in Figure 4-5 examined only those smokers who did not change the number of cigarettes that they reported smoking per day over the multiple follow-up measurements. This group constituted approximately one-third of all smokers. When using the baseline values for tar and cigarettes smoked per day in these analyses, it was impossible to eliminate the influence of compensatory changes in cigarettes per day that occurred prior to the baseline measurement. However, by selecting a group that did not change the number of cigarettes that they reported smoking during the survey, it is possible that a group may have been identified that also had more stable smoking practices with regard to number of cigarettes smoked per day prior to entry into the study. When this group was examined using the baseline number of cigarettes smoked per day and tar levels, there was no effect of tar level of the cigarette smoked on the odds ratio for lung cancer risk. This suggested that, at least in this group with stable smoking behavior, there was no relationship between the type of cigarette smoked and the degree of lung cancer risk. However, it was not possible to conclude from these analyses that the difference in lung cancer risk by type of cigarette smoked in the larger group containing all smokers was due to compensatory changes in the number of cigarettes smoked per day.

Cardiovascular Disease Table 4-2 presents the epidemiological studies that examined cardiovascular disease risks. Relative risks of cigarette smoking for heart disease are in the 2-4 range in contrast to the very high relative risks for lung cancer. These lower relative risks, and the influence of the other cardiovascular risk factors, make examination of differences in cardiovascular risks among populations who use different types of cigarettes more difficult. In contrast to the table on lung cancer risks (Table 4-1), there is no clear consensus on coronary heart disease (CHD) risks in relation to use of filtered or low-yield cigarettes. Some studies show increased risks and others

Table 4-2

Epidemiological Studies of Low-Yield Cigarettes and Heart Disease

Citation	Population	Time Period	Cigarette Type	Relative Risk	Comments
Lee, P.N., Garfinkel, L. Mortality and type of cigarette smoked. *J Epidemiol. Community Health* 35:16-22, 1981.	12-year follow-up of CPS-I; a prospective mortality study of over 1 million men and women.	1960-1972	Tar yield: low/high	CHD: Male RR= 0.90; female= 0.81	CHD risks are significantly different, but emphysema risks are not.
Higenbottam, T. *et al*. Cigarettes, lung cancer, and coronary heart disease: The effects of inhalation and tar yield. *J. Epidemiol. Community Health* 36:113-117, 1982.	10-year follow-up of 17,475 male civil servants, aged 40-64, and a sample of male British residents.	1965-1975	Tar yield	There was a small effect of tar on CHD mortality in the inhalers	
Todd, G.F. *et al*. Four cardiorespiratory symptoms as predictors of mortality. *J. Epidemiol. Community Health* 32:267-274, 1978.	12.4-year prospective follow-up of 10,063 subjects aged 35-69 from a random sample of the population in Great Britain.	1965-1977	Filter/Non-filter	0.75 for males and 1.03 for females	The increase in lung cancer mortality with filter use was not statistically significant, and there was a statistically significant decrease in all-cause mortality and male CHD mortality with filter use (standardized for number of cigarettes/day).
Hawthorne, V.M., Fry, J.S. Smoking and health: The association between smoking behavior, total mortality, and cardiorespiratory disease in West Central Scotland. *J. Epidemiol. Community Health* 32:260-266, 1978.	Prospective follow-up of 18,786 people attending a multiphasic screening examination.	1965-1977	Filter/Non-filter	1.05 for CHD mortality	No difference in mortality rates for filter users for lung cancer or cardiovascular disease. Smokers of plain cigarettes had lower rates of respiratory symptoms than filter smokers
Borland, C. *et al*. Carbon monoxide yield of cigarettes and its relation to cardiorespiratory disease. *BMJ* 287:1583-1586, 1983.	Prospective 10-year follow-up of the Whitehall study where 4,910 men had known CO yields of the cigarettes that they smoked.	1967-1979	CO yield	1.47 for CHD mortality in those smoking cigarettes with less than 18 mg CO yield compared to those smoking 20+ mg CO yield cigarettes	Controlled for age, grade of employment, cigarettes/day, and tar yield. Those who smoked high CO-yield cigarettes (>20 mg) tended to smoke fewer cigarettes/day.

Table 4-2 (continued)

Citation	Population	Time Period	Cigarette Type	Relative Risk	Comments
Tang, J.L. *et al*. Mortality in relation to tar yield of cigarettes: a prospective study of four cohorts. *BMJ* 311:1530-1533, 1995.	Four prospective mortality studies from the United Kingdom.	1967-1982	Filter/Non-filter and tar yield	Tar CHD: 0.93 (0.80-1.07); stroke: 0.81 (0.59-1.12)	Relative risks for all tobacco-related diseases combined were statistically significant. Relative risks are adjusted for age, study, and number of cigarettes/day.
Kuller, L.H. *et al.* Cigarette smoking and mortality. MRFIT Research Group. *Preventive Med*. 20:638-654, 1991.	10.5-year follow-up of the MRFIT participants.	1972-1985	Tar level, nicotine level	CHD: nicotine RR of 1.0 for nicotine level ≤1 mg. 1.04 (0.8-1.35) for 1.1-1.4 mg, and 1.27 (0.92-1.77) for 1.5+ mg; tar RR of 1.0 for tar level ≤15 mg, 1.08 (0.8-1.45) for 16-19 mg, and 1.19 (0.86-1.65) for 20+ mg.	Adjusted for age, serum cholesterol, diastolic blood pressure, and cigarettes/day. Low-tar and low-nicotine cigarette smokers tended to smoke more cigarettes/day.
Benhamou, E. *et al*. Lung cancer and women: Results of a French case-control study. *Br. J. Cancer* 55:91-95, 1987.	Case-control study of 96 women with lung cancer and 192 matched hospital controls.	1976-1980	50+% filter/ 100% non-filter	0.31	Controlled for number of cigarettes/day, duration, and inhalation.
Alderson, M.R. *et al.* Risks of lung cancer, chronic bronchitis, ischaemic heart disease, and stroke in relation to type of cigarette smoked. *J. Epidemiol. Community Health* 39:286-293, 1985.	Case-control study of 12,693 in-patients.	1977-1982	Always filter/ non-filter	Age 35-54: male=1.78; female=0.24 Age 55-74: male=2.67; female=1.32	Adjusted for number of cigarettes/day.

Table 4-2 (continued)

Citation	Population	Time Period	Cigarette Type	Relative Risk	Comments
Petitti, D.B., Friedman, G.D. Cardiovascular and other diseases in smokers of low yield cigarettes. *J. Chron. Dis.* 38:581-588, 1985.	4-year prospective follow-up of 16,270 current regular smokers and 42,113 subjects who never used any form of tobacco.	1979-1982	Tar yield; high- and low- (less than 15 mg tar and 1 mg nicotine) yield determined at the start of the study.	1.15 (1.03-1.28) for all cardiovascular diseases and 1.25 (0.99-1.58) for myocardial infarction for a 5-mg increase in tar.	Controlled for age, sex, race, and number of cigarettes/day.
Palmer, J. *et al.* Low yield cigarettes and the risk of nonfatal myocardial infarction in women. *NEJM* 320: 1569-1573, 1989.	Case-control study of 910 women with a first myocardial infarction under age 65 and 2,375 hospital controls.	1985-1988	Nicotine and CO levels	The estimated relative risk for women who smoked cigarettes with the lowest level of nicotine and CO was similar to that for women who smoked the brands with the highest levels of nicotine and CO.	Included in the model were terms for age, hypertension, angina, diabetes, cholesterol, family history of myocardial infarction, body mass index, type A behavior, exercise, education, residence, estrogen or oral contraceptive use, coffee consumption, alcohol consumption, and number of cigarettes/day.
Negri, E. Tar yield of cigarettes and risk of acute myocardial infarction. *BMJ* 306:1567-1569, 1993.	Case-control study of 916 patients with acute myocardial infarction without history of ischemic heart disease and 1,106 hospital controls in a multi-center Italian study.	1988-1989	Tar level	<10 mg=1, 10-15 mg=1.2 (0.7-2.1), >15-20 mg=0.8 (0.5-1.3), >20 mg= 1 (0.5-1.8).	

Table 4-2 (continued)

Citation	Population	Time Period	Cigarette Type	Relative Risk	Comments
Powell, J.T. *et al*. Risk factors associated with the development of peripheral arterial disease in smokers: A case-control study. *Atherosclerosis* 129:41-48, 1997.	291 smokers with newly referred peripheral arterial disease and 828 controls without the disease from outpatient clinics.	1988-1992	Tar/Nicotine	Peripheral artieral disease odds ratios 1.75 for tar 14+ compared to <9 mg; 1.54 for 1.2+ mg nicotine compared to <0.8 mg; 1.62 for carboxyhemoglobin 4.5+ compared to <2.7.	Odds ratios adjusted for age, sex, and depth of inhalation.
Parish, S. *et al.* Cigarette smoking, tar yields, and non-fatal myocardial infarction: 14,000 cases and 32,000 controls in the United Kingdom. The International Studies of Infarct Survival (ISIS) Collaborators. *BMJ (Clin Res Ed)* 311(7003):471-477, 1995.	In the United Kingdom in the early 1990s, 14,000 cases of nonfatal myocardial infarctions and 32,000 relatives (controls) (ISIS-3 & -4) responded to questionnaires. 4,923 cases and 6,880 controls were current smokers and used in study. Unmatched case-control study assessed effects of cigarettes.	1990	Two groups: low-tar users (<10 mg, 7.5 mg mean) and medium-tar users (<10 mg, 13.3 mg mean)	1.166 (1.025-1.326) for age 30-59 for medium tar compared to low tar.	Controlled for age, sex, and number of cigarettes/day.

show decreased risks, and in many of the studies the risks are not statistically significant.

In a prospective evaluation of four cohorts from the United Kingdom (Tang *et al.*, 1995) that included 56,255 males who were followed for an average of 13 years, a statistically significant reduction in risk of CHD mortality (0.77; 95 percent CI, 0.61–0.97) was demonstrated with decreasing tar yield, but the decline with filtered cigarette use was not statistically significant. These risks were adjusted for age, study, and number of cigarettes smoked per day.

An evaluation of CHD mortality from one of these cohorts (Borland *et al.*, 1983) revealed that CHD mortality was increased among smokers of high carbon monoxide (CO)-yield cigarettes in an analysis that controlled for age, employment grade, amount smoked, and tar yield of the cigarette smoked. The differences were not statistically significant. Smokers of high CO-yield cigarettes also tended to smoke fewer cigarettes per day. There was little correlation between tar yield and CO yield among the different brands of cigarettes smoked in this study, but these researchers raised the possibility that factors other than tar levels may be important in defining the exposures relevant to CHD risk.

A case-control study of nonfatal myocardial infarction in women (Palmer *et al.*, 1989) examined disease risk in relation to nicotine yield and CO yield of the cigarette smoked at the time of admission to the hospital. Included in the model were terms for age, hypertension, angina, diabetes, cholesterol, family history of myocardial infarction, body mass index, type A behavior, exercise, education, residence, estrogen or oral contraceptive use, coffee consumption, alcohol consumption, and number of cigarettes smoked per day. Multivariate relative risk estimates were similar across the categories of nicotine and CO yields from the highest to the lowest, and the risks were not significantly different.

Parish and colleagues (1995) found that the risk ratio of nonfatal myocardial infarction was 1.104 higher (95 percent CI, 0.998-1.222; P = 0.06) among smokers of medium-tar cigarettes compared to low-tar cigarettes in a case-control study of 14,000 survivors of myocardial infarction, compared to 32,000 relatives who served as controls. These analyses were controlled for age, gender, and amount smoked. When the analysis was limited to those with no previous disease, the risk ratio declined to 1.055 (95 percent CI, 0.910-1.223, P = 0.1), raising the question of whether some of those smokers with previously diagnosed disease might have switched to lower yield cigarettes in an effort to reduce their risks of subsequent illness.

An analysis of the 15-year follow-up of the Multiple Risk Factor Intervention Trial (MRFIT) participants (Kuller *et al.*, 1991) showed that either tar or nicotine content of the cigarette smoked was only modestly, and not statistically significantly, associated with CHD mortality in an analysis controlled for age, serum cholesterol, diastolic blood pressure, and cigarettes smoked per day. Petitti and Friedman (1985) found a small but statistically significant increased risk of CHD and myocardial infarction related to increased tar yield among 16,270 smokers compared to 42,133

never smokers who were followed for 4 years. These analyses were adjusted for age, sex, race, and number of cigarettes smoked per day as covariates. Results were similar when those with prior heart disease were removed and when the analyses were adjusted for other cardiovascular risk factors. Higenbottam and associates (1982) found a small increase in CHD mortality with lower tar yield, but the effect was evident only in the approximately 80 percent of smokers who inhaled. Todd and colleagues (1978) found a decline in CHD mortality among males, but not among females, who smoked filtered cigarettes.

In summary, while the data are not as compelling for alterations in CHD risk compared to lung cancer risk among populations who smoke low-yield cigarettes, several well-conducted epidemiological studies have demonstrated a difference in cardiovascular risk among those who smoke low-yield cigarettes when the analyses were controlled for number of cigarettes smoked per day. The complexity of examining the effect of low-yield cigarette smoking on CHD risk is exacerbated by the greater independence of the ratio of CO-to-nicotine yield among different brands of cigarettes in comparison to the ratio of tar-to-nicotine yield. CO is considered to be a major etiological agent in cardiovascular disease, and the factors that determine the CO yield of a cigarette are different from those that determine tar yield. Individual changes in cigarette design may influence tar and CO yields in different directions. These differences make interpretation of studies of cardiovascular disease risk in relation to tar yield or among filter cigarette smokers more difficult. Once again, the question that remains is whether this difference in CHD experience is due to the difference in machine-measured tar yield of the cigarettes smoked, due to the differences in other characteristics of the smokers who use these products, due to differences in other cardiovascular risk factors among smokers of different yield cigarettes, or due to differences introduced by controlling for intensity and duration of smoking in these studies.

Chronic Respiratory Symptoms and Disease

Table 4-3 presents the epidemiological studies that have examined respiratory disease risks. Since symptomatic chronic lung disease is commonly present for long periods prior to resulting in death, and because many smokers will quit smoking once chronic shortness of breath is manifest, it is difficult to evaluate the effect of smoking low-yield cigarettes on chronic obstructive pulmonary disease mortality. A reduced death rate from emphysema was demonstrated in the CPS-I 12-year follow-up (Lee and Garfinkel, 1981) at a point when lower yield products had not been on the market for an extended period of time. Other mortality outcome studies (Tang *et al.,* 1995; Lang *et al.*, 1992; Petitti and Friedman, 1985) have not demonstrated a similar reduction in lung disease mortality.

Sparrow and colleagues (1983) examined the relationship of tar yield to pulmonary function measurements in a group of 383 current smokers for whom pulmonary function measurements were available at two points in time 5 years apart. In a multivariate regression analysis, tar level of the cigarette smoked was not significantly associated with the forced vital capacity (FVC) or forced expiratory volume in 1 second (FEV1) in the initial exami-

Table 4-3
Epidemiological Studies of Low-Yield Cigarettes and Respiratory Disease

Citation	Population	Time Period	Cigarette Type	Relative Risk	Comments
Lee P.N., Garfinkel, L. Mortality and type of cigarette smoked. *J. Epidemiol. Community Health* 35:16-22, 1981.	12-year follow-up of CPS-I; a prospective mortality study of over 1 million men and women.	1960-1972	Tar yield: low/high	Emphysema: male=0.78; female=0.59	CHD risks are significantly different, but emphysema risks are not.
Hawthorne, V.M., Fry, J.S. Smoking and health: The association between smoking behavior, total mortality, and cardiorespiratory disease in West Central Scotland. *J. Epidemiol. Community Health* 32:260-266, 1978.	Prospective follow-up of 18,786 people attending a multiphasic screening examination.	1965-1977	Filter/Non-filter	0.61 for chronic	No difference in mortality rates for filter users for lung cancer or cardiovascular disease. Smokers of plain cigarettes had lower rates of respiratory symptoms than filter smokers.
Tang, J.L. *et al*. Mortality in relation to tar yield of cigarettes: a prospective study of four cohorts. *BMJ* 311:1530-1533, 1995.	Four prospective mortality studies from the United Kingdom.	1967-1982	Filter/Non-filter and tar yield	Tar yield chronic obstructive pulmonary disease 0.94 (0.64-1.37)	Relative risks for all tobacco-related disease combined were statistically significant. Relative risks are adjusted for age, study, and number of cigarettes/day.
Sparrow, D. *et al.* The relationship of tar content to decline in pulmonary function in cigarette smokers. *Am. Rev. Resp. Dis.* 127:56-58, 1983.	383 current smokers enrolled in a longitudinal study of aging who had spirometry performed 5 years apart.	1969-1980	Tar level	In a multiple regression analysis, tar level did not influence FVC or FEV 1 at baseline or change in these measures at follow-up.	Controlled for age, height, and number of cigarettes/day.
Dean, G. *et al*. Factors related to respiratory and cardiovascular symptoms in the United Kingdom. *J. Epidemiol. Community Health* 32:86-96, 1978.	Sample of 12,736 men and women aged 37-67 living in England, Scotland, and Wales.	1972	Filter/Non-filter	Of eight respiratory and cardiovascular symptoms, morning cough in men and women and shortness of breath in women were lower in filter cigarette smokers.	Controlled for age, social class, number of cigarettes/day, inhalation, and occupation.

Table 4-3 (continued)

Citation	Population	Time Period	Cigarette Type	Relative Risk	Comments
Lange, P. *et al*. Relationships of the type of tobacco and inhalation pattern to pulmonary and total mortality. *Eur. Resp. J.* 5:1111-1117, 1992.	6,511 men and 7,703 women selected randomly after age stratification from the general population in Copenhagen, followed for 13 years.	1976-1989	Filter/Non-filter	Chronic obstructive pulmonary disease: male=1.23; female= 1.07	
Alderson, M.R. *et al*. Risks of lung cancer, chronic bronchitis, ischaemic heart disease, and stroke in relation to type of cigarette smoked. *J. Epidemiol. Community Health* 39:286-293, 1985.	Case-contrl study of 12,693 in-patients.	1977-1982	Always filter/ non-filter	Chronic bronchitis: male=0.25; female=0.75	Adjusted for number of cigarettes/day.
Petitti, D.B., Friedman, G.D. Cardiovascular and other diseases in smokers of low yield cigarettes. *J. Chron. Dis.* 38:581-588, 1985.	4-year prospective follow-up of 16,270 current regular smokers and 42,113 subjects who never used any form of tobacco.	1979-1982	High and low (less than 15 mg tar and 1 mg nicotine) yield determined at the start of the study	0.97 (0.84-1.13) for all diseases of the respiratory system for a 5-mg increase in tar.	Controlled for age, sex, race, and number of cigarettes/day.
Krzyanowski, M. *et al*. Relationship of respiratory symptoms and pulmonary function to tar, nicotine, and carbon monoxide yield of cigarettes. *Am. Rev. Resp. Dis.* 143:306-311, 1991.	690 smokers from a sample of households in Tucson, Arizona; followed to 1988.	1981-1988	Tar, nicotine, and CO yield	After adjustment for intensity and duration of smoking and depth of inhalation, there was no effect of tar or nicotine on chronic phlegm, cough, or dyspnea. Tar and nicotine content had no independent effect on pulmonary function.	

Table 4-3 (continued)

Citation	Population	Time Period	Cigarette Type	Relative Risk	Comments
Brown, C.A. *et al.* Cigarette tar content and symptoms of chronic bronchitis: Results of the Scottish Heart Health Study. *J. Epidemiol. Community Health* 45: 287-290, 1991.	2,801 current cigarette smokers (1,154 males, 1,647 females), 40-59 years of age, from 22 districts of Scotland (Scottish Heart Health Study): cross-sectional random sample. Cigarettes smoked by subjects were assigned to one of three tar level groups: <12 mg/cig (low); 13-14 mg/cig (middle); 15+ mg/cig (high).	1984-1986	Tar level	Rates of chronic cough and chronic phlegm were higher for women who smoked high-tar cigarettes, but not for men.	Women in the middle-tar and high-tar group had smoked for longer and had significantly higher breath CO levels, serum thiocyanate levels, and daily cigarette consumption than women in the low-tar group. This pattern was not seen in men.
Withey, C.H. *et al*. Respiratory effects of lowering tar and nicotine levels of cigarettes smoked by young male middle tar smokers. II. Results of a randomised controlled trial. *J. Epidemiol. Community Health* 46(3): 281-285, 1992.	Intervention trial in 21 local authority districts in England; male middle-tar smokers aged 18-44 years; 7,029 smokers selected from 265,016 sent questionnaires; 643 controls. Assigned 1 of 3 different types of cigarettes for 6 months.	1985-1989	Mid-tar smokers (>12 mg/cigarette) assigned to test low-tar/middle-nicotine, middle-tar/middle-nicotine, or low-tar/low-nicotine cigarettes for6 months.Three cigarette groups: LM: low-tar/mid-nicotine, MM: mid-tar/mid-nicotine, LL: low-tar/low-nicotine. Per cigarette: LM: 9.5 mg tar/ 1.16 mg nicotine; MM:13.8 mg tar/ 1.24 mg nicotine; LL: 9.3 mg tar/1.04 mg nicotine.	No difference in respiratory symptoms with switching to different types of cigarettes.	Analysis of urinary nicotine metabolites showed that smokers allocated to the different cigarette type study adjusted their smoking so that throughout the trial their nicotine inhalation differed little from their pretrial intakes when they were smoking their usual cigarette for a 6-month period.

nation, nor to change in these measures over the 5-year interval. The analyses were controlled for age, height, number of cigarettes smoked per day, and baseline lung function in the follow-up analysis.

The frequency of respiratory symptoms also has been evaluated in relation to the type of cigarette smoked. Alderson and associates (1985) demonstrated a lower risk of chronic bronchitis among those who had smoked only filtered cigarettes in an analysis adjusted for number of cigarettes smoked per day. In contrast, a smaller case-control study (Krzyzanowski *et al.*, 1991) found no difference in respiratory symptoms in relation to the tar yield of the cigarette smoked with an analysis adjusted for the duration and intensity of smoking as well as the depth of inhalation. Brown and colleagues (1991) demonstrated lower rates of chronic cough and phlegm among female smokers of lower tar cigarettes, but the effect was not evident in males. In an intervention trial (Withey *et al.*, 1992) that involved switching 7,029 smokers to one of three different types of cigarettes, no difference in respiratory symptoms after a 6-month interval was noted among those who switched to lower yield cigarettes.

In summary, there is little evidence for a substantial difference in mortality from chronic obstructive lung disease among smokers who use low-yield cigarettes. There is equivocal evidence for a reduced rate of respiratory symptoms.

Summary of the Epidemiological Evidence

Studies published in the epidemiological literature support a difference in lung cancer and possibly heart disease risks, but not in chronic lung disease risks, between populations of individuals who smoke filtered or lower yield cigarettes compared with individuals who smoke unfiltered or higher yield cigarettes. However, there is marked variability among the studies, with many studies finding no effect or an effect too small to be statistically significant. In some studies, the heart disease and lung cancer risks appeared to change in opposite directions with low-yield cigarette use, as did risks for male and female smokers. Most of the major studies that defined this risk used the number of cigarettes smoked per day as a measure to control for the intensity of cigarette smoking and, therefore, they may be subject to confounding due to a compensatory increase in the number of cigarettes smoked per day by some smokers when they shifted to lower yield cigarettes. Given the variability of these results, the potential for confounding and in the analyses, and the difficulty of examining the continually changing cigarette product, it is difficult to conclude from these data that there is a clearly demonstrable harm reduction that is due to the use of filtered or lower yield cigarettes in comparison to unfiltered or higher yield cigarettes.

These epidemiological data were also recently reviewed by the Tobacco Advisory Group of the Royal College of Physicians (2000) in conjunction with the evidence for compensation in smoking behavior with use of low-yield brands. They concluded, "There are therefore reasonable grounds for concern that low tar cigarettes offer smokers an apparently healthier option while providing little if any true benefit."

BIOLOGIC IMPLICATIONS OF COMPENSATION FOR CHANGES IN CIGARETTE DESIGN

The biological significance of compensatory smoking may be more complex than is portrayed by measures of nicotine absorption or CO levels. Addition of a filter to a cigarette lowers the particulate mass passing into the smoker's mouth, and that reduction in particulate mass is usually measured as a reduction in milligrams of tar. The effects of filters and other changes in cigarette design on the particle-size distribution of the smoke are complex and somewhat dependent on the compensatory behavior of the smoker.

Filtration of cigarette smoke with a cellulose acetate filter alters the distribution of particle size in the smoke, preferentially reducing particles 0.5-micron mass median diameter (MMD) and larger as well as those particles below 0.1 micron MMD (Kieth and Derrick, 1960; Keith, 1982). The net result is a lowering of the MMD of filtered tobacco smoke. The MMD of the smoke reaching the smoker is concentrated in that range where deposition in the lung is most efficient and where there is relatively less deposition in the mouth and throat compared to the lung (International Committee on Radiation Protection, 1966; Committee on Health Risks of Exposure to Radon [BEIR VI], 1999).

Morie and colleagues (1973) examined the fibers in cigarette filters microscopically to examine the mechanism by which filters would preferentially remove both large and very small particles. They found that fibers oriented parallel to the smoke stream showed heavy deposition of particles with MMD less than 0.1 micron. Fibers oriented perpendicular to the smoke stream were coated with particles larger than 0.5 micron MMD. This finding suggests that diffusion of particles smaller than 0.1 micron MMD was the principal mechanism for deposition of these small particles on filter fibers oriented parallel to the smoke stream, and that the particles larger than 0.5 micron were trapped by interception on the fibers oriented perpendicular to the smoke stream. Particle size is a principal determinant of the deposition site of particles, with particles smaller than 0.5 micron MMD depositing in the lung rather than the upper airway (International Committee on Radiation Protection, 1966; Committee on Health Risks of Exposure to Radon [BEIR VI], 1999).

An investigation of the effect of filters on particle size, conducted for Philip Morris soon after filters had been widely introduced (Holmes *et al.*, 1959; Mitchell, 1958), suggested that filters lowered the particle size of the smoke produced by cigarettes. For example, Philip Morris regular (unfiltered) cigarettes produced smoke with an MMD of 0.94 micron and Benson and Hedges® with the filter removed produced smoke with an MMD of 1.0 micron. In contrast, filtered Parliament® cigarettes produced smoke with an MMD of 0.84 micron and Benson and Hedges® with the filter in place produced smoke with an MMD of 0.82 micron. More recent investigations (McClusker *et al.*, 1983) revealed that the particle size of the smoke generated by lower yield cigarettes is the same with and without removal of the filters. This difference in results may relate to the effect of filter ventilation on particle size. Increased ventilation results in an increase in the particle size of the smoke generated (Kieth, 1982). This effect is thought to occur

because the addition of dilution, particularly in the filter, slows down the rate at which the smoke passes through the cigarette, allowing more time for coagulation of the smoke particles. This increase in particle size due to coagulation may counterbalance the reduction in particle size produced by filtration. Removal of the perforated filters on low-yield cigarettes removes both the ventilation and the filtration. As discussed elsewhere in this volume (see Chapter 3), smokers of cigarettes with ventilated filters often cover the filters with their lips or fingers in order to increase the yield of the cigarette. When these ventilation holes are occluded, the result may be filtration without increased ventilation, and particle size may be reduced. However, no studies of particle size distribution with occlusion of the ventilation holes are available.

Particles with an MMD larger than 0.75 micron contain much more tar than do smaller particles because of their larger size, but they are more likely to be deposited in the mouth before reaching the respiratory track. Thus, a filtered cigarette with a smaller particle-size distribution may deliver much more of its dose of tar to the lung than will a nonfiltered cigarette with the same machine-measured tar yield. This may result in a relative preservation of the carcinogenic dose delivered to the lung when filters are used to reduce the tar delivered at the mouth.

Nicotine in smoke is absorbed from both smoke deposited in the mouth and smoke inhaled into the lung. Venous blood levels of nicotine reflect the total smoke exposure of the smoker, not where in the respiratory track the smoke particles are deposited. Large particles contain larger amounts of nicotine, but will preferentially be deposited in the mouth and throat. Selective removal of these large particles through filtration will reduce the fraction of nicotine that is deposited in the upper airway, but may have little effect on the fraction of smoke inhaled into the lung. If the smoker compensates for the reduction in total nicotine delivery by generating and inhaling more smoke to preserve total nicotine intake, then the larger mass of smaller particles delivering that dose of nicotine in filtered smoke might produce an increased deposition of tar in the lung for the same dose of nicotine delivered to the bloodstream.

Changes in pattern of deposition of smoke aerosol have been postulated (Thun *et al.,* 1997a) as one mechanism underlying the dramatic increase in adenocarcinoma (a cancer felt to arise from the more peripheral structures of the lung) seen over the last several decades (Travis *et al.*, 1995) in the United States and other countries (Russo *et al.,* 1997; Levi *et al.*, 1997). An additional concern has been increases in the levels of tobacco-specific nitrosamines in cigarettes over time, particularly NNK, which is a potent lung carcinogen for adenocarcinoma in animals (Hecht, 1998; see Chapter 5). Recently, it was suggested (Peel *et al.*, 1999) that the formation of tobacco-specific nitrosamines in flue-cured tobacco in the United States is largely the result of using propane gas heaters in the curing process. Oxides of nitrogen generated from burning the liquid propane combine with the nicotine in the tobacco leaf to form the tobacco-specific nitrosamines. These changes in curing methods were introduced in the mid 1960s and are

Table 4-4
Percentage of Smokers of Different Ages and Durations of Smoking Who Smoke Cigarettes with Different Tar Yields (American Cancer Society's Cancer Prevention Study I)

	Age (Years)					
Tar Level (mg)	<45	45-55	55-65	65-75	>75	**Total**
Low ≤17.6	12.82	13.14	14.36	14.36	13.46	13.72
Mid 17.6-25.8	52.24	51.74	53.14	52.23	51.22	52.36
High >25.8	34.94	35.12	32.49	33.41	35.32	33.93
	Duration (Years)					
	<20	20-29	30-39	40-49	50+	**Total**
Low ≤17.6	16.18	14.60	13.48	13.37	12.77	13.72
Mid 17.6-25.8	53.95	52.25	52.24	52.70	51.28	52.36
High > 25.8	29.87	33.15	34.28	33.93	35.95	33.93

likely to have resulted in a substantial increase in the levels of tobacco-specific nitrosamines present in cigarettes containing tobacco cured with this method. Increased levels of tobacco-specific nitrosamines have the potential to make cigarettes manufactured after the 1960s more carcinogenic and may have contributed to the rise in adenocarcinoma, which has become the most common form of lung cancer.

CORRELATION OF CIGARETTE BRAND CHOICE WITH NUMBER OF CIGARETTES SMOKED PER DAY AND DURATION OF SMOKING

As discussed above, examinations of disease risks produced by lower yield cigarettes commonly adjust for differences in intensity and duration of cigarette smoking. Those adjustments can be complicated if characteristics of the cigarette itself cause changes in measures of intensity of smoking, or if concerns about disease risk influence the choice of cigarette smoked. This section examines cross-sectional and cohort studies of the correlation between type of cigarette smoked and smoking intensity or duration.

Data from the CPS-I study for the type of cigarette smoked by White male smokers of different ages and smoking durations are presented in Table 4-4 for all of the baseline and follow-up surveys combined. The fraction of smokers who smoked low-yield cigarettes was relatively constant across different ages, which was in marked contrast to the pattern of increasing use of low-yield cigarettes with advancing age that was evident in the California data from 1996 (see Figure 4.1). It is worth noting, however, that the distribution of low-tar cigarette use with duration of smoking, in contrast to age, is not uniform. When the duration of any cigarette smoking (cigarettes of any tar level) is examined, those who reported smoking high tar cigarettes at the time of follow-up had been smoking for more years than smokers of lower tar cigarettes. It is unlikely that this effect is a function of older age among high tar cigarette smokers as the distribution of tar level by age is much more uniform in the table.

As part of a case-control study of lung cancer, Augustine and colleagues (1989a & b) constructed lifetime smoking histories by cigarette brand and number of cigarettes smoked per day with each brand. They compared the mean number of cigarettes smoked per day when subjects smoked nonfil-

tered cigarette brands to the mean number after they switched to filtered brands. The differences in cigarettes smoked per day were adjusted for nonfilter cigarettes smoked per day (before switching), duration of nonfilter and filter smoking, age at diagnosis, and age at switching. Among males, 45 percent of cases and 41 percent of controls increased the number of cigarettes that they smoked per day when they switched to filtered cigarettes. The mean increase in cigarettes per day was 5.9 for the cases and 3.9 for the controls. The percentages were even higher among females, with 59 percent of cases and 48 percent of controls increasing the number of cigarettes smoked per day. The mean increase in cigarettes per day was 7.8 for the cases and 4.7 for the controls. As measured by this study, compensation by increasing the number of cigarettes smoked per day upon switching to filtered cigarettes was common and involved substantial increases in the number of cigarettes smoked per day.

Assessing the impact of switching to low-yield cigarettes on the number of cigarettes smoked per day from cross-sectional data is complicated by multiple factors that may influence both choice of cigarette and the number smoked daily. The strength of nicotine addiction is correlated with the number of cigarettes smoked per day, and it is possible that more-addicted smokers may not be successful in switching to low-yield cigarettes. Smokers who are trying to quit, or who are interested in quitting, may smoke fewer cigarettes per day and shift to low-yield cigarettes as part of their effort to quit.

The concentration of cotinine in the blood is correlated with the number of cigarettes smoked per day (Benowitz *et al.*, 1983). Higher nicotine demand per day is met by smoking more cigarettes per day, and possibly by smoking each cigarette with more puffs and deeper inhalation. Less-addicted smokers have lower nicotine requirements and generally smoke fewer cigarettes per day. These lower nicotine requirements may allow the less-addicted smoker to satisfy their need for nicotine even with cigarettes that deliver lower levels of nicotine. The more heavily addicted smoker may not be able to extract sufficient nicotine from a low-yield cigarette to satisfy his or her addiction, or he or she may have to work so hard to extract the nicotine that the experience of smoking lower yield products is unpleasant. This effect would tend to concentrate more-addicted smokers who smoke more cigarettes per day in the higher yield brands. The result of such a phenomenon in cross-sectional examinations of cotinine levels among smokers of cigarettes with different machine-measured yields would be a slight slope of increasing cotinine levels with increasing machine-measured nicotine yields, even if complete compensation occurs at the level of the individual smoker.

A similar effect would be expected if smokers who tried to quit switched to low-yield brands as part of their effort to quit, or as an effort to moderate their risk upon relapsing to cigarette smoking. Efforts to cut down prior to quitting may also involve efforts to reduce the number of cigarettes smoked per day, and those who relapse may smoke fewer daily cigarettes for a period of time after reinitiating smoking. These influences have been reported as reasons why smokers choose low-yield brands (Giovino *et al.*, 1996), and

they would also be expected to influence the cross-sectional relationship between machine-measured nicotine yields and biological measures of nicotine intake.

Even with these influences potentially biasing the results, cross-sectional evaluations of blood cotinine levels have shown little or no relationship with machine-measured nicotine yields (Benowitz *et al.*, 1983; Benowitz, 1996; see Chapter 2). Benowitz and colleagues (1983) examined cotinine levels in smokers who smoked cigarettes with different nicotine yields as measured by the FTC method, and demonstrated a nonstatistically significant positive slope of the relationship between cotinine level in the smoker and nicotine yield of the brand smoked. In a similar comparison, but on a randomly selected population sample in the United Kingdom, a small, statistically significant positive slope was demonstrated between cotinine level in the smoker and nicotine yield of the brand smoked (Jarvis *et al.*, 2001).

In summary, these data suggest that choice of cigarette brand is only a relatively minor determinant of the amount of nicotine (and tar) that the smoker will derive from smoking. This issue is examined in more depth in Chapter 2.

Change in Number of Cigarettes Smoked per Day with Differences in Machine-Measured Nicotine Yields in the American Cancer Society's Cancer Prevention Study I

The CPS-I recorded cigarette brand and number of cigarettes smoked per day at five points during the 12 years of follow-up. Therefore, it was possible to examine both cross-sectional relationships between the number of cigarettes smoked per day and the machine-measured yield of the cigarette smoked, as well as the changes that take place when a smoker switches brands (see Appendix).

Table 4-5 presents the observed percentages of smokers of different numbers of cigarettes per day who smoked low-, mid-, and high-tar yield cigarettes among the CPS-I population for all of the baseline and follow-up surveys combined. The relationship between cigarettes per day and tar yield of the cigarette smoked is complex, as low-tar cigarette smokers were overrepresented in both the 1-9 and 40+ cigarettes per day categories. This may suggest that choice of cigarette is conditioned by multiple factors, including the possibility that smokers with greater nicotine demands are less likely to choose and be satisfied by lower yield cigarettes, and the possibility that smokers who switch to lower yield brands increase the number of cigarettes that they smoke per day.

Hammond and Garfinkel (1964) examined the first 2 years of follow-up of the CPS-I data (1959-1961). They did not demonstrate a relationship between an increased, decreased, or unchanged tar and nicotine yield of the cigarettes smoked and a change in the categorical measure of number of cigarettes smoked per day. In an analysis that examined change over the 12-year follow-up of the CPS-I data, and which examined continuous as opposed to categorical measures of numbers of cigarettes smoked per day, Garfinkel (1979, 1980) showed a modest difference between increasing tar and nicotine yield of the cigarettes smoked and decreased numbers of cigarettes smoked per day, particularly for females, but the effect was small.

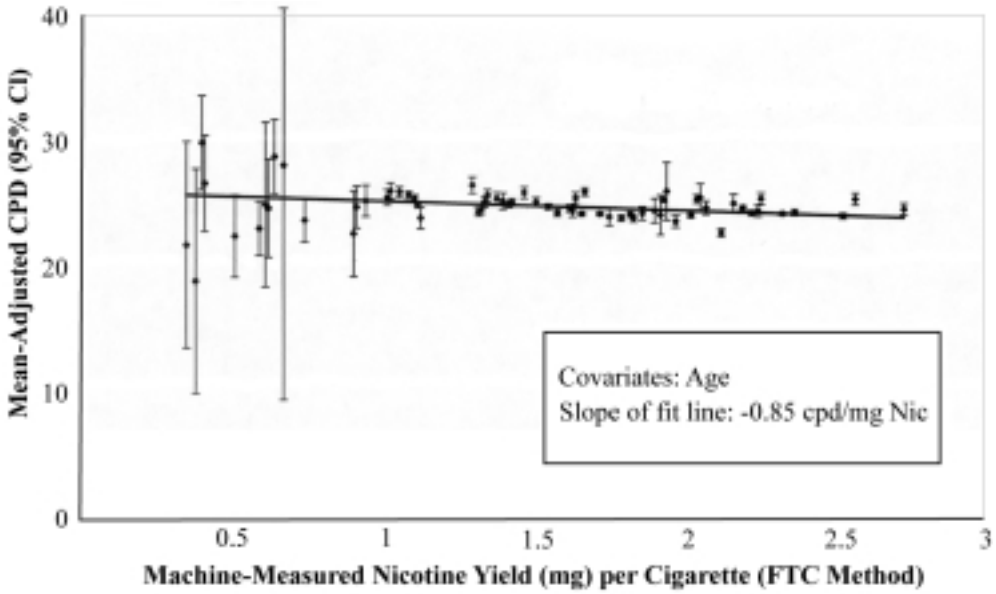
Table 4-5

Percentage of Smokers of Different Numbers of Cigarettes per Day Who Smoke Cigarettes with Different Machine-Measured Tar Yields (American Cancer Society's Cancer Prevention Study I)

	Cigarettes Smoked per Day						
Tar Level (mg)	1-9	10-19	20	21-39	40	>40	**Total**
Low ≤17.6	17.37	13.91	11.64	14.49	27.27	15.44	13.72
Mid 17.6-25.8	54.64	53	52.63	51.22	54.76	50.7	52.36
High >25.8	27.99	33.08	35.73	34.3	17.97	33.86	33.93

Figure 4-6

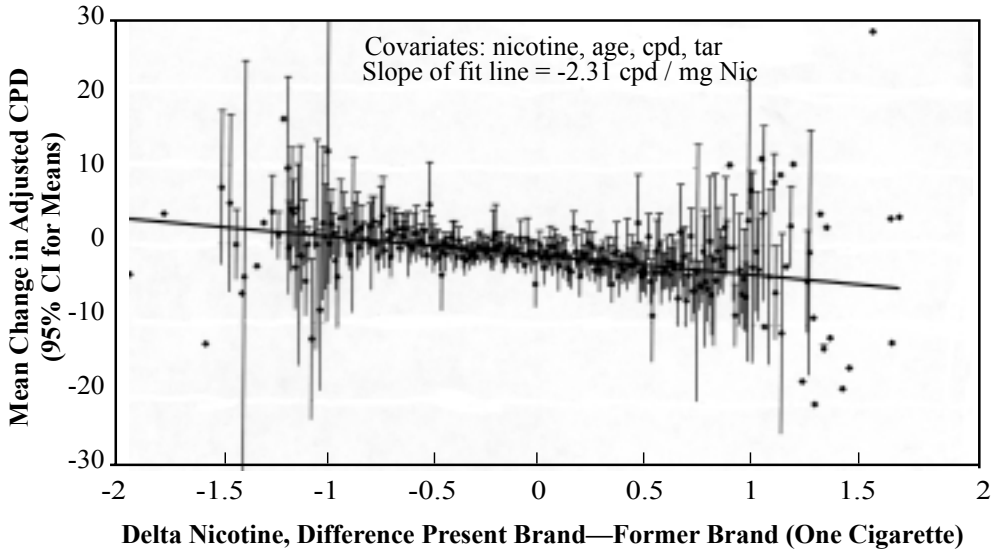
Nicotine Level of Brand Smoked versus Mean-Adjusted CPD Reported for All White Male Smokers (*N*=169,610): ACS CPS-I Study, Followed 1960-1972



Source: ACS CPS-I, White male current cigarette-only smokers.
Note: Nicotine and tar levels interpolated by year and brand from Reader's Digest *(Miller & Monahan, 1959) and FTC (for years 1967-1973) data, mean CPD by nicotine value using the weighted mean value for each categorical level of CPD. The mean CPD values are adjusted for age and regressed on nicotine yield per cigarette. For the graph, covariate coefficients are calculated in a general regression, then points are graphed as adjusted for the covariate with the regression line shown through the adjusted points.*

The relationship between nicotine yield of the cigarette smoked and the number of cigarettes smoked per day is reexamined in this report for individual smokers among the CPS-I population of White males. Figure 4-6 presents the mean number of cigarettes smoked per day by all smokers of a given brand with the machine-measured nicotine yield of the cigarette brand. Cigarettes smoked per day were adjusted for age because of the influence of age on reported number of cigarettes smoked per day. The results were similar without the age adjustment. There was a statistically significant slope, with a 0.8 cigarette per day increase for a 1 mg decline in nicotine.

Figure 4-7
Mean Change in Adjusted CPD Reported for Subjects Changing Brand Smoked v. Changes in Machine-Measured Nicotine Yield per Cigarettes: White Male Smokers (*N*=169,610), ACS CPS-I Study, Followed 1960-1972

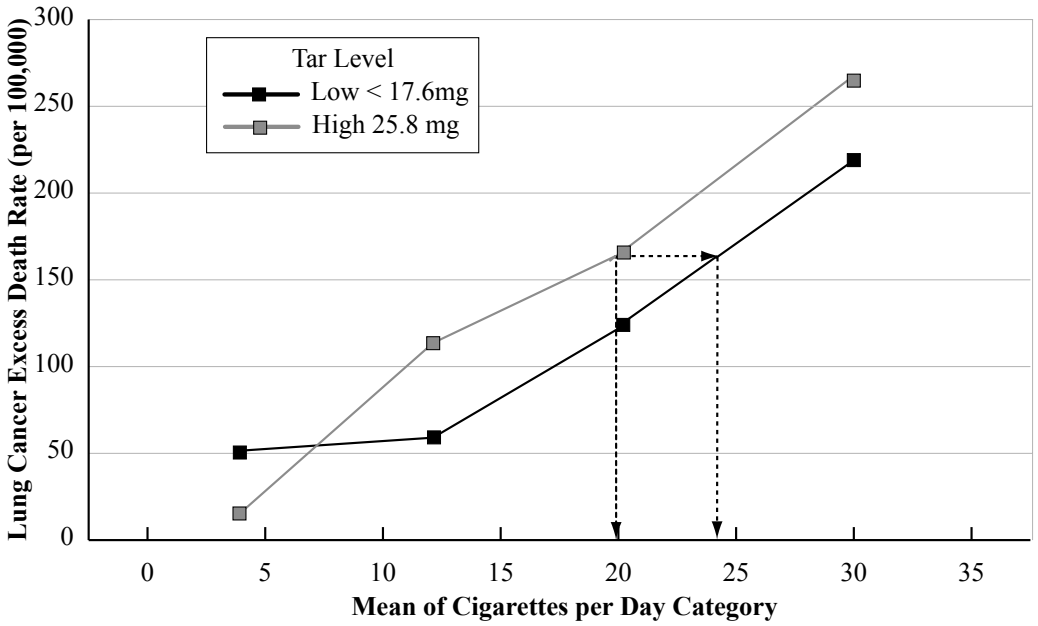


Source: ACS CPS-I, White male current cigarette-only smokers.
Note: Nicotine and tar levels interpolated by year and brand from Reader's Digest *(Miller & Monahan, 1959) and FTC (for years 1967-1973) data. Each data point combines subjects with the same change in nicotine (before—after). For each CPD category, the value used in the calculations is the mean CPD value for the category as calculated across all subjects falling in the category from the final follow-up questionnaire, which has continuous CPD values available. The mean change in CPD is the average difference (after—before) in reported CPD level across subjects with the given change in nicotine. Mean change in CPD, adjusted for age, cpd, and for tar and nicotine level before changing brand, is regressed on change in nicotine yield per cigarette. For the graph, covariate coefficients are calculated in a general regression, then points are graphed as adjusted for the covariates with the regression line shown through the adjusted points.*

When the analysis was limited to those who had changed the brand of cigarettes that they reported smoking in sequential follow-up surveys, the slope of mean number of cigarettes per day in relation to change in machine-measured level of nicotine for the brand was -2.31 cigarettes/day/mg nicotine (see Figure 4-7). This analysis controlled for age, cigarettes smoked per day prior to switching brands, and tar and nicotine yields of the cigarette smoked before the switch.

The implications of these shifts in number of cigarettes smoked per day with changes in nicotine yield of the cigarette are presented in Figure 4-8. Lung cancer risks from the CPS-I study for smokers of high-tar (more than 25.8 mg) and low-tar (less than 17.6 mg) cigarettes are presented by number of cigarettes smoked per day at the baseline survey. It is possible to estimate from this figure how much compensation by number of cigarettes per day would be required to eliminate the benefit of shifting from one line to the other (*i.e.*, changing to a low-yield cigarette). In this comparison, it would require a 20-cigarette-per-day smoker who switched from a high-tar to a low-tar cigarette to smoke only 4 more cigarettes per day in order to eliminate the benefit in lung cancer risk estimated from the CPS-I data. This difference in number of cigarettes per day is that which would be predicted from a change in nicotine of 1.7 mg for individuals who switched brands in

Figure 4-8
Excess Lung Cancer Death Rates for Smokers of Different Numbers of Cigarettes by Tar Level of Cigarette Smoked, American Cancer Society Cancer Prevention Study I



Source: ACS CPS-I White male current cigarette-only smokers.
Note: Tar levels interpolated by year and brand from Reader's Digest *(Miller & Monahan, 1959) and FTC (for years 1967-1973) data. Uses base survey (1959) tar and CPD values. Restricted to subjects who smoke throughout study to personal endpoint (end of study, death, or lost-to-follow-up). The summary rates shown are age-adjusted and duration-adjusted rates for CPD and tar-level categories. For each CPD category, the value used is the mean CPD value for the category as calculated across all subjects falling in the category from the final follow-up questionnaire, which has continuous CPD values available.*

the CPS-I analysis described in the previous paragraph. High tar and nicotine was defined in the CPS-I study as between 2-2.7 mg nicotine, and low tar and nicotine was below 1.2 mg nicotine. The mean nicotine level for the high-tar group in Figure 4-8 was 2.36 mg and the mean nicotine level for the low-tar group was 1.03 mg, a difference of 1.33 mg. In another context, the sales-weighted nicotine yield of U.S. cigarettes has declined from approximately 2.6 mg in the 1950s to 0.9 mg currently (see Chapter 5), a change of 1.7 mg of nicotine. The magnitude of this upward compensation, if it occurred across the entire population using lower yield cigarettes in the CPS I, is large enough to explain much of the reduction in lung cancer risks found among low yield cigarette smokers..

Number of Cigarettes Smoked per Day among Smokers of Cigarettes with Different Machine-Measured Nicotine Yields for Current Cigarettes—California Data

The relationship between the machine-measured nicotine yields and the number of cigarettes smoked per day was also examined for cigarettes with nicotine yields similar to those currently used in the United States. The 1990 and 1996 California Tobacco Surveys (CTS) were utilized to examine the effects of low tar and nicotine on the number of cigarettes smoked per day. This analysis was confined to a population of adult smokers who were not in the process of changing their smoking

behaviors. Respondents must have smoked at least 100 cigarettes in their lifetime, smoked cigarettes daily 1 year prior to the survey, and smoked daily at the time of the survey. The analysis was further restricted to respondents who were 25-64 years old, smoked five or more cigarettes per day, and who had not tried to quit smoking in the previous 12 months. These restrictions reduced the possible influences of individuals who were starting to smoke or trying to quit, were less likely to be using cigarettes because of their dependence on nicotine as defined by smoking fewer than five cigarettes per day (Shiffman, 1989; Benowitz and Henningfield, 1994), or were switching brands based on development of an illness (those aged 65 and older).

Respondents to the 1996 CTS were asked to read the barcode number printed on the side of the cigarette package. The brand descriptions for UPC codes, versions A and E, were provided by Matthew Farrelly of the Research Triangle Institute. These brand descriptions were used to obtain the corresponding machine-measured nicotine levels provided by the FTC for the year 1996. The resulting population was 2,140.

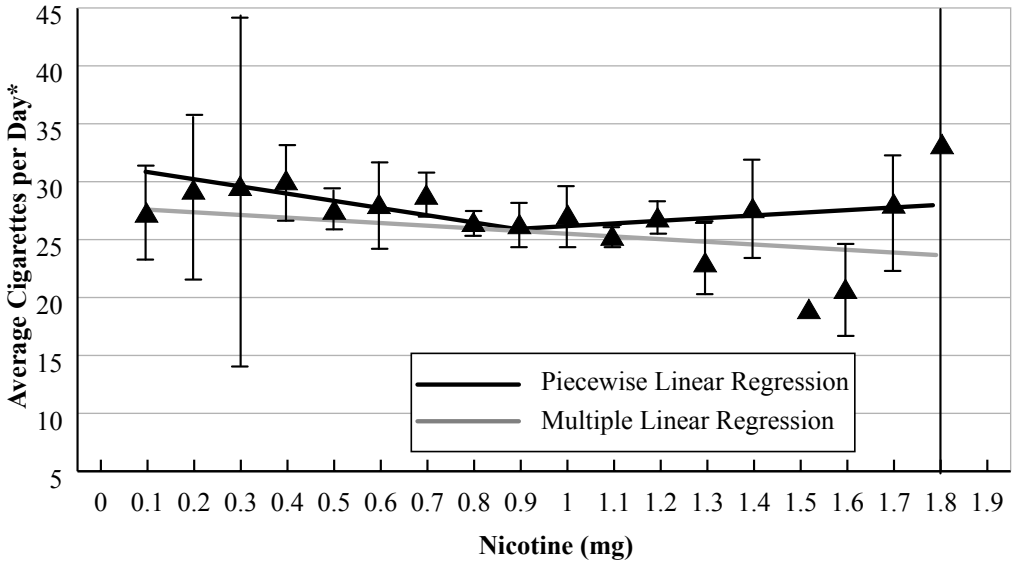
The data were modeled using a multiple linear regression that controlled for the effects of age, gender, race/ethnicity, and level of education, variables significantly associated with number of cigarettes smoked per day in the model. This analysis was based on individual subspecies brand data and cigarettes smoked per day. Figure 4-9 shows an increase in number of cigarettes per day for smokers of low-nicotine cigarettes (slope = -2.41 cig/mg nicotine, $P < 0.005$).

This finding was supported by analyses of the CTS from 1990 and 1996 using sales-weighted nicotine as the measure of the nicotine yield of the brand smoked. Data on brand smoked were available from the 1990 CTS, but survey respondents only provided the name of the brand family and not the specific brand subspecies. An overall sales-weighted nicotine value was calculated using the 1990 and 1996 CTS for each brand using the sales and nicotine-yield data for each brand subspecies (see Appendix). The resulting populations were 2,964 in 1990 and 2,239 in 1996.

Figure 4-10 demonstrates the relationship of mean cigarettes per day to the level of nicotine in cigarettes for the 1990 and 1996 CTS. Significantly more cigarettes were smoked per day by ultralow nicotine cigarette smokers than by smokers of cigarettes with machine-measured yields of 0.75-0.90, 0.90-1.05, and 1.05+ mg nicotine in both survey years. There were no significant differences between mean cigarettes smoked per day for the 0.75-0.90, 0.90-1.05, and 1.05+ mg nicotine categories.

Data from the 1990 and 1996 CTS were modeled using a piecewise multiple linear regression that controlled for the effects of age, gender, race/ethnicity, and level of education. This model allowed for changes in the slope of the cigarettes per day versus nicotine yield line, with break points dividing the lines at defined levels of nicotine yield. The slopes of the two regression lines were compared; the left side of the piecewise regression modeled cigarettes per day for nicotine levels below 0.95 mg, while the

Figure 4-9
Piecewise Linear Regression and Multiple Linear Regression of Cigarettes per Day, CTS, 1996, Using Individual Brand Nicotine Yield Data

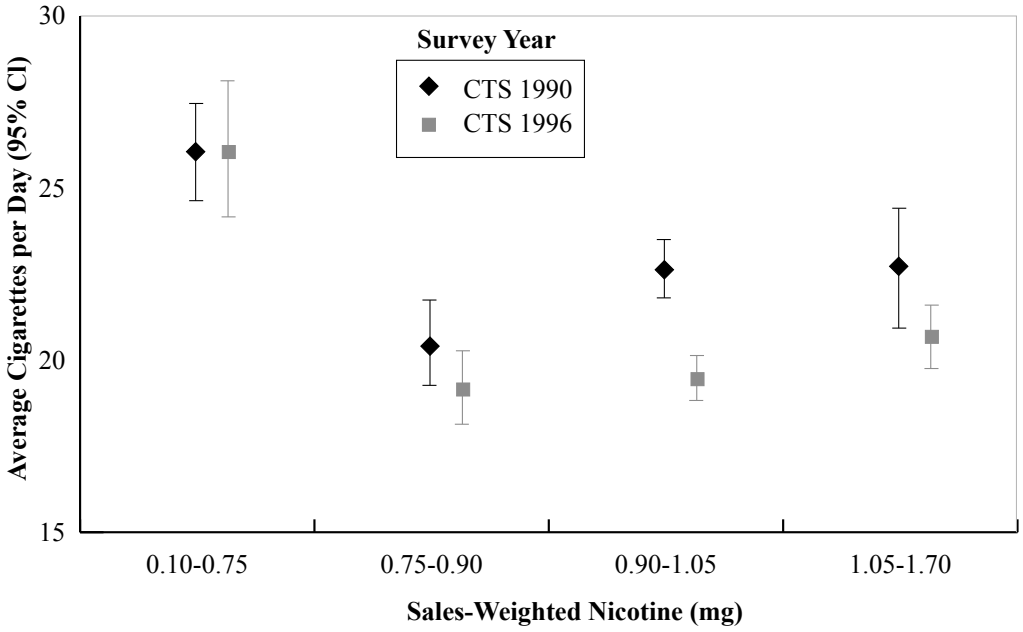


**Controlling for age, gender, race/ethnicity, and education level.*
Note: The break point used for the piecewise regression was 0.95 mg of nicotine. FTC data for year 1996 were obtained from the FTC reports on the tar, nicotine, and carbon monoxide of domestic cigarettes (FTC, 1999). The population consisted of respondents, aged 25-64, who had smoked 100 cigarettes, smoked daily one year prior to the survey, smoked daily at the time of the survey, had not made a quit attempt in the past 12 months, and currently smoked 5+ cigarettes per day. The P*-values and slopes of the piecewise regresssion are ($slope_{<0.95}$=-5.61, $P_{<0.95}$=0.0013) and ($slope_{>0.95}$=1.51, $P_{>0.95}$=0.5316).*

right side modeled cigarettes per day for nicotine levels greater than or equal to 0.95 mg. Figure 4-11 shows that there was an impact on the number of cigarettes per day for smokers of cigarettes with machine-measured nicotine yields below 0.95 mg nicotine. The slopes for the lines above 0.95 mg nicotine were not statistically different from zero. The nonstatistically significant difference in the slope of the lines from the two surveys was an artifact introduced because Marlboro® had a sales-weighted nicotine value of 0.94 in 1990 that increased slightly to 0.98 in 1996. This increase shifted the large population of Marlboro® smokers from one side of the 0.95-mg point to the other between the two analyses, and this shift resulted in a slight, nonsignificant shift in the slope of the lines above the 0.95 break point.

These analyses of the California Tobacco Surveys show a relationship between average daily cigarette consumption and the FTC nicotine yield of the cigarette smoked. More specifically, the sales-weighted analyses revealed that the average number of cigarettes smoked per day varies as a function of nicotine content below approximately 0.95 mg nicotine per cigarette. Smokers of cigarettes with ultralow nicotine levels showed a 20 percent increase in the number of cigarettes smoked per day compared to smokers of medium-nicotine cigarettes. Yet adults who smoked medium-tar and -nicotine cigarettes showed no significant difference in the mean number of

Figure 4-10
Cigarettes Smoked per Day by Level of Sales-Weighted Nicotine Yield (California Data)



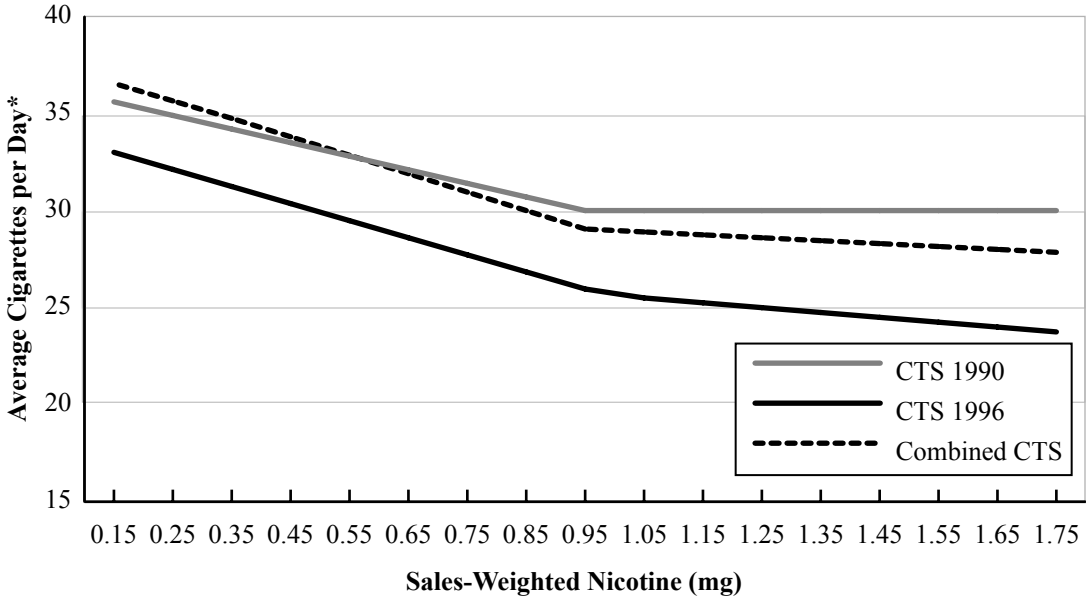
Source: FTC data for years 1990 and 1996 were obtained from two FTC reports on the tar, nicotine, and carbon monoxide of domestic cigarettes (FTC, 1992 & 1999). Sales data for 1990 were obtained from the Maxwell Report (Maxwell, 1994). Sales data for 1996 were not available to the public. The tobacco companies, therefore, provided the 1996 sales-weighted nicotine levels using the same methodology used for the 1990 analysis. Sales-weighting for overall brand was accomplished by weighting each sub-brand nicotine level by its corresponding 1990/1996 market share. The sum of the weighted sub-brand nicotine levels provided the overall nicotine level for the brand. The population consisted of respondents, aged 25-64, who had smoked 100 cigarettes, smoked daily one year prior to the survey, smoked daily at the time of the survey, had not made a quit attempt in the past 12 months, and were currently smoking 5+ cigarettes per day.

cigarettes per day when compared to those who smoked relatively high-tar and -nicotine cigarettes. With current cigarette designs, which depend heavily on ventilated filters to lower the machine-measured yield, smokers appear to be able to compensate within a single cigarette to maintain nicotine intake obtained from cigarettes that yield more than approximately 0.95 mg nicotine. Below that level of nicotine, compensation with increasing number of cigarettes smoked per day may also play a role. This bifurcated response of cigarettes per day with nicotine yield may be a characteristic of the engineering of cigarettes for elasticity of delivery described in the early sections of this chapter, and may not have occurred in cigarettes without ventilated filters.

TEMPORAL TRENDS IN LUNG CANCER AND OTHER DISEASES IN MAJOR COHORT STUDIES

Two major prospective mortality studies of smoking and disease bridged the period of greatest reduction in tar levels of cigarettes. Further examinations of these studies have revealed changes in smoking risks that have occurred as lower yield cigarettes were introduced and gained widespread acceptance.

Figure 4-11
Piecewise Linear Regression of Cigarettes Smoked per Day by Sales-Weighted Nicotine Yield of the Brand Smoked (California Data)



**Controlling for age, sex, race/ethnicity, and level of education.*
Note: The break point used was 0.95 mg of nicotine for all three piecewise regressions. FTC data for years 1990 and 1996 were obtained from two FTC reports on the tar, nicotine, and carbon monoxide of domestic cigarettes (FTC, 1992 & 1999). Sales data for 1990 were obtained from the Maxwell Report (Maxwell, 1994). Sales data for 1996 were not available to the public. The tobacco companies, therefore, provided the 1996 sales-weighted nicotine levels using the same methodology used for the 1990 analysis. Sales-weighting for overall brand was accomplished by weighting each sub-brand nicotine level by its corresponding 1990/1996 market share. The sum of the weighted sub-brand nicotine levels provided the overall nicotine level for the brand. The population consisted of respondents, aged 25-64, who had smoked 100 cigarettes, had smoked daily one year prior to the survey, had not made a quit attempt in the past 12 months, and were currently smoking 5+ cigarettes per day. The p-values and slopes of the piecewise regression for CTS 1990 are ($slope_{<0.95}$=-7.12, $P_{<0.95}$<0.0001) and ($slope_{>0.95}$=-0.16, $P_{>0.95}$=0.9517). The p-values and slopes of the piecewise regression for CTS 1996 are ($slope_{<0.95}$=-9.13, $P_{<0.95}$<0.0001) and ($slope_{>0.95}$=-2.77, $P_{>0.95}$=0.5117). The P-values and slopes of the piecewise regression for the combined data are ($slope_{<0.95}$=-8.69, $P_{<0.95}$<0.0001) and ($slope_{>0.95}$=-0.80, $P_{>0.95}$=0.7171).

The British Physicians Study examined lung cancer mortality rates (Doll *et al.*, 1994) with a follow-up period of over 40 years. The follow-up interval was divided into two 20-year periods, 1951-1971 and 1971-1991. Lung cancer death rates in male smokers, age-standardized to the same age distribution in the two follow-up intervals, increased by 19 percent to 314 per 100,000 during the second half of the study compared to 264 per 100,000 during the first 20 years of follow-up. This increase occurred during a period when the tar level of cigarettes in the United Kingdom had fallen dramatically. Lung cancer death rates for the entire U.K. population fell for males aged 35-54 and 55-74 during the 1971-1991 period (Peto *et al.*, 2000).

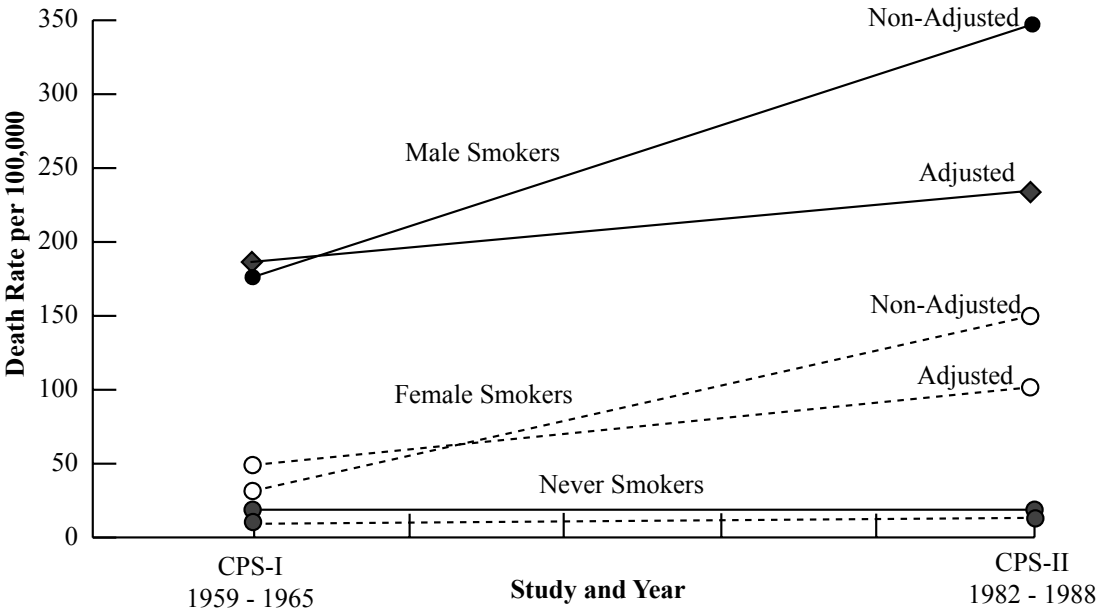
Differences in intensity and duration of smoking for the smokers examined in the two follow-up periods may have contributed to the increase in lung cancer death rates. Increased rates of cessation in the general population clearly contributed to the discordance of increasing lung cancer death rates among male smokers in the study as contrasted with decreasing lung cancer death rates for the male population as a whole. However, these

increasing death rates among smokers also suggest that smoking may have become more hazardous over the follow-up interval. If there has been any benefit of the introduction of lower yield cigarettes in the United Kingdom for the physicians followed in the British Physicians Study, it is small enough to have been overwhelmed by the differences in intensity and duration of smoking between the first and second 20-years of the study.

Findings were similar for a comparison of the two Cancer Prevention Studies (CPS I and CPS II) which had very similar designs, but were conducted 23 years apart—CPS-I began in 1959 and CPS-II began in 1982. Comparisons of the first 6 years of follow-up in the two studies (Thun and Heath, 1997; Thun *et al*., 1997b) demonstrated that lung cancer death rates increased between the two follow-up periods, a timeframe where substantial falls in machine-measured tar yields occurred for U.S. cigarettes. Detailed examination of the two populations studied showed that there were substantial differences in these two populations in the duration and number of cigarettes smoked per day, particularly for females (Thun *et al*., 1997b), and these differences in smoking behaviors explained some but not all of the differences in lung cancer death rates. Figure 4-12 presents age-standardized death rates for male and female participants of CPS-I and CPS-II. There was no change in the death rates for male and female never smokers between the two studies, but the lung cancer death rates for current smokers increased dramatically between the two studies. The increase in lung cancer death rates between the two time periods was reduced, but not eliminated, when the rates were adjusted for differences in the number of cigarettes smoked per day and duration of smoking.

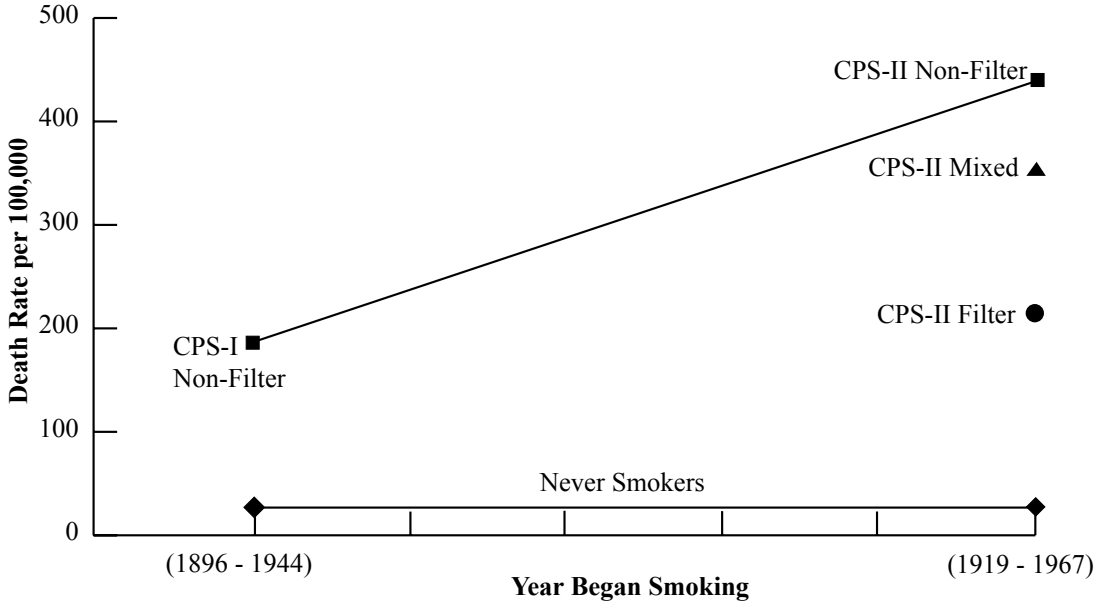
Nonfiltered cigarette smokers in CPS-I were compared to nonfiltered, mixed, and filtered cigarette smokers in CPS-II. Among males (see Figure 4-13), there was a dramatic increase in lung cancer risk for nonfilter smokers in CPS-II compared to CPS-I, and even the filter smokers in CPS-II had slightly higher lung cancer rates than the nonfilter smokers in CPS-I. Among females (see Figure 4-14), there were dramatically higher rates for all three categories of smokers in CPS-II compared to CPS-I. The rates in Figures 4-13 and 4-14 were age-standardized, but were not adjusted for differences in the number of cigarettes smoked per day or duration of smoking; it is likely that these differences may have contributed to the differences in lung cancer mortality between the two studies, particularly for females. However, the comparisons do not suggest that even filter smokers in CPS-II had any reduction in lung cancer risk when compared to smokers in CPS-I more than 20 years earlier. Some of this increase in lung cancer risk between the two studies may have resulted from greater availability of cigarettes and resultant heavier smoking among adolescents during the period when smokers in CPS-II were initiating their smoking behaviors. Alternatively, increased depth of inhalation with lower yield cigarettes and higher levels of tobacco-specific nitrosamines in the tobacco used in more recent cigarettes (see Chapter 5) may also have contributed to the increases. But detailed examination of the risks in these two studies separated by over 20 years does not suggest a reduction in risk resulting from lower yield cigarettes.

Figure 4-12
Death Rates from All Lung Cancers by Smoking Status, CPS-I and CPS-II (Adjusted for Current Amount and Duration of Smoking)



Note: Death rates from lung cancer by smoking status, CPS-I and CPS-II (adjusted and unadjusted for current amount and duration).

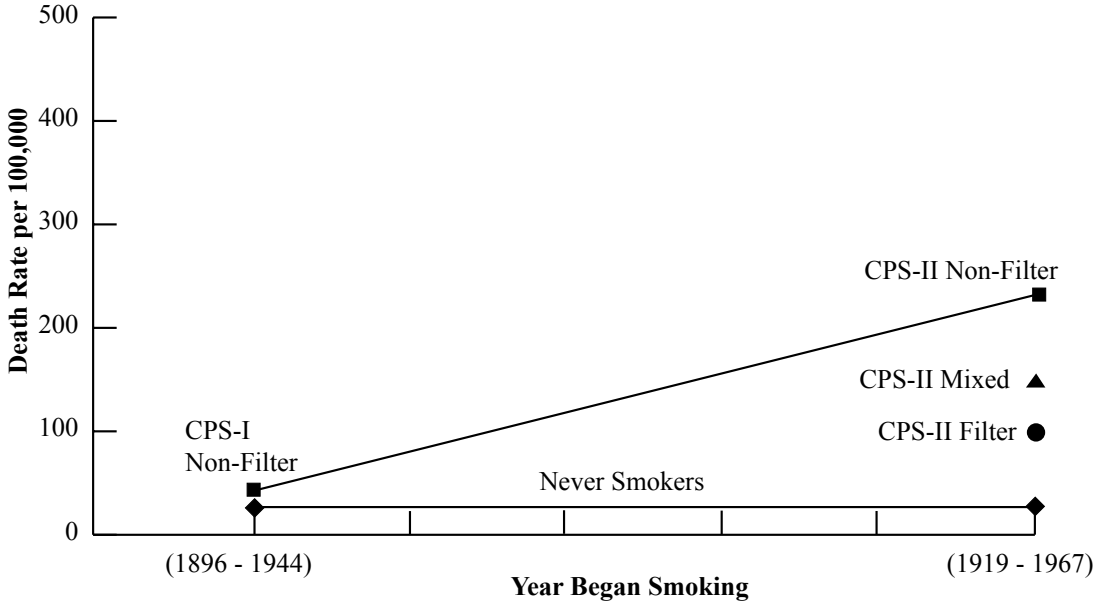
Figure 4-13
Male Lung Cancer Death Rates by Filter Use, CPS-I and CPS-II



Note: Death rates form all lung cancers among men by filter use, CPS-I and CPS-II.

Both of these studies indicate that the lung cancer relative risks associated with smoking increased over the same time period when smokers in the U.S. and U.K. were switching to lower yield and filtered cigarettes in substantial numbers.

Figure 4-14
Female Lung Cancer Death Rates by Filter Use, CPS-I and CPS-II



Note: Death rate from all lung cancers among women by filter use, CPS-I and CPS-II.

TEMPORAL TRENDS IN NATIONAL LUNG CANCER DEATH RATES AND SMOKING BEHAVIORS

The ultimate measure of a benefit from any reduction in the risk of smoking is a change in national death rates. Lung cancer death rates in both the United States and United Kingdom have declined among males in recent years. Several investigators have examined the relationships between smoking behaviors and changes in lung cancer mortality in both countries, and these analyses are now considered in relation to trends in tar yields of the cigarettes smoked in both countries.

Published Models Using Smoking Behavior to Predict National Lung Cancer Death Rates

In postulating the multi-stage model of carcinogenesis, Armitage and Doll (1961) suggested that multiple inheritable changes in the cell are required to cause malignant transformation. In this model, successive stages in the transformation of one cell may be separated from each other by several years, and the factors influencing early stages may be different from those influencing later stages. In its simplest form, this model implies that incidence of lung cancer at a given age is a constant times age raised to a power. Doll and Peto (1978) formulated the equation for lung cancer as Incidence = $0.273(\text{cigarettes/day} + 6)^2(\text{age} - 22.5)^{4.5}$, with the values in the formula derived from the lung cancer mortality experience of British physicians. The term (age – 22.5) was derived by assuming a uniform age of smoking uptake of 19 years and a 3.5-year latency from carcinogenic transformation of the cell to death from lung cancer. This term becomes duration of smoking prior to carcinogenic transformation for current smokers.

Variations of this model have been used by a number of investigators to match British national smoking prevalence data with British lung cancer

death rates. Stevens and Moolgavkar (1979, 1984) and Moolgavkar and colleagues (1989) used birth-cohort data on tobacco prevalence and birth-cohort-specific, cumulative tar-weighted cigarette consumption to construct a model that fit British birth-cohort/lung cancer death-rate data. Townsend (1978) expanded the basic multistage model to include birth-cohort-specific duration of exposure and number of cigarettes smoked per day. This model used the prevalence of smoking estimated in 5-calendar-year increments to divide each birth cohort into strata with different durations of smoking. A weighted mean of the number of cigarettes smoked per day at each age was used as the dosage term.

However, the weighting used assumed that recent smoking was more important than past smoking, decreasing the weight of duration of smoking. The number of cigarettes was also adjusted by assuming that filtered cigarettes were 40 percent less carcinogenic and that the carcinogenic risk of a cigarette was directly proportional to the machine-measured tar yield of the cigarette. The estimated lung cancer occurrence for each of the fractions with different durations of exposure was summed and added to the never-smoker risk to predict the lung cancer death rate for the birth cohort. Never-smoker death rates were taken from the American Cancer Society's prospective mortality study of 1 million males and females (Hammond, 1966).

To test this model, Townsend (1978) varied the constants in the model over a range and found the values that resulted in the best fit of the model to the British age-specific lung cancer mortality data. When the exponent for the duration of exposure term was set at 5 (the best-fit value), the model explained 98 percent of the variation in excess mortality in the male birth cohorts but only 84.8 percent of the variation in females.

Townsend's study was intended to develop a model of U.K. lung cancer mortality and was not intended to directly examine the question of risk reduction with low-yield cigarettes. The author assumed that the risk was directly proportional to the tar value of the cigarette smoked in creating their model. Adjustments for filters and tar content of the cigarettes in this study reduced the predicted risk of cigarettes by almost 40 percent from 1946 to 1966. The fit of the tar data in the model may be the result of the reduced weight given past smoking behaviors.

Brown and Kessler (1988) used a multistage model to predict U.S. lung cancer death rates to the year 2025. This model incorporated terms for calendar-year effects and a term for cohort effects and used a tar-weighted consumption measure for the number of cigarettes smoked per day. The model assumed a linear relationship between tar content and lung cancer risk and used a single cohort term to model the complex effects of differences in age of initiation and duration of exposure that occur across cohorts. These assumptions resulted in a model that predicted that lung cancer death rates in males would change very little between 1985 and 2010. The projection was not consistant with the decline in lung cancer death rates among white males that occurred following a peak in age-adjusted white male death rates in 1990 (Wingo *et al.*, 1999).

In contrast, Tolley and colleagues (1991) used a compartment model (*i.e.*, discrete state-discrete time model of health processes) to estimate lung cancer death rates using birth-cohort-specific smoking initiation, prevalence, and cessation rates for the United States and the relationship of dose and duration of smoking developed from the British Physicians Study (Peto, 1986). Without any adjustment for tar, they predicted that changes in smoking prevalence rates alone would project a decline in white male lung cancer death rates during the mid 1980s, a prediction that closely matched the actual death rate trends.

Swartz (1992) used birth-cohort-specific smoking rates estimated by Harris (1983) and a multistage carcinogenesis model developed by Whittemore (1988) to estimate U.S. lung cancer mortality. The modeled estimates predicted a 12-percent decline in lung cancer rates from 1970 to 1985, a period when lung cancer death rates increased by 26 percent. Substantial declines in tar yield of cigarettes occurred prior to and during this period, and this model suggested that risks of cigarette smoking increased rather than decreased over the period when tar yield was falling.

More recently, Mannino and colleagues (2001) examined age- and birth-cohort-specific U.S. lung cancer death rates for White males and White females, adjusting for age- and birth-cohort-specific differences in prevalence and duration of smoking. Differences between male and female lung cancer rates, and differences in lung cancer rates across birth cohorts, were eliminated by adjusting for differences in smoking prevalence and duration of smoking. These researchers noted: "Differences in lung cancer death rates across birth cohorts of U.S. men and women primarily reflect differences in the prevalence and duration of smoking. Changes in cigarette design that have greatly reduced tar yields have a relatively small effect compared with that of people's smoking status and duration of smoking."

National lung cancer death rate data in the United Kingdom were compared to two lung cancer mortality studies conducted 40 years apart (1950 and 1990) to examine the effects of changes in smoking prevalence (Peto *et al.*, 2000). The lung cancer risk produced by being a cigarette smoker increased between 1950 and 1990. This increase was attributed to the longer durations of smoking experienced by smokers as of 1990. The changes in smoking prevalence were consistent with the changes in lung cancer death rates for females and for older males, but younger males had declines in age-specific lung cancer death rates over time that were much larger than those in smoking prevalence. Reduction in lung cancer risks from smoking low-yield cigarettes was suggested as an explanation for this observation.

Influence of Smoking Behaviors on Lung Cancer Death Rates in the United States and United Kingdom

When considering a potential effect of changing cigarette design over time on national lung cancer death rates, it is necessary to control for changes in smoking prevalence and intensity over time because smoking intensity and duration are more powerful predictors of lung cancer risk in epidemiological studies than is tar yield of the cigarette smoked. Cigarette smoking was more widely prevalent during the early part

of the twentieth century in the United Kingdom than in the United States. For example, per-capita consumption of cigarettes in the United Kingdom for the year 1905 was 380 cigarettes per adult over age 15 (Wald and Nicolaides-Bouman, 1991), whereas per-capita consumption in the United States was only 70 cigarettes per adult over age 18 for the same year (Burns *et al.*, 1997a). In contrast, filtered and low-yield cigarettes were introduced and widely accepted in the United States ahead of their use in the United Kingdom (see Figure 4-15).

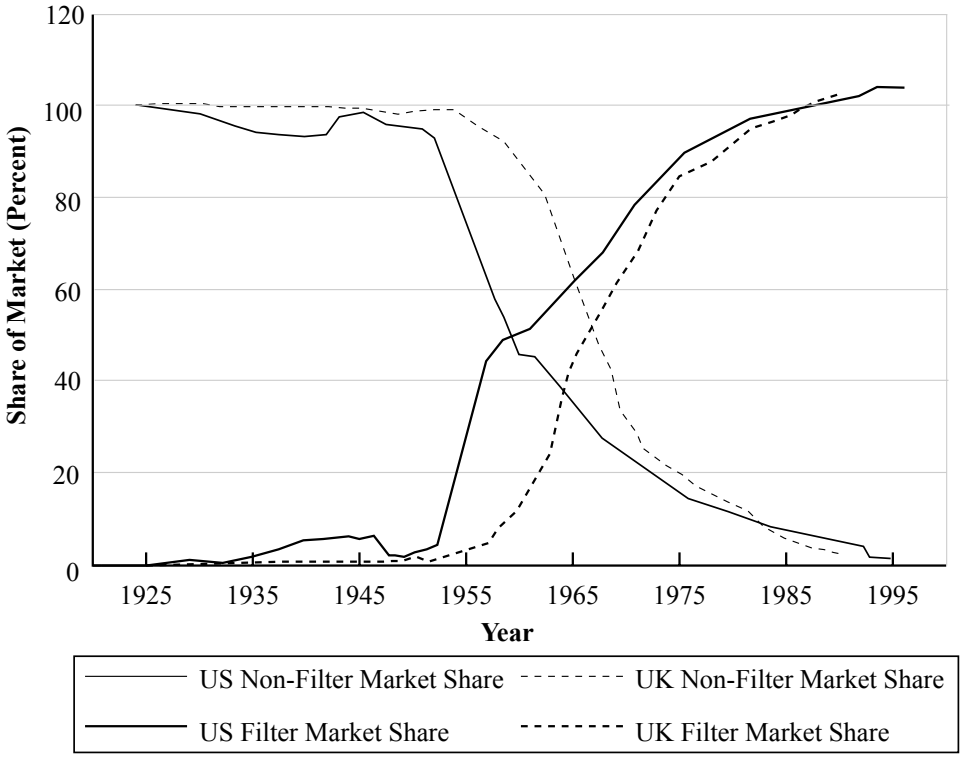
Lung cancer death rates over time reached peak levels that were much higher in the United Kingdom than in the United States, particularly among males. However, male lung cancer death rates peaked earlier (around 1970) in the United Kingdom (Peto *et al.*, 2000) compared to the United States (around 1990), and they declined more steeply in the United Kingdom than in the United States. Lung cancer death rates in the United Kingdom are now lower than those in the United States for both males and females under age 70 (Peto *et al.*, 2000).

In both the United States and the United Kingdom, the prevalence of smoking among males born in the early part of the last century exceeded 70 percent, with peak smoking prevalence rates among males in the United Kingdom being somewhat higher (more than 85 percent) (Burns *et al.*, 1997a; Wald and Nicolaides-Bouman, 1991). Additionally, males among the older birth cohorts in the United Kingdom smoked hand-rolled cigarettes in high percentages (Wald and Nicolaides-Bouman, 1991). The prevalence of ever smoking has declined among male birth cohorts born after 1930 in both countries.

Lung cancer occurs predominantly at older ages due to the powerful effect of duration of smoking on lung cancer rates. However, because of the temporal trends in type of cigarettes manufactured and sold, older smokers also began smoking with much higher yield cigarettes, and they smoked these cigarettes for much more of their smoking experience than did younger smokers. As a result, changes over time in age-specific lung cancer death rates at younger ages have been suggested as a more sensitive measure of the population impact of lower yield cigarettes on lung cancer rates. Younger smokers are, on average, more likely than older smokers to have begun their smoking with filtered and lower yield cigarettes and would have smoked them for a larger fraction of their smoking experience. In addition, age-specific lung cancer death rates are available from the 1950s onward allowing a long period of observation during which most of the changes in cigarette design took place.

The use of temporal changes in age-specific lung cancer death rates at younger ages as a measure of change in disease risks from low-yield cigarettes is somewhat limited by the observation that most younger smokers in the United Kingdom (Wald and Nicolaides-Bouman, 1991) and the United States (CDC, 2000) use cigarettes with mid-range yields of tar rather than the ultralow yield products. However, the tar values of these mid-range yield cigarettes are substantially lower than the tar yields of cigarettes sold 20-40 years earlier. In addition, use of low tar-yield cigarettes is currently

Figure 4-15
Market Share of Filter and Non-Filter Cigarettes in the United States and United Kingdom, 1925-1990



Note: U.S. data were obtained from Maxwell Report (Maxwell, 1994). British data were obtained from UK Smoking Statistics *(Wald and Nicolaides-Bouman, 1991).*

more common among older smokers than among younger smokers in both the U.S. and U.K. (see Figure 4-1 and Wald and Nicolaides-Bouman 1991), suggesting that a population effect of reduction in risk with use of these cigarettes, if present, might be larger among these older smokers. Indeed, it is among older smokers that the epidemiological data presented earlier in this chapter have suggested a decreased risk. The reduction in disease risk over time, out of proportion to declines in prevalence, is evident predominantly among younger age groups in the United Kingdom. The decline in lung cancer risk over time among older age groups is more closely matched by the decline in smoking prevalence (Peto *et al.*, 2000).

There is a difference between the United States and the United Kingdom in the rate of rise of lung cancer with age. This difference is evident across most of the birth cohorts presented in Table 4-6. Figure 4-16 presents age-specific lung cancer death rates for two separate birth cohorts. Age-specific rates in the United States start lower than in the United Kingdom but then rise more rapidly with age for both younger and older birth cohorts.

This higher rate of lung cancer at younger ages may be due to differences in the distribution of age of initiation among younger male smokers

in the two countries. Table 4-7 presents self-reported recall of the age of smoking initiation by smokers who were at different ages at the time of the survey. Data are presented for three surveys conducted in the United Kingdom in 1971, 1981, and 1987 (Wald and Nicolaides-Bouman, 1991) and for data from the National Health Interview Survey of the United States for the years closest to the U.K. data when the question on age of initiation was asked. For both sets of surveys, the data presented are for the entire population and age of initiation is reported for current and former smokers combined. Initiation rates prior to age 13 are similar for both countries, but there is a substantially higher rate of initiation among those 14-15 years old in the United Kingdom. This higher rate of initiation early in adolescence could contribute to the higher rate of lung cancer deaths at younger ages observed in Figure 4-16.

The reasons for the higher rate of rise with age of lung cancer death rates in the United States compared to the United Kingdom are less clear, but may relate to cessation during young adulthood in the United Kingdom occurring earlier in calendar years compared to the United States, thereby lowering the lung cancer risk as the birth cohort aged. Data are not available to make this direct comparison of cessation, but by 1984, the prevalence rates for 25- to 34-year-old males in the United Kingdom (born 1950–1959) were 39 percent (Wald and Nicolaides-Bouman, 1991), whereas the rates in comparable cohorts of White males in the United States were somewhat higher (42-43 percent) (Burns *et al.*, 1997a). This lesser cessation in the United States could contribute to the more rapid rise in lung cancer death rates with age.

The observed difference in lung cancer death rates may also relate to differences in the pattern of cigarette use at younger ages in the two countries. Differences in age of initiation, intensity of smoking during early adolescence, and rates of cessation during young adulthood all may influence lung cancer death rates at younger ages. Lung cancer death rates rise with increasing number of cigarettes smoked per day and even more powerfully with the duration of smoking (Doll and Peto, 1978), but this increase occurs with a lag of approximately 20 years from onset of exposure. That is, approximately a 20-year duration of smoking is required before lung cancer rates in smokers begin to significantly exceed those in never smokers (Burns *et al.*, 1997b). As a result, lung cancer death rates at age 35 among smokers are much more influenced by that group of smokers who began to smoke before age 15, in contrast to those smokers who first started to smoke in their mid to late 20s. The epidemiological data would suggest that it is unlikely that those smokers who began smoking after age 15 make a substantive contribution to lung cancer death rates at age 35, given the 20-year lag time demonstrated between onset of smoking and increases in the risk of lung cancer due to smoking.

Differences in the intensity of smoking at younger ages during the process of becoming a regular smoker may also play a role. To the extent that the pattern of early smoking (prior to age 15) is episodic and confined to a few cigarettes per month, which is the pattern most commonly described among adolescent smokers currently under age 15 (Johnston *et*

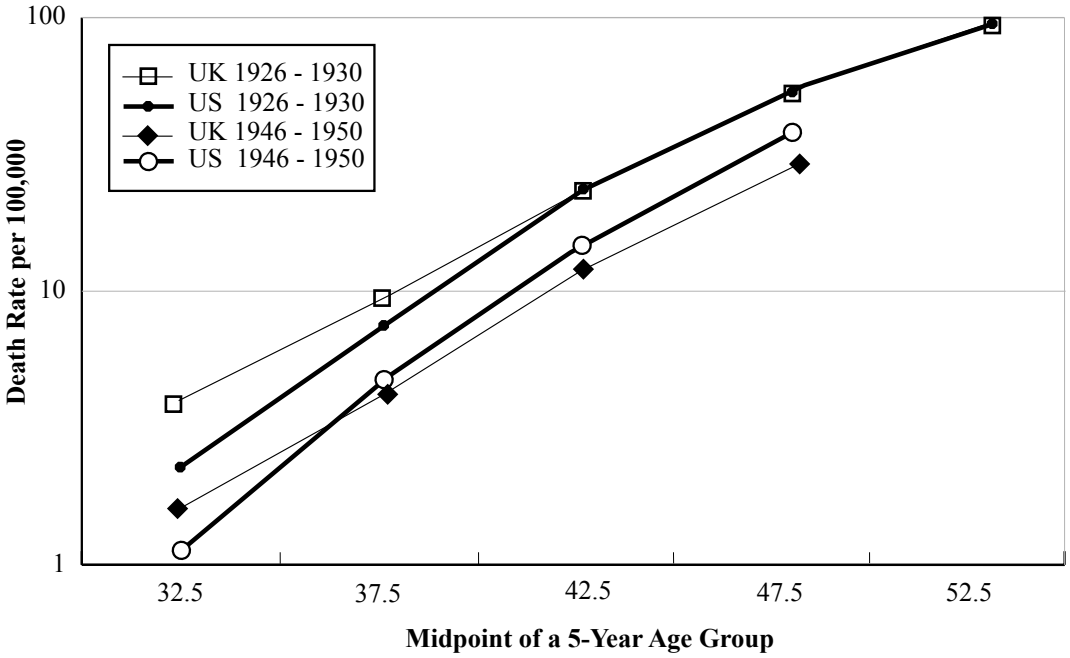
Table 4-6
Age- and Birth-Cohort-Specific Lung Cancer Death Rates for the United States and United Kingdom

	Lung Cancer Death Rate*										
	Age (Midpoint of 5-Year Age Group)										
Midpoint of	United Kingdom										
Birth Cohort	32.5	37.5	42.5	47.5	52.5	57.5	62.5	67.5	72.5	77.5	82.5
1873											167.30
1878										243.01	259.83
1883									305.25	377.48	391.85
1888								329.25	431.62	506.16	509.23
1893							289.47	428.10	538.81	650.73	679.95
1898						219.13	353.38	512.62	662.33	764.63	812.65
1903					126.17	232.18	374.27	528.11	682.74	796.69	832.76
1908				59.72	125.16	228.23	369.44	514.73	655.69	756.35	767.28
1913			24.87	57.76	120.75	215.69	344.15	479.32	616.24	678.27	669.39
1918		9.78	25.00	55.08	111.60	202.32	316.22	437.96	553.20	592.54	
1923	3.76	9.47	22.38	53.96	106.37	184.94	294.74	402.30	475.24		
1928	3.53	9.06	21.01	46.80	92.11	158.66	245.40	326.52			
1933	2.80	6.29	16.30	36.15	69.26	122.78	184.53				
1938	2.49	5.90	12.96	29.62	59.51	102.18					
1943	2.24	4.97	11.24	26.26	49.74						
1948	1.56	4.07	9.72	20.74							
1953	1.09	3.13	8.02								
1958	0.77	2.13									
1963	0.65										
	United States										
1873											116.80
1878										138.60	176.30
1883									148.90	199.60	222.60
1888								157.80	232.20	268.30	325.40
1893							135.50	219.70	302.60	380.60	431.60
1898						95.90	180.70	277.30	371.00	464.00	477.70
1903					58.20	114.92	199.88	306.95	418.93	502.80	543.33
1908				30.40	68.71	127.55	228.01	329.42	458.80	546.20	584.96
1913			11.60	31.79	76.79	152.13	244.30	359.11	470.70	565.40	580.60
1918		4.90	13.99	38.61	84.32	150.01	255.74	367.06	485.89	529.90	
1923	1.70	5.73	17.26	44.03	90.91	162.93	262.46	374.07	470.90		
1928	1.97	7.05	21.54	47.86	95.28	167.41	268.18	359.60			
1933	2.00	7.34	19.30	45.44	86.59	159.35	233.60				
1938	2.03	6.15	17.43	40.26	80.52	132.70					
1943	1.80	5.29	15.19	34.64	66.10						
1948	1.12	4.32	11.63	26.20							
1953	0.98	3.85	9.50								
1958	1.16	3.30									
1963	1.20										

**Deaths per 100,000*

al., 2000), the exposure would not be expected to contribute substantively to lung cancer death rates at age 35. To the extent that the pattern of early smoking is regular smoking of one-half pack or more per day, it would be expected to contribute relatively more to lung cancer death rates at younger ages. There are few data available to assess changes over time in the intensi-

Figure 4-16
Birth-Cohort-Specific Male Lung Cancer Death Rates by Age



Note: U.S. lung cancer death rates were provided for the years 1960-1994 by D.M. Mannino (personal communication, 2000).

ty of smoking during early adolescence in either the United States or United Kingdom, but it might be expected that the intensity of smoking during early adolescence may have changed in the direction of reduced intensity due to the tobacco education and control efforts implemented in both countries. Data from the Monitoring the Future Study (Johnston *et al.*, 2000) for high school seniors in the United States showed a decline from the late 1970s to the present in the percentage of those adolescents who had smoked within 30 days of the survey who were either daily smokers or smokers of one-half pack of cigarettes per day or more. These data demonstrate a decline in intensity of smoking among high school seniors over the last 25 years, and a similar decline may have occurred among all adolescents from the mid 1950s when concerns about the disease risks of smoking were first widely publicized.

Patterns of cessation can also influence rates of lung cancer at early ages. Among birth cohorts born before 1900, the pattern of smoking behavior with age did not include substantial rates of cessation under age 60 (Burns *et al.*, 1997a). However, beginning with the widespread publication of the disease risks associated with smoking in the mid 1950s, smokers began to quit at younger ages, so more recent birth cohorts have substantial fractions of smokers who have quit prior to age 30. These smokers who quit early would not accumulate a substantial duration of smoking, and therefore would have very low risks.

Table 4-7
Percentage of Men Starting to Smoke Any Tobacco in the United States and the United Kingdom at Different Ages (by Age at time of Survey)

			Percentage					
			United States			United Kingdom		
Age at Time of Survey	Age at Initiation	Year of Survey:	1970	1980	1987	1971	1981	1987
20-24	13 and less		6.9	8.4	9.7	31	9	10
	14-15		8.3	11.6	6.8		15	17
	16-17		19.6	18.2	10.0	21	19	17
	18-19		18.9	8.7	9.0	11	5	6
	20-24		6.9	6.2	3.5	2	2	1
	Don't know		2.5	1.8	0	2	3	3
	Never smoked		36.9	45.1	61.0	34	47	47
			100	100	100	100	100	100
25-34	13 and less		8.6	7.6	8.8	29	.	.
	14-15		11.8	11.5	10.8		.	.
	16-17		16.6	14.6	12.1	24	.	.
	18-19		17.9	17.1	9.9	13	.	.
	20-24		12.5	10.7	7.3	8	.	.
	25-29		1.6	0.8	1.1	1	.	.
	30-34		0.2	0	0	0	.	.
	Don't know		2.8	1.7	0	2	.	.
	Never Smoked		28.0	36.0	49.9	22	.	.
			100	100	99.9	100		
25-29	13 and less		9.4	8.3	9.1	.	8	9
	14-15		11.7	10.1	10.6	.	19	16
	16-17		15.9	14.8	12.7	.	21	15
	18-19		18.3	16.6	8.8	.	7	6
	20-24		11.0	8.3	6.7	.	5	5
	25-29		0.8	1.1	1.3	.	1	1
	Don't know		2.4	1.4	0.0	.	5	3
	Never Smoked		30.5	39.4	50.8	.	34	46
			100	100	100		100	100
30-34	13 and less		7.5	6.8	8.6	.	9	12
	14-15		11.9	13.1	10.9	.	17	14
	16-17		17.4	14.4	11.6	.	19	13
	18-19		17.3	17.7	11.2	.	8	9
	20-24		14.6	13.5	7.8	.	6	4
	25-29		2.8	0.4	0.9	.	2	2
	30+		0.4	0	0	.	0	0
	Don't know		3.5	2.1	0	.	4	5
	Never Smoked		24.5	32.1	49.0	.	36	42
			99.9	100.1	100		100	100

Note: The British data were obtained from UK Smoking Statistics *(Wald and Nicolaides-Bouman, 1991). The U.S. data were obtained from NHIS 1970, 1980, and 1987. The population consisted of United States White males, aged 20+, who were self-respondents for the above-mentioned NHIS years.*

In the United States, most first use of cigarettes occurs before age 18 (U.S.DHHS, 1994). Changes in smoking prevalence after reaching adulthood reflect rates of cessation almost exclusively. However, data from Table 4-8 suggests that, at least for the period after 1976 and perhaps during the 1950s, the prevalence of smoking among 20-24 year old males in the

United Kingdom was substantially higher than the prevalence reported four years earlier for 16-19 year old males. This suggests that a substantial fraction of initiation in the U.K. may have occurred after age 20. These smokers will not have accumulated twenty years of smoking until they are at least 40-44 years old and are unlikely to meaningfully contribute to the lung cancer death rate for ages under age forty.

In summary, a variety of changes in the patterns of cigarette smoking have occurred in both the United States and the United Kingdom, including changes in smoking initiation as well as smoking cessation. These changes may be responsible for many of the differences across time and between the countries in national lung cancer mortality rates.

Examination of Trends Over Time in Age-Specific Lung Cancer Death Rates in the United States and United Kingdom

Age-specific lung cancer death rates in the United Kingdom have declined dramatically in the last several decades, and these reductions have exceeded the declines in smoking prevalence among the same age groups for those under age 45 (Peto *et al.*, 2000). One possible explanation for the more rapid decline over time in lung cancer death rates compared to trends in smoking prevalence is decreased risk from smoking lower yield cigarettes. A reduced risk from smoking lower yield products might be first evident among those who are younger because they would have had a larger proportion of their smoking experience with these lower yield cigarettes. However, as discussed in the previous section, it is important to examine other aspects of smoking behavior that could also account for changes in lung cancer rates before attributing the differences in lung cancer death rates to changes in cigarette yield.

Age- and birth-cohort-specific lung cancer death rates for the United States and United Kingdom are presented in Table 4-6. The data for the United Kingdom are those provided by Peto and associates (2000) as the mean lung cancer death rates for sequential groups of 5 calendar years presented as 5-year age-specific death rates. These rates were converted to birth-cohort rates by subtracting the mid point of the age group from the 5-year-calendar period over which the death rates were averaged to approximate the years of birth for that age group. Rates for the United States are actual birth-cohort- and age-specific lung cancer death rates provided by Mannino and colleagues (2001).

It is evident that there have been very dramatic percentage declines in male lung cancer death rates in the United Kingdom among those under age 50, with particularly dramatic percentage declines under age 40. Rates for those aged 40-49 declined by about two-thirds, with rates in the youngest age group declining by approximately 85 percent. These declines exceed the approximately 50 percent decline in smoking prevalence over time at these same ages (see Table 4-8). Among those over age 50 in the United Kingdom, declines in smoking prevalence and lung cancer death rates approximate each other more closely.

In the United States, there have been much less dramatic declines in lung cancer death rates among white males under age 50, and they more

closely match changes in smoking prevalence. Data on smoking prevalence and lung cancer death rate by birth cohort and age are available for the United States and are presented in Table 4-9 for White males. At ages 30-34, the fall in lung cancer death rates across sequential birth cohorts is similar in magnitude to that observed for the fall in smoking prevalence, particularly for the fall in smoking prevalence for the same birth cohort when the cohort was age 12. At ages 35-39, lung cancer death rates fall approximately 48 percent from their peak in the 1931-1935 birth cohort to the 1951-1955 cohort, whereas smoking prevalence falls only 39 percent. However, there is also a 48 percent fall in the prevalence of smoking at age 12 across the same cohorts. Similarly, there is a 46 percent decline in lung cancer death rates at ages 40-44 from a peak in the 1926-1930 birth cohort to the last birth cohort where smoking prevalence data are available, with a decline in smoking prevalence of 36 percent, but the decline in smoking prevalence at age 12 is also 36 percent. Given the limited precision of these estimates and the difficulty in defining the exact measure of smoking behavior that should be compared (*e.g.*, no measures of intensity of smoking at younger ages are available), the changes in smoking behaviors across birth cohorts may well explain the changes in lung cancer death rates in the United States A more detailed examination of this relationship for all birth cohorts born after 1910 is presented later in this chapter.

Examination of the changes in lung cancer death rates at ages 30-34 and 35-39 with sequential birth cohorts in the United Kingdom (see Table 4-6) reveals that rates have fallen dramatically, particularly for those born after 1945. Lung cancer death rates currently occurring in those age groups in the United Kingdom approximate rates estimated for nonsmokers in these age groups by extrapolating retrogressively the rates observed among older nonsmokers in the CPS-I study to include these age groups. The rates for never smokers estimated are 1.2 at ages 30-34 and 1.9 at ages 35-39. These dramatic changes in lung cancer death rates at these younger ages in the United Kingdom are consistent with the essential elimination of a smoking effect at ages 30-34 and a near elimination of the effect at ages 35-39.

It is theoretically possible that this reduction in age-specific lung cancer death rates is due to a reduction in the carcinogenicity of the cigarettes smoked to almost zero in this younger age population, who would have initiated smoking cigarettes with substantially lower tar yields when compared with older birth cohorts, but this explanation is unlikely. In the United Kingdom (Wald and Nicolaides-Bouman, 1991), as is true in the United States, approximately 90 percent of young smokers smoke cigarettes with 10 mg or more tar yields, and approximately one-half smoke cigarettes with yields of 15 mg tar or higher. This distribution of cigarettes smoked, as well as the very modest risk reductions demonstrated in epidemiological studies and the current understanding of compensation (see Chapter 2), make it biologically implausible that smoking low-yield cigarettes would have almost no risk. An alternate, explanation is that prevalence of intense smoking at very young ages has declined dramatically, following demonstration in the 1950s of increased disease risks due to smoking and the

Table 4-8
Prevalence of Cigarette Smoking among British Males Aged 16 and Over, by Age: ONS General Household Survey, 1976-1996

	Age					
Year	**16-19**	**20-24**	**25-34**	**35-59**		**60+**
1948	61	74	76	70		39
1949	54	73	71	68		38
1950	51	68	70	66		38
1951	51	68	70	66		42
1952	47	62	67	64		40
1953	47	61	67	64		42
1954	46	63	66	63		42
1955	47	59	67	62		39
1956	52	65	67	65		45
1957	59	61	66	63		45
1958	54	63	65	63		42
1959	60	62	65	63		48
1960	65	67	64	64		46
1961	61	67	60	61		46
1962	61	62	59	60		44
1963	56	65	60	54		42
1964	56	61	55	57		45
1965	50	63	56	56		44
1966	54	60	59	56		44
1967	52	61	56	56		45
1968	57	69	57	57		46
1969	53	62	60	54		44
1970	55	58	60	55		46
1971	53	57	55	50		43
1972	51	60	54	51		42
1973	49	62	53	49		41
1974	48	55	55	51		40
1975	49	53	46	49		41
	16-19	**20-24**	**25-34**	**35-49**	**50-59**	**60+**
1976	38	46	48	49	49	40
1978	35	46	49	47	47	38
1980	33	44	47	45	45	34
1982	31	39	40	39	41	32
1984	28	39	39	38	38	29
1986	30	41	37	37	34	28
1988	28	37	37	36	32	25
1990	28	39	37	34	27	24
1992	29	39	35	31	27	20
1994	28	42	34	31	26	17
1996	25	43	38	30	27	17

Note: The prevalence of smoking for years 1976 to 1996 was obtained from the Office for National Statistics General Household Survey, 1976 to 1996 (ONS, 1998).

social policy changes that followed the publication of the Royal College of Physicians' report on smoking (Royal College of Physicians, 1962).

Lung cancer death rates for males in the United Kingdom have also declined for ages 40-44 and ages 45-49 with each age group declining to one-third of its peak value, a proportionate reduction that exceeds the

Table 4-9

Comparison of Birth-Cohort-Specific Current Smoking Prevalence at Different Ages with Birth-Cohort- and Age-Specific Lung Cancer Death Rates for White Males in the United States

	Age (Years)											
	Birth-Cohort-Specific Current Smoking Prevalence					**Lung Cancer Death Rate**	Smoking Prevalence	**Lung Cancer Death Rate**	Smoking Prevalence	**Lung Cancer Death Rate**	Smoking Prevalence	**Lung Cancer Death Rate**
BirthCohort	12	17	22	27	30	30-34	35	35-39	40	40-44	45	45-49
1906-1910	10.89	41.60	71.20	76.46	77.59	—	76.89	—	72.12	—	69.73	30.40
1911-1915	8.87	42.42	73.15	78.26	79.31	—	77.57	—	74.43	11.60	70.01	31.79
1916-1920	9.74	43.11	72.32	78.15	78.45	—	75.65	4.90	71.66	13.99	65.83	38.61
1921-1925	8.27	40.61	75.36	78.55	77.90	1.70	73.92	5.73	68.20	17.26	60.74	44.03
1926-1930	7.59	44.64	74.39	75.81	75.06	1.97	70.63	7.05	63.68	21.54	55.76	47.86
1931-1935	7.55	43.69	71.89	72.75	70.75	2.00	64.61	7.34	56.59	19.30	49.96	45.44
1936-1940	6.66	40.80	68.38	68.19	65.10	2.03	58.05	6.15	51.72	17.43	45.09	40.26
1941-1945	6.04	41.40	66.09	62.85	59.67	1.80	53.69	5.29	46.98	15.19	40.14	36.64
1946-1950	4.85	34.85	58.57	54.81	51.47	1.12	45.78	4.32	40.46	11.63	—	26.20
1951-1955	3.90	32.48	50.26	47.01	43.91	0.98	39.50	3.85	—	9.50	—	—
1956-1960	3.85	33.06	44.38	41.59	39.69	1.16	—	3.30	—	—	—	—
1961-1965	4.54	28.90	39.36	—	—	1.20	—	—	—	—	—	—

Note: U.S. smoking prevalence was obtained from NCI Smoking and Tobacco Control Monograph No. 8 (Burns et al., 1997a). U.S. lung cancer death rates were obtained for years 1955 to 1995. The death rate for 1955 came from the NCI Monograph 59 (NCI, 1982). Death rates for the years 1960-1994 were provided by D.M. Mannino (personal communication, 2000). The death rate for 1995 was obtained from NCHS data.

change in smoking prevalence within these age groups. Declines in lung cancer death rates among older age groups are more modest and are consistent with changes in smoking prevalence.

Unfortunately, birth cohort analyses of smoking behavior using the U.K. data are not available to generate a table similar to that provided for the United States (see Table 4-9). However, data are available on the prevalence of smoking by males of different ages for the calendar years 1948-1996 (see Table 4-8). These data offer some insight into the changes in age of smoking initiation and rates of cessation that have occurred among males in the United Kingdom over the time periods that relate to changes in lung cancer death rates among sequential birth cohorts of males 40-44 and 45-49 years old, as seen in Table 4-6.

The smoking prevalence rates estimated prior to 1976 in Table 4-8 for the United Kingdom are from the Tobacco Research Council/Tobacco Advisory Council surveys as reported by Wald and Nicolaides-Bouman (1991). Data after that point are from the General Household Survey (ONS, 1998), which began in 1976. The smoking prevalence estimates for males 16-19 years old prior to 1976 vary substantially from year to year, and they are too unstable to define year-to-year-to-year changes with precision. The data for males 20-24 and 25-34 years old are more stable.

In 1950, the birth cohort born between 1926 and 1930 would have been 20-24 years old, and that age group had a smoking prevalence of 68 percent in 1950 (see Table 4-8). In 1975, the 1951-1955 birth cohort would have been 20-24 years old, and that age group had a smoking prevalence of 53 percent in 1975. The decline in smoking prevalence was 22 percent in contrast to a decline of 62 percent in lung cancer rates at ages 40-44 across the same cohorts.

The birth cohort born between 1926 and 1930 had a smoking prevalence of 68 percent in 1950, and 20 years later, when they would have been ages 40-44, they had a prevalence of approximately 55 percent (as represented by the 35- to 59-year-old age group in Table 4-8). The 1951-1955 birth cohort had a prevalence of 53 percent at ages 20-24; 20 years later in 1996, their smoking prevalence would be approximately 30 percent. These changes in prevalence rates suggest that at least 19 percent of smokers in the 1926-1930 cohort had quit smoking by ages 40-44, whereas at least 43 percent of smokers in the 1951-1955 cohort had quit. These estimates are conservative because any individuals who initiated smoking after age 24 would reduce the estimated rates of cessation prior to age 40 among those smokers who initiated smoking prior to age 24. This increase in cessation during young adulthood would be expected to add to the decline in lung cancer risk produced by the fall in smoking prevalence at ages 20-24 because it would reduce the number of smokers with duration of smoking sufficient to increase their lung cancer risk.

A second characteristic of smoking behavior that differs across these birth cohorts in the United Kingdom is age of smoking initiation, particularly initiation prior to or early in adolescence. Comparison of the smoking prevalence rates in Table 4-8 at ages 20-24 in a given calendar year to those

of 16- to 19-year-old smokers from 4 calendar years earlier offers some insight into the fraction of 20- to 24-year-old smokers who initiated after age 19 and who would, therefore, have had shorter durations of smoking by ages 40-44. Some caution needs to be exercised in interpreting these prevalence ratios because of the previously mentioned variability in prevalence rates for the 16- to 19-year-old smokers, but it is generally true that the fraction of 20- to 24-year-old smokers who are likely to have initiated after age 19 increased from the early 1950s, peaked in the late 1950s at approximately 25 percent of the smokers at ages 20-24, and then declined to the mid 1970s. Data from the General Household Survey have more stable rates for the 16- to 19-year-old group. These data reveal a steady fall in the ratio of 16- to 19-year-old smoking prevalence compared with the 20- to 24-year-old prevalence 4 years later. The data in Table 4-8 suggest that as of 1980, 14 percent of 20- to 24-year-old smokers began smoking after age 19. By 1996, approximately one-third of the 20- to 24-year-old smokers had begun to smoke after age 19. As described above, these late-initiating smokers will add to the smoking prevalence at age 40, but they are unlikely to contribute to an increased lung cancer risk at that age due to their short duration of smoking. They may, however, mask the reduction in smoking prevalence through cessation for those who have been smoking long enough to be at increased risk of lung cancer (those who began smoking before age 20). This masking effect might result in a greater decline in lung cancer risk at ages 40-44 than would be expected from the decline in smoking prevalence at the same age.

In summary, a combination of the decline in smoking prevalence and the increase in late initiation of smoking could explain the excess decline in lung cancer death rates observed in the United Kingdom. These considerations should be part of an examination of the dramatic decline over time in lung cancer death rates at younger ages among males in the U.K. The changes in lung cancer death rates in the United States appear to be consistent with changes in smoking prevalence.

Matching U.S. Smoking Rates to U.S. Lung Cancer Death Rates

The question of whether U.S. lung cancer death rates have declined in a way consistent with a lowering of the lung cancer risk of smoking due to the use of lower yield cigarettes can be also examined by modeling the lung cancer death rate trends expected over time from the smoking behaviors of the U.S. population (see Appendix). The lung cancer risks that result from varying smoking intensity and duration can be defined using data from the CPS-I study. These risks can be fit to a model of lung cancer risk developed by Doll and Peto (1978) and the best fit of the CPS-I data to this model can be estimated. National birth cohort specific smoking behavior data can be used to predict national lung cancer death rates by utilizing the model of lung cancer risk derived from the CPS-I data to estimate the lung cancer rates for current, former and never smokers. Trends in these predicted estimates can be compared to the trends in actual observed lung cancer death rates. If the trends in predicted and observed rates are similar, there is no need to postulate an effect produced by changing cigarette design. If the trends are discordant, a term for changes in the tar yield of the cigarette smoked over

time can be added to the model to determine whether adjusting for the changing tar yield of the cigarette improves the fit of the model.

Population data on smoking behavior over time in the United States provide the smoking intensity and duration estimates that allow the model to predict the national lung cancer death rates expected from those smoking behaviors. These predicted national rates can be compared with the actual observed U.S. mortality rates over time to evaluate whether the risks of smoking measured during the period 1960-1972 (CPS-I) continue to predict current lung cancer death rates, overestimate lung cancer rates over time suggesting a decline in the risk of smoking as the cigarettes smoked had lower machine-measured yields, or underestimate lung cancer rates over time as suggested by the comparison of the risks of smoking in CPS-I and CPS-II. The purpose of this analysis is not to develop a model of lung cancer risk, but rather to examine whether lung cancer risks, measured in a population smoking higher yield cigarettes, overestimates or underestimates current lung cancer mortality rates in a population smoking cigarettes with much lower machine-measured tar and nicotine yields than those smoked by the participants in CPS-I. If the risk is overestimated, it would suggest that cigarette smoking has become less hazardous over time. If the risk is underestimated, it suggests that smoking has not become less hazardous over time and may have become more hazardous.

Smoking prevalence estimates were based on the National Health Interview Survey data from 1965 to 1994 (Burns *et al.*, 1997a) and were adjusted for the differential mortality that occurs in smokers compared with never smokers. The smoking behaviors were estimated for each 5-year birth cohort (individuals born within the same 5 calendar years) from 1910 through 1960. Lung cancer risk estimates were derived by fitting the CPS-I data to a published model of lung cancer risk (Doll and Peto, 1978) that relates lung cancer death rates to the intensity and duration of smoking. The formulation of this model is lung cancer death rate = $K(\text{cigarettes/day} + 6)^x(\text{duration} - 3.5)^y$. The best-fit estimate for this equation using the CPS-I data yields values of K = 0.00000000017196, x = 0.85, and y = 3.71. Lung cancer death rates were calculated for each single year of age of initiation (which, when subtracted from age, yields duration of smoking) within each birth cohort for current smokers. The mean value for cigarettes smoked per day for all white male smokers in the National Health Interview Survey (16.45) was used as the term for cigarettes per day. The weighted sum of all the rates for individual ages of initiation yields the rate for the smokers in the cohort.

Rates in former smokers were estimated by modeling the fractional change in excess lung cancer death rates with duration of cessation using the CPS-I data (Burns, 1998). The fraction of the excess lung cancer death rate that remained with each increasing year of smoking duration was then multiplied by the excess death rate between smokers of that duration and nonsmokers of the same age. The fraction of the population who quit smoking in each year was estimated from the National Health Interview Survey data, and it was assumed that the distribution of smoking duration for those who quit was the same as that for current smokers in that year.

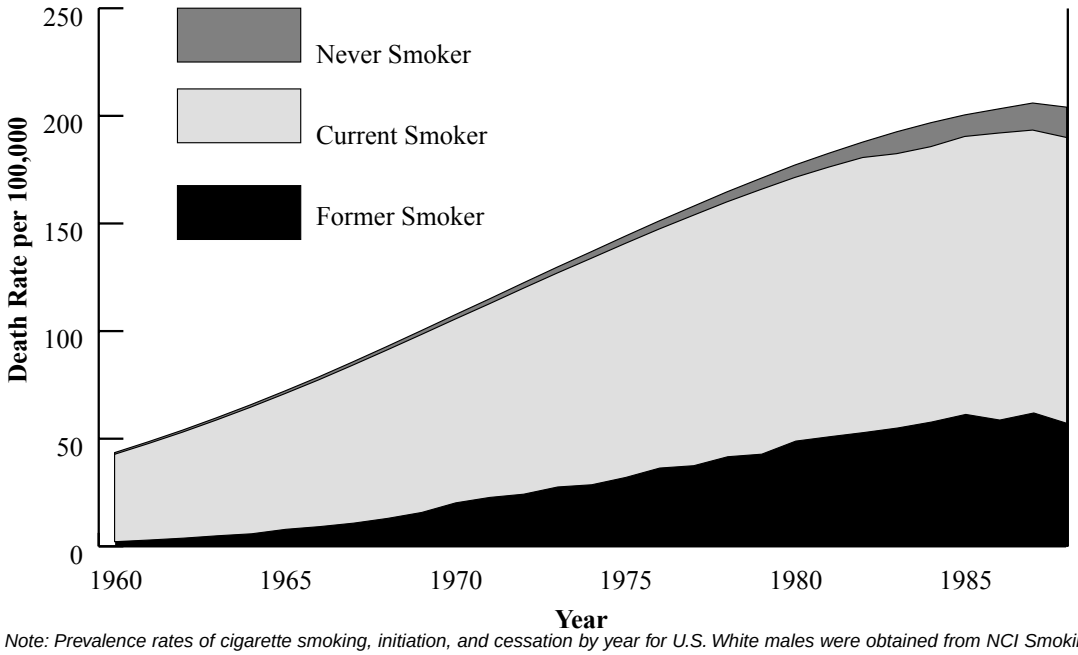
This generated individual cells of fractions of each cohort that had duration of smoking and duration of cessation specified by single years. Lung cancer death rates were calculated for each of these cells by subtracting the risk in never smokers from that of continuing smokers of the same age of initiation, multiplying the result by the fraction of excess mortality remaining at the appropriate duration of cessation, and adding back the rate in never smokers. The prevalence-weighted sum of all of these cells is the lung cancer death rate in former smokers for that birth cohort in that calendar year. Lung cancer death rates for never smokers were those estimated from CPS-I data (Burns *et al.*, 1997b).

Lung cancer death rates for each cohort in each calendar year were generated by summing the rates for current smokers, former smokers, and never smokers, weighted by their respective prevalence in that year. Figure 4-17 presents an example of these estimates for the cohort born between 1910 and 1914. Rates are presented by calendar year; but because the rates are for a population born during a fixed set of years, the calendar year axis also reflects increasing age of the birth cohort. This explains the increasing never smoker lung cancer death rates with calendar year in the figure, when age-specific lung cancer death rates in never smokers have not changed over time (Thun and Heath, 1997; Thun *et al.*, 1997a).

Actual observed lung cancer mortality rates by birth cohort were obtained from the U.S. mortality data and are those presented by Mannino and colleagues (2001). The birth cohorts for smoking and lung cancer are 1-year discordant, but it is unlikely that this difference contributes substantively to the results. Lung cancer death rates estimated from smoking behaviors and CPS-I risk data were scaled to the actual U.S. mortality rates to derive a single exponential scaling factor for all of the cohorts. The value for this scaling factor was 1.25. Differences between the predicted and actual lung cancer death rates were examined across calendar years for each birth cohort. A term proportional to the sales-weighted tar yield of U.S. cigarettes for each calendar year was applied to the predicted rates as c times the tar value, and the optimum value for c was calculated. The resultant tar-adjusted rates were tested to determine whether the addition of the term for tar to the predicted rates improved the goodness of fit of the predicted data to the observed U.S. lung cancer mortality rates by cohort. These three sets of rates (U.S. mortality, CPS-I predicted, and tar-adjusted CPS-I predicted) are presented in Figures 4-18a to 4-18i, with one graph for each 5-year birth cohort.

The fit of the CPS-I predicted rates was improved by the addition of the tar term, but the improved fit was in the direction of declining tar values increasing the risk. There was excellent agreement between the CPS-I predicted rates and the real U.S. lung cancer death rates in each cohort until the late 1970s. However, beginning in 1979 and in later years, there was a progressive underestimation of U.S. lung cancer mortality when the dose and duration risk relationships from CPS-I and U.S. smoking prevalences by birth cohort were used to estimate lung cancer death rates. In order to account for the difference in timing between transformation of a cell into a cancer and death from the growth of that cancer, the analysis was repeated

Figure 4-17
Contribution to White Male Lung Cancer Rates by Smoking Status: Birth Cohort 1910-1914



Note: Prevalence rates of cigarette smoking, initiation, and cessation by year for U.S. White males were obtained from NCI Smoking and Tobacco Control Monograph No. 8 (Burns et al., 1997a). U.S. population estimates stratified by age, sex, and race were obtained from CDC and U.S. Bureau of the Census web sites (CDC, 2000c; USBC, 2000). U.S. lung cancer mortality of White males were provided by D.M. Mannino (personal communication). These risk data were stratified by 5-year birth cohorts for each calendar year, 1960-1994. The 5-year birth cohorts began with 1901-1905 and ended with 1961-1965. See Appendix for details.

with the tar values lagged by 4 years, and the results were not substantively nor significantly different. These analyses suggest that, if anything, there has been an increase rather than a decrease in the carcinogenicity of smoking over the last several decades in the United States.

In order to address the question of changes in age-specific lung cancer death rates at younger ages, the difference was examined between the observed lung cancer death rates and the death rates predicted using the CPS-I risk data (without a term for tar) at fixed ages across multiple birth cohorts. If the most recent birth cohorts have lung cancer death rates that are declining more rapidly than would be predicted from differences in their smoking prevalence (*i.e.*, an effect suggesting a reduction in risk of smoking with lower yield cigarettes), then the difference between actual and predicted lung cancer death rates at fixed ages should have a slope when plotted across sequential cohorts. When sequential birth cohorts are examined in this manner for age-specific lung cancer death rates at ages under 50, there is no discernible slope for cohorts born after 1930, and the slope for older cohorts and for older ages is in the direction of increasing risk with the younger cohorts. Therefore, even when the model is examined in an age-specific format and confined to younger ages, there is no evidence to suggest that there is a decline in risk for smokers who would have had higher proportions of their smoking experience using filtered or low-yield cigarettes.

Figure 4-18a
Lung Cancer Death Rates: White Males, Birth Cohort 1910-1914

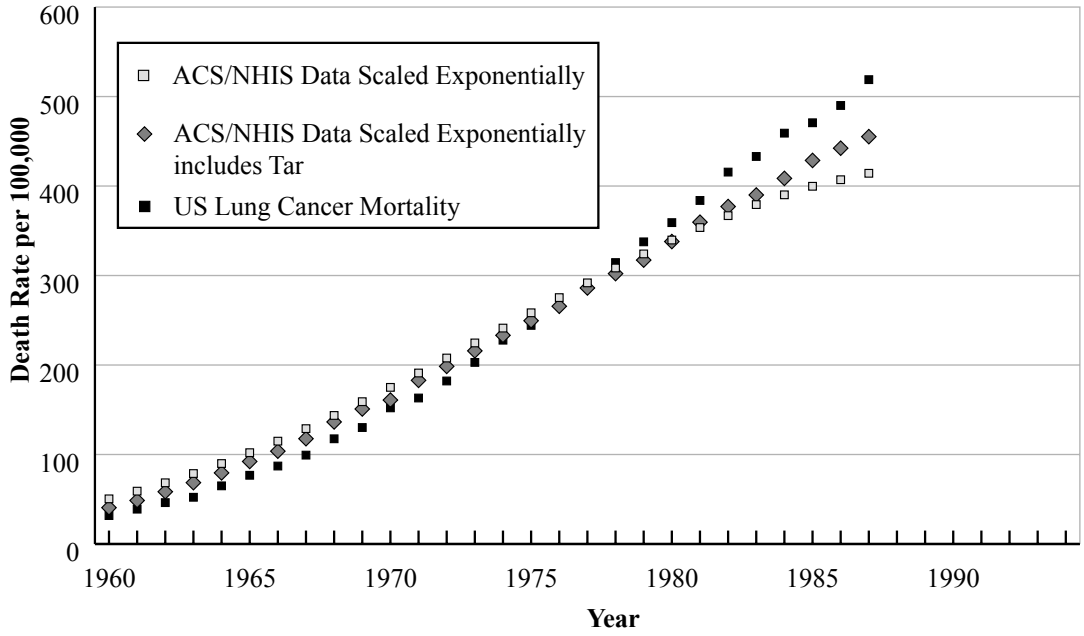


Figure 4-18b
Lung Cancer Death Rates: White Males, Birth Cohort 1915-1919

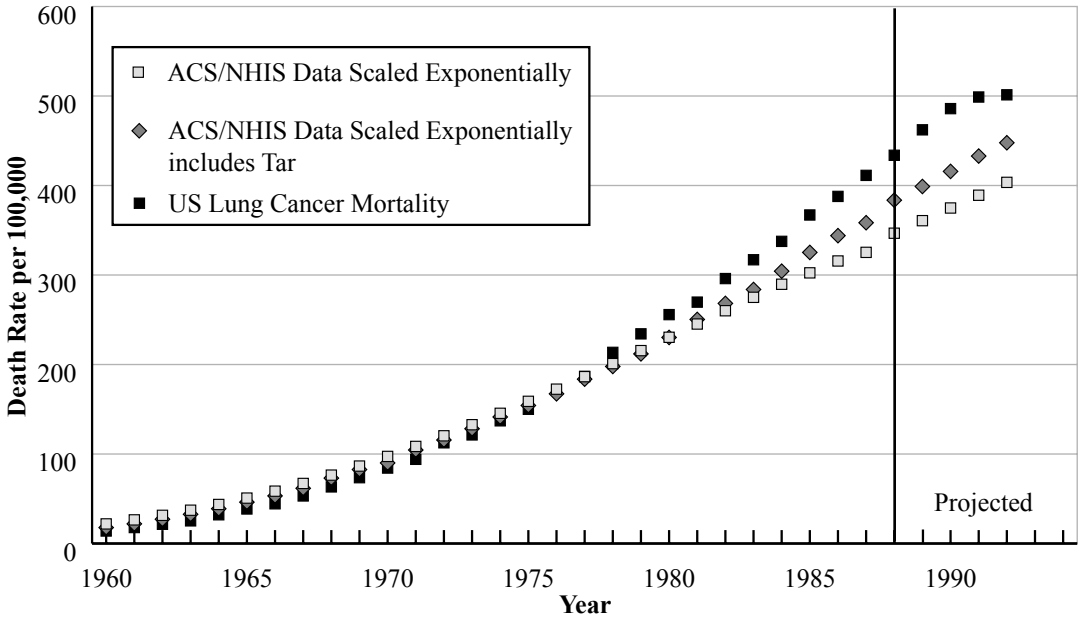


Figure 4-18c
Lung Cancer Death Rates: White Males, Birth Cohort 1920-1924

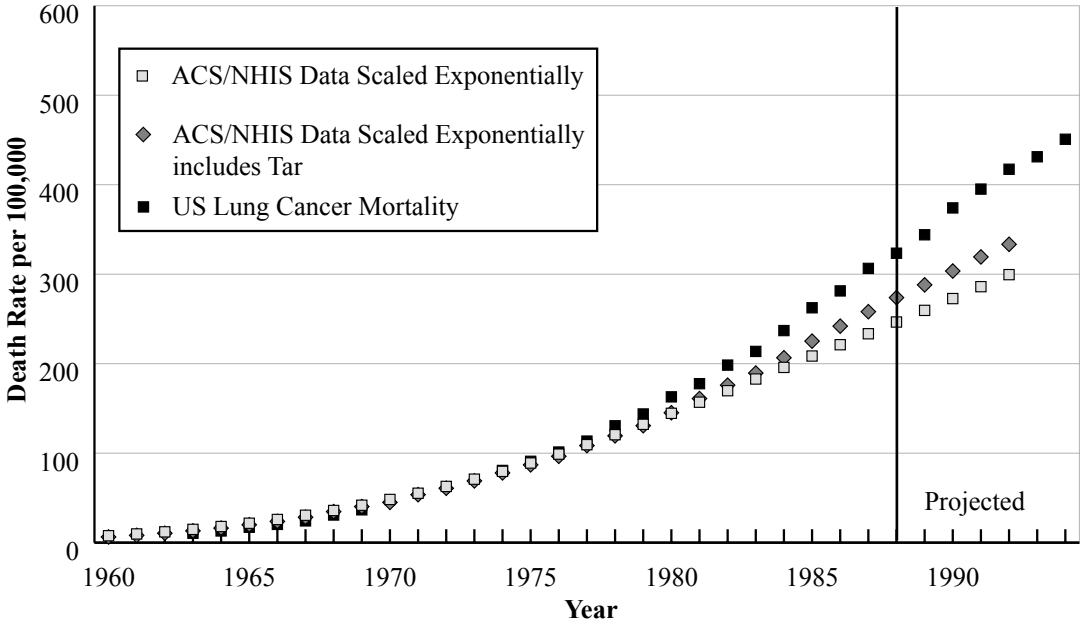


Figure 4-18d
Lung Cancer Death Rates: White Males, Birth Cohort 1925-1929

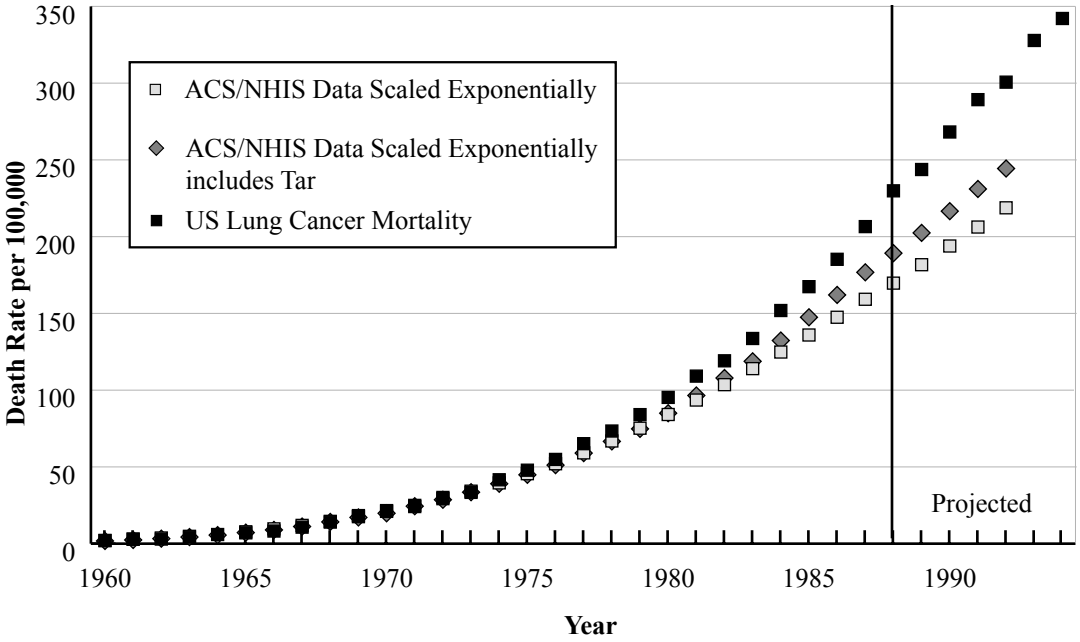


Figure 4-18e
Lung Cancer Death Rates: White Males, Birth Cohort 1930-1934

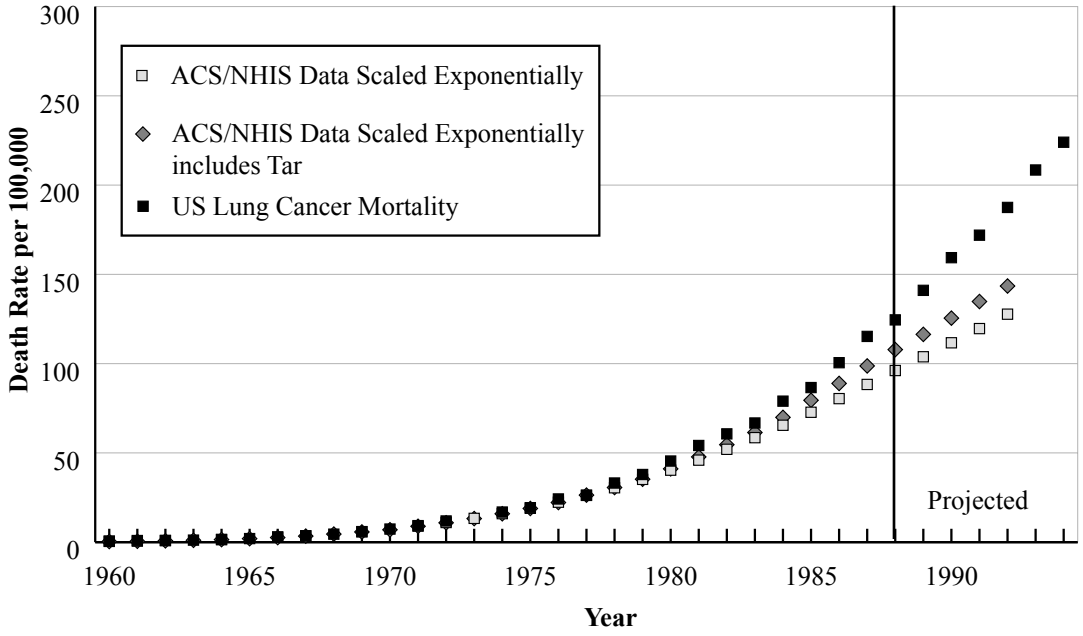


Figure 4-18f
Lung Cancer Death Rates: White Males, Birth Cohort 1935-1939

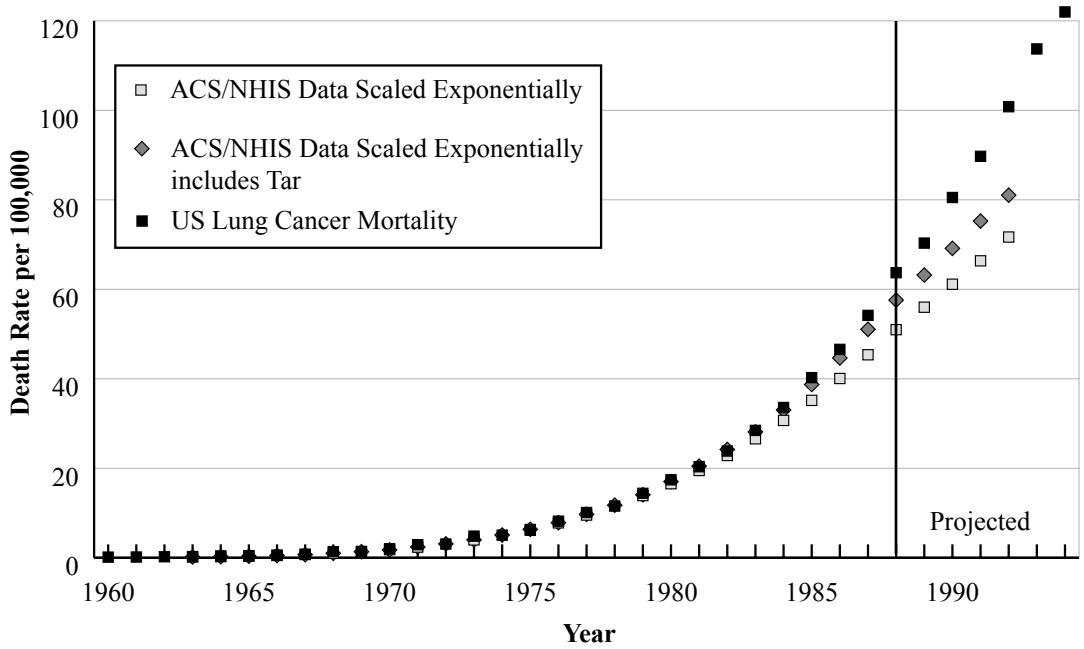


Figure 4-18g
Lung Cancer Death Rates: White Males, Birth Cohort 1940-1944

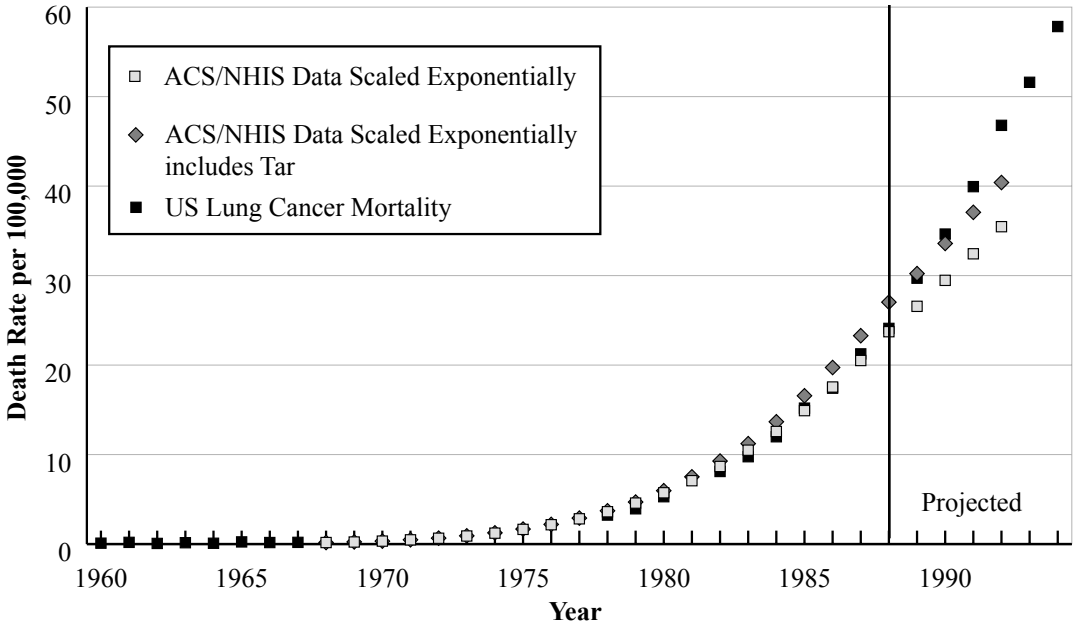


Figure 4-18h
Lung Cancer Death Rates: White Males, Birth Cohort 1945-1949

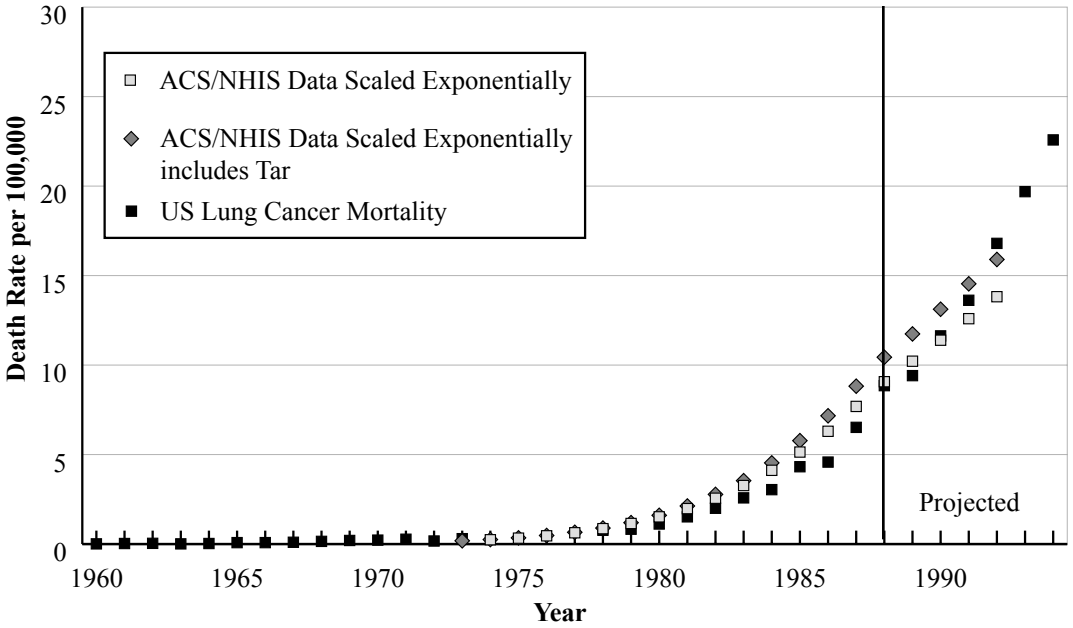
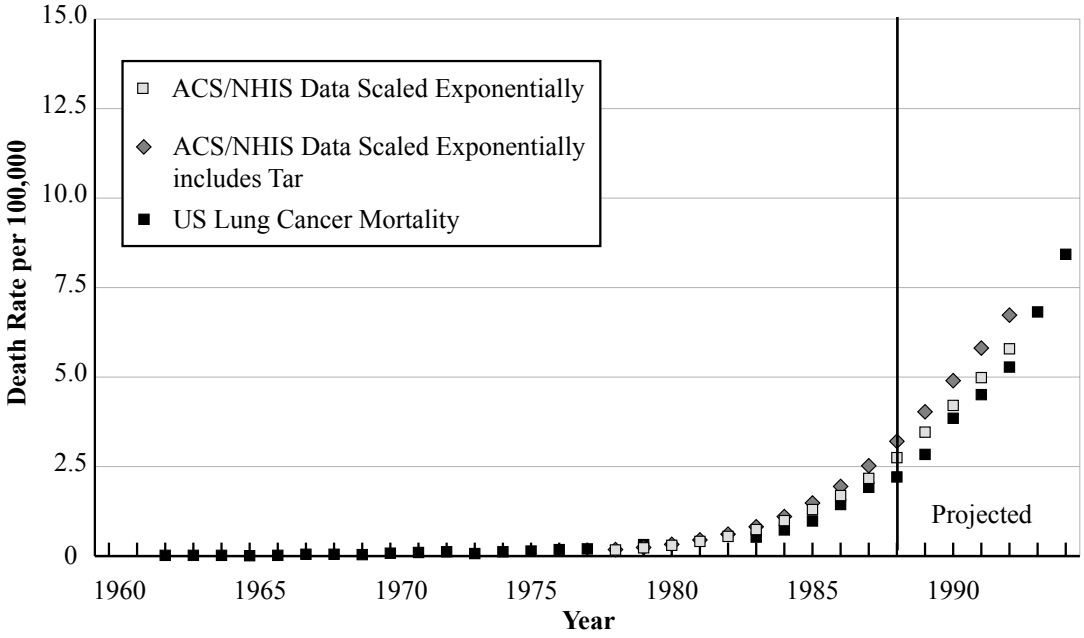


Figure 4-18i
Lung Cancer Death Rates: White Males, Birth Cohort 1950-1954



Note for Figures 18a-18i: Estimated lung cancer death rates were obtained by using a model developed by Peto (Doll and Peto, 1978). U.S. lung cancer death rates were provided for the years 1960-1995 by D.M. Mannino (personal communication, 2000). See Appendix for further details.

In these analyses, tar is a surrogate for the overall changes in cigarette design and manufacture over the last five decades, rather than a specific measure of the actual tar intake by the smoker. This analytical approach is an attempt to answer the question of whether the sum total of the changes occurring in cigarette design and composition over the last 45 years produced a reduction in carcinogenicity of smoking, and there appears to be little evidence for a population effect in the direction of a reduced risk. Moreover, this analysis supports the comparison of the two American Cancer Society prospective mortality studies (CPS-I and CPS-II) in suggesting that cigarette smoking may have become more, rather than less, hazardous, based on the cumulative effects of all the changes in cigarette design and manufacture that have occurred over the last half century.

SUMMARY

The three lines of evidence on lung cancer risk in relation to changes in cigarette design provide somewhat inconsistent findings, perhaps reflecting methodological limitations and the limited number of studies available. Detailed examination of lung cancer rates by age in the United States and the United Kingdom provide seemingly conflicting patterns from the two countries. Lesser risks for more recent cigarettes are one potential explanation for the rapid decline of lung cancer mortality at younger ages in the United Kingdom over recent years. However, the temporal pattern of lung cancer mortality at younger ages in the United States is not consistent with

this explanation. The temporally cross-sectional findings from several case-control and cohort studies provide some evidence of reduced risk for smokers of lower yield products at time points across the 1960s through the 1980s. These studies, however, provide only relative comparisons of risk and data analysis methods raise concern about biased findings in some. Finally, both the British Physician's Study and the CPS I and II studies provide powerful evidence that both relative and absolute risks of lung cancer in smokers have risen from the 1950s through the 1980s. The different findings across these three lines of epidemiological evidence cannot be reconciled with available information. Overall, however, they do not provide evidence that public health has benefited from changes in cigarette design and manufacture over the last fifty years.

CONCLUSIONS

1. Changes in cigarette design and manufacturing over the last fifty years have substantially lowered the sales-weighted, machine-measured tar and nicotine yields of cigarettes smoked in the United States.

2. Cigarettes with low machine-measured yields by the FTC method are designed to allow compensatory smoking behaviors that enable a smoker to derive a wide range of tar and nicotine yields from the same brand, offsetting much of the theoretical benefit of a reduced-yield cigarette.

3. Existing disease risk data do not support making a recommendation that smokers switch cigarette brands. The recommendation that individuals who cannot stop smoking should switch to low yield cigarettes can cause harm if it misleads smokers to postpone serious efforts at cessation.

4. Widespread adoption of lower yield cigarettes by smokers in the United States has not prevented the sustained increase in lung cancer among older smokers.

5. Epidemiological studies have not consistently found lesser risk of diseases, other than lung cancer, among smokers of reduced yield cigarettes. Some studies have found lesser risks of lung cancer among smokers of reduced yield cigarettes. Some or all of this reduction in lung cancer risk may reflect differing characteristics of smokers of reduced-yield compared to higher-yield cigarettes.

6. There is no convincing evidence that changes in cigarette design between 1950 and the mid 1980s have resulted in an important decrease in the disease burden caused by cigarette use either for smokers as a group or for the whole population.

Appendix

Description of Cancer Prevention Study-I Data and Methods of Analysis

The first Cancer Prevention Study (CPS-I) was a major cohort study carried out by the American Cancer Society (ACS). Over one million individuals were followed for more than 12 years, from 1959 to 1972. The protocol included a baseline survey that covered smoking history and present use, as well as information about health history and behaviors. The major outcome variable was mortality by specific cause as indicated on the death certificate. CPS-I provided strong evidence that confirmed relationships between smoking and specific diseases, including lung cancer and coronary heart disease.

DESCRIPTION OF THE DATA The focus of this analysis is the White male subset of cigarette smokers. The baseline data were gathered in 1959 and included 174,997 White male current cigarette smokers who were not using other forms of smoked or oral tobacco. These are the subjects for the present analysis. Major follow-ups were conducted in 1961, 1963, 1965, and 1972 that included questions about the brand of cigarette smoked and number of cigarettes smoked per day. This provided enough information to be able to consider the changing smoking habits during the 12-year period as well as relationships to disease outcomes.

TAR AND NICOTINE LEVEL The database available from ACS did not retain the specific brand smoked from the baseline survey, but it has the brands recoded into categories of tar and nicotine level crossed by filter/nonfilter. This simplification of the data can be understood by recalling that this was the era of data entry and analysis using punched cards. For the present study, this means that the baseline tar and nicotine levels for individuals are not known explicitly beyond a category of combined tar and nicotine levels. The subsequent follow-up efforts did retain the specific brand smoked by the individual, though the particular subspecies of the brand was not retained, such as king size or regular, low tar versus full flavor, etc.

The tar and nicotine levels for specific brands were determined in 1959 in laboratory studies commissioned and published by the *Reader's Digest* (Miller and Monahan, 1959). These values were used by the ACS for the baseline categorizations. Subsequently, brand-specific tar and nicotine assessments were carried out by the Federal Trade Commission (FTC) in 1967, 1970, and 1974 (FTC, 1967, 1970, 1974). Because these years do not correspond to the years of the CPS-I follow-up surveys, linear interpolation was used within brands to estimate tar and nicotine levels for the years of the follow-up. When multiple subspecies were tested by the FTC within brands, market share information from the Maxwell Report (Maxwell, 1994) was used to develop a market-share-weighted tar and nicotine value for each brand for each survey year. These values allowed a specific tar and nicotine estimate to be attached to each smoker at each follow-up period for which he provided a brand. When an individual showed a consistent

pattern of smoking the same brand and when the tar and nicotine level for that brand was consistent with the category assigned to that individual at baseline, it was assumed that he smoked that brand at baseline and the category values were adjusted to the explicit tar and nicotine values for that brand.

CIGARETTES PER DAY At baseline as well as for the follow-up surveys, smokers were asked how many cigarettes were smoked each day. Responses were categorized into levels 1-9, 10-19, 20, 21-39, 40, 40+ for all except the final follow-up, where the specific number of cigarettes smoked per day was recorded. For most analyses, the final follow-up was also converted to the categorical levels with 40 and 40+ combined. When an explicit value for a category was needed for graphing or regression, the weighted mean value for the category was used, based on the distribution of observed cigarettes per day values at the time of the final follow-up. These means were: 4.48, 11.97, 20, 29.15, and 43.52, respectively.

CHANGES IN TAR AND NICOTINE AND CIGARETTES PER DAY ACROSS YEARS OF STUDY The cross-sectional follow-up surveys provided estimates of tar and nicotine level and cigarettes per day for each smoker. By comparing responses at subsequent surveys, changes over time in the balance of tar and nicotine and cigarettes per day can be assessed. The baseline and four follow-up surveys provided four sequential measures of change for each subject who completed the five cross-sectional surveys. The cross-sectional combination of variables and changes between adjacent surveys allowed analysis of temporal changes in the interrelationships of these variables.

ASSEMBLING DATA SET FOR ANALYSIS SAS and Pascal programs were used to assemble simplified data sets for analysis. For a given subject, the four periods of follow-up were assembled with the tar and nicotine levels for the beginning of the follow-up period and the reported cigarettes per day level at that time. Additional criteria were sometimes used to isolate individuals who: changed brands, did not change brands, never reported an attempt to quit, changed to a cigarette with a lower tar value, etc. For each individual, possible endpoints included death with date and international code for cause of death (WHO, 1957), lost to follow-up, or censored at end of study.

METHODS OF ANALYSIS Several kinds of regression analyses were undertaken. These included survival analysis, regression analysis of log of death rates on tabular data, and regression analysis of interrelationships between factors.

Survival Analysis Survival analysis was undertaken using the SAS *lifereg* procedure, using a database of individual subjects with the combinations of factors present at the beginning of the interval and an observed time period of follow-up with factors assumed at that level. Generally, the dependent variable for these analyses was the likelihood of death by a specific cause, such as lung cancer. The independent variables included combinations of tar level (continuous or stratified to 3-5 levels), cigarettes per day (continuous or stratified), age (continuous), and duration of smoking (continuous).

Regression Analysis of Tabular Data

Alternatively, in some instances the observations were assembled into cells of observations stratified by 5-year age groups, 5-year duration groups, cigarettes per day level, and tar level (3-5 levels), with observed death rates calculated for each cell. Typically, these cell-wise analyses were carried out in S-Plus2000, as a *glm* (generalized linear model) regression analysis of the log of the death rates or excess mortality rates (compared to never smokers), and regressed on the explanatory variables.

Regression Analysis of Combinations of Factors

Several analyses were also undertaken to examine the interrelationships between factors, such as the relationship between nicotine level and cigarettes smoked per day. In these analyses, the data points representing combinations reported by individuals at various points in the follow-up were analyzed. These analyses included examination of distributions of factors occurring together, and examination of relationships between changes in one factor as related to changes in another. For these analyses, the database assembled was similar to that reported for survival analyses, but sometimes also included changes in factors between consecutive follow-up surveys. Generally, these regression analyses were undertaken in SAS using the GLM procedure.

DETAILED NOTES TO FIGURE 4-17

This figure shows the estimated population-based lung cancer death rates for the specific birth cohort by smoking status (current, former, or never smokers). Ever and current smoking prevalence among 5-year birth cohorts of U.S. White males were obtained from Chapter 2 of the National Cancer Institute's (NCI) Monograph 8 (Burns *et al.*, 1997a). Former smoking prevalence in a given year was obtained by subtracting the current smoking from the ever smoking prevalence in the same year. The prevalence of never smokers in a given year was obtained by subtracting the prevalence of ever smokers from 100 percent, where 100 percent represents the entire population.

To determine the contribution of current and former smokers to the overall lung cancer death rate, the prevalence rates and risks of death from lung cancer were linked over time, accounting for changes in initiation and cessation rates of white males by specific 5-year birth cohorts.

Current Smokers' Contributions

The age-of-initiation profile for each birth cohort was estimated using the change in prevalence of ever smoking by year under age 30. The rate of initiation in a given year was estimated by taking the difference between the ever smoking prevalence for a given year and that for the previous year. This generated a distribution of age of initiation by age/calendar year for those in the cohort who started smoking under the age of 30. The percentage of the population who are current smokers of given durations for each calendar year of a birth cohort was obtained by proportioning the current smokers to the age-of-initiation profile.

Data on lung cancer death rates among smokers of different durations along with numbers of cigarettes smoked per day were used to estimate the parameters for a model of lung cancer risk in relation to smoking behaviors (Doll and Peto, 1978). These fitting parameters were applied to the data on birth-cohort-specific smoking prevalence by duration to obtain estimates of lung cancer death rates for current smokers. An average number of 16.45

cigarettes smoked per day was used in this calculation based on the average number of cigarettes per day reported in the National Health Interview Surveys (NHIS). These surveys were conducted between 1965 and 1999 and controlled for age and race. This model required estimation of three parameters. The maximum likelihood procedure was applied to lung cancer deaths of White male cigarette smokers using data from the ACS CPS-I to estimate the necessary parameters (a = 0.85285 the exponent on the cigarettes/day term; b = 3.70895 the exponent on the duration term; and c = 1.7196×10^{-10}, a constant).

The current smokers' contribution to the national lung cancer death rate for each calendar year equals the sum of the predicted lung cancer death rates for smokers of each given duration divided by the white male population for that year, and it is expressed per 100,000.

Former Smokers' Contributions The incidence of smoking cessation in each cohort for each calendar year was estimated by subtracting the prevalence of former smokers in a given year from the prevalence of former smokers in the previous year. The fraction of the population that quit in a given year is distributed into discrete durations of smoking using the distribution of age of initiation for that cohort and the year of the estimate.

Modeled estimates were generated for given durations of smoking as described for current smokers. However, for former smokers, the estimated lung cancer death rates were reduced using length of time since quitting. The fractions of excess lung cancer risk (risk in smokers minus the risk in nonsmokers) that remained after increasing durations of cessation were estimated using data from the ACS CPS-I study (Shanks, 1999).

To determine the contribution of former smokers to the national White male lung cancer rate for each birth cohort by calendar year, the predicted death rates for each duration of smoking at each duration of cessation for each calendar year were summed and divided by that year's corresponding White male population for the birth cohort. The result was expressed per 100,000.

Never Smokers' Contributions The observed lung cancer death rates for White male never smokers by 5-year age groups were obtained from NCI Monograph 8, page 303 (see Burns *et al.*, 1997b), using data from CPS-I. Using the midpoint of each 5-year age group, the observed death rates were modeled using linear regression of log rates weighted to person-years of observation to obtain the death rates for each age in 1-year increments (from ages 25 to 88), using S-Plus software (S-Plus 2000, June 1999).

To determine the contribution of never smokers to the national White male lung cancer rate for each birth cohort by calendar year, the predicted death rates were calculated as the product of the prevalence of never smokers in the year, the death rate of never smokers for that cohort in that year using the median age of the birth cohort at each calendar year, and the corresponding White male population for the birth cohort. The result was expressed per 100,000. Nine sequential birth cohorts were evaluated, the first being 1910-1914 and the last being 1950-1954.

DETAILED NOTES TO FIGURES 4-18a TO 4-18i

The estimated lung cancer death rates by smoking status (current, former, and never smokers) for individual birth cohorts of the U.S. White male population were summed to obtain the total death rates for each birth cohort by year. Total lung cancer death rates were then scaled to the actual national death rates for each birth cohort and year strata using a single exponential scaling factor.

To investigate the effects of tar on lung cancer death rates, a term for sales-weighted tar was added. Fit of the modeled lung cancer rate data to actual lung cancer death rates was examined before and after adding tar. The model was further enhanced by including an additional term for the mean cigarettes smoked per day for each calendar year. The GLM procedure in SAS/STAT was used to obtain mean cigarettes per day by year while controlling for age and race. Data sources for the means were the NHIS for the years 1965-1995. The mean cigarette per day rates for the years 1960-1964 were assumed to equal that of the NHIS for 1965.

To compare these estimates to the actual lung cancer death rates, the estimates were scaled exponentially and graphed against the actual national lung cancer mortality. Sales-weighted average tar deliveries of U.S. cigarettes for the years 1954-1994 were provided by The American Health Foundation (Hoffmann, 1997). The modeling procedures were performed using S-Plus 2000 software (S-Plus 2000, June 1999).

REFERENCES

Agudo, A., Barnadas, A., Pallares, C., Martinez, I., Fabregat, X., Rosello, J., Estape, J., Planas, J., Gonzalez, CA. Lung cancer and cigarette smoking in women: a case-control study in Barcelona (Spain). *International Journal of Cancer* 59:165-169, 1994.

Alderson, M.R., Lee, P. N., Wang, R. Risks of lung cancer, chronic bronchitis, ischaemic heart disease, and stroke in relation to type of cigarette smoked. *Journal of Epidemiology & Community Health* 39:286-293, 1985.

Armadans-Gil, L. Vaque-Rafart, J., Rossello, J., Olona, M., Alseda, M. Cigarette smoking and male lung cancer risk with special regard to type of tobacco. *International Journal of Epidemiology* 28:614-619, 1999.

Armitage, P., Doll, R. Stochastic models for carcinogenesis. *Proceedings of the Fourth Berkeley Symposium on Mathematical Statistics and Probability, Vol. 4*. Berkeley, CA: University of California Press, 1961.

Auerbach, O., Hammond, E.C., Garfinkel, L. Changes in bronchial epithelium in relation to cigarette smoking, 1955–1960 vs. 1970–1977. *New England Journal of Medicine* 300:381-385, 1979.

Augustine, A. Harris R.E., Wynder E.L. Compensation as a risk factor for lung cancer in smokers who switch from nonfilter to filter cigarettes. *American Journal of Public Health* 79:188-191, 1989a.

Augustine, A. Harris R.E., Wynder E.L. Compensation as a risk factor for lung cancer in smokers who switch from nonfilter to filter cigarettes. *Progress in Clinical and Biological Research* 293:221-230, 1989b.

Benhamou, E., Benhamou, S. Black (air-cured) and blond (flue-cured) tobacco and cancer risk. VI: Lung cancer. *European Journal of Cancer* 29A(12):1778-1780, 1993.

Benhamou, E., Benhamou, S., Auquier, A., Flamant, R. Changes in patterns of cigarette smoking and lung cancer risk: Results of a case-control study. *British Journal of Cancer* 60:601-604, 1989.

Benhamou, E., Benhamou, S., Flamant, R. Lung cancer and women: Results of a French case-control study. *British Journal of Cancer* 55:91-95, 1987.

Benhamou, S., Benhamou, E., Auquier, A., Flamant, R. Differential effects of tar content, type of tobacco and use of a filter on lung cancer risk in male cigarette smokers. *International Journal of Epidemiology* 23:437-443, 1994.

Benhamou, S., Benhamou, E., Tirmarche, M., Flamant, R. Lung cancer and use of cigarettes: A French case–control study. J*ournal of the National Cancer Institute* 74:1169-1175, 1985.

Benowitz, N.L. Biomarkers of cigarette smoking. *The FTC Cigarette Test Method for Determining Tar, Nicotine, and Carbon Monoxide Yields of U.S. Cigarettes. Report of the NCI Expert Committee*. Smoking and Tobacco Control Monograph No.7. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, NIH Publication No. 96-4028, 1996.

Benowitz, N.L., Hall, S.M., Herning, R.I., Jacob, P., Jones, R.T., Osman, A. Smokers of low-yield cigarettes do not consume less nicotine. *New England Journal of Medicine* 309:139-42, 1983.

Benowitz, N.L., Henningfield, J.E. Establishing a nicotine threshold for addiction. *New England Journal of Medicine* 331:123-125, 1994.

Borland, C., Chamberlain, A., Higenbottam, T., Shipley, M., Rose, G. Carbon monoxide yield of cigarettes and its relation to cardiorespiratory disease. *British Medical Journal* 287:1583-1586, 1983.

British American Tobacco Company. Structured creativity group. Thoughts by C.C. Greig – R&D, Southampton, Marketing scenario. Florida AG tobacco litigation, undated. Bates No. 100515909.

Bross, I.D., Gibson, R. Risks of lung cancer in smokers who switch to filter cigarettes. *American Journal of Public Health and the Nations Health* 58(8):1396-1403, 1968.

Bross, I.D. Effect of filter cigarettes on lung cancer risk. *Toward a Less Harmful Cigarette*. NCI Monograph No. 28. Wynder, E.L., Hoffmann, D. (Editors.). U.S. Department. of Health, Education, and Welfare, National Institutes of Health, National Cancer Institute, 1968.

Brown, C., Kessler, L. Projections of lung cancer mortality in the United States: 1985–2025. *Journal of the National Cancer Institute* 80:43-51, 1988.

Brown, C.A., Crombie, I.K., Smith, W.C., Tunstall-Pedoe, H. Cigarette tar content and symptoms of chronic bronchitis: Results of the Scottish Heart Health Study. *Journal of Epidemiology and Community Health* 45:287-290, 1991.

Buffler, P.A., Contant, C.F., Pickle, L.W., Burau, K., Cooper, S.P., Mason, T.J. Environmental associations with lung cancer in Texas coastal counties. *Lung Cancer: Current Status and Prospects for the Future. Twenty-eighth Annual Clinical Conference on Cancer.* Mountain, C.F., Carr, D.T. (Editors.). Houston, Texas, USA, November 7–10, 1984. Austin, TX: University of Texas Press, 1986.

Burns, D. *Primary prevention, smoking, smoking cessation—Implications for future trends in lung cancer prevention*. Proceedings of the International Conference on Prevention and Early Diagnosis of Lung Cancer. Varese – Ville Ponti, December 9-10, 1998. Dominioni, L., Strauss, G. (Editors.), 1998.

Burns, D., Lee, L., Shen, Z., Gilpin, B., Tolley, D., Vaughn, J., Shanks, T. Cigarette smoking behavior in the United States. *Changes in Cigarette-Related Disease Risks and Their Implication for Prevention and Control*. Smoking and Tobacco Control Monograph No. 8. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, NIH Publication No. 97-4213, 1997a.

Burns D., Shanks, T., Choi, W., Thun, M., Heath, C., Garfinkel L. The American Cancer Society Cancer Prevention Study I: 12-year follow-up of 1 million men and women. *Changes in Cigarette-Related Disease Risks and Their Implication for Prevention and Control*. Smoking and Tobacco Control Monograph No. 8. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, NIH Publication No. 97-4213, 1997b.

Centers for Disease Control and Prevention. Cigarette smoking among adults—United States, 1998. *Morbidity and Mortality Weekly Report* 49(39):881-884, 2000a.

Centers for Disease Control and Prevention. Ahern, C.H., Batchelor, S.M., Blanton, C.J., Law, M., Loo, C.M., Pevzner, E.S., Ryan, H.A., Stolfus, S.A., Tabladillo, M., Warren, C.W., Zinner, L.R., Eriksen, M.P., Healton, C.G., Messeri, P.A., Reynolds, J.H., Stokes, C., Ross, J.G., Flint, K., Robb, W.H. Youth tobacco surveillance—United States, 1998–1999. *Morbidity and Mortality Weekly Report* 49(SS10):1-93, 2000b.

Centers for Disease Control and Prevention. *U.S. Population Estimates by Age, Sex, Race.* Centers for Disease Control and Prevention, 2000. Available from www.cdc.gov/nchs/datawh/statab/unpubd/mortabs/pop6079.html.

Cohen, J. B. Consumer/smoker perceptions of Federal Trade Commission tar ratings. *The FTC Cigarette Test Method for Determining Tar, Nicotine, and Carbon Monoxide Yields of U.S. Cigarettes. Report of the NCI Expert Committee.* Smoking and Tobacco Control Monograph No. 7. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, NIH Publication No. 96-4028, 1996a.

Cohen, J. B. Smokers' knowledge and understanding of advertised tar numbers: Health policy implications. *American Journal of Public Health* 86:18-24, 1996b.

Committee on Health Risks of Exposure to Radon (BEIR VI). *Health Effects of Exposure to Radon: BEIR VI*. National Research Council. Washington, DC: National Academy Press, 1999.

Dean, G., Lee, P.N., Todd, G.F., Wicken, A.J., Sparks, D.N. Factors related to respiratory and cardiovascular symptoms in the United Kingdom. *Journal of Epidemiology and Community Health* 32:86-96, 1978.

De Stefani, E. Mate drinking and risk of lung cancer in males: A case-control study from Uruguay. *Cancer Epidemiology, Biomarkers and Prevention* 5:515-519, 1996.

Doll, R., Hill, A.B. A study of the aetiology of carcinoma of the lung. *British Medical Journal* 2:1271-1286, 1952.

Doll, R., Hill, A.B. The Mortality of doctors in relation to their smoking habits: A preliminary report. *British Medical Journal* 1(4877):1451-1455 (June 26), 1954.

Doll, R., Peto, R. Cigarette smoking and bronchial carcinoma: dose and time relationships among regular smokers and lifelong non-smokers. *Journal of Epidemiology and Community Health* 32:303-313, 1978.

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* 309:901-911, 1994.

Engeland, A., Haldorsen, T., Andersen, A., Tretli, S. The impact of smoking habits on lung cancer risk: 28 years' observation of 26,000 Norwegian men and women. *Cancer Causes and Control* 7:366-376, 1996.

Federal Trade Commission. *Report of Tar and Nicotine Content of the Smoke of 59 Varieties of Cigarettes*. Federal Trade Commission, Washington, D.C., 1967.

Federal Trade Commission. *Report of Tar and Nicotine Content of the Smoke of 126 Varieties of Cigarettes [for year 1968].* Federal Trade Commission, Washington, D.C., 1969.

Federal Trade Commission. *Report of Tar and Nicotine Content of the Smoke of 118 Varieties of Cigarettes*. Federal Trade Commission, Washington, D.C., 1969.

Federal Trade Commission. *Report of "Tar" and Nicotine Content of the Smoke of 120 Varieties of Cigarettes*. Federal Trade Commission, Washington, D.C., 1970.

Federal Trade Commission. *Report of "Tar" and Nicotine Content of the Smoke of 130 Varieties of Cigarettes*. Federal Trade Commission, Washington, D.C., 1974.

Federal Trade Commission. *Report of "Tar" and Nicotine Content of the Smoke of 145 Varieties of Cigarettes [for year 1975].* Federal Trade Commission, Washington, D.C., 1976.

Federal Trade Commission. *Report of "Tar" and Nicotine Content of the Smoke of 166 Varieties of Cigarettes [for year 1976].* Federal Trade Commission, Washington, D.C., 1977.

Federal Trade Commission. *Report of "Tar" and Nicotine Content of the Smoke of 167 Varieties of Cigarettes [for year 1977].* Federal Trade Commission, Washington, D.C., 1978.

Federal Trade Commission. *Report of "Tar", Nicotine and Carbon Monoxide of the Smoke of 187 Varieties of Cigarettes [for year 1979].* Federal Trade Commission, Washington, D.C., 1981.

Federal Trade Commission. *Report of "Tar", Nicotine and Carbon Monoxide of the Smoke of 200 Varieties of Cigarettes [for year 1981].* Federal Trade Commission, Washington, D.C., 1981.

Federal Trade Commission. *Report of "Tar", Nicotine and Carbon Monoxide of the Smoke of 207 Varieties of Domestic Cigarettes [for year 1982].* Federal Trade Commission, Washington, D.C., 1984.

Federal Trade Commission. *Report of "Tar", Nicotine and Carbon Monoxide of the Smoke of 207 Varieties of Domestic Cigarettes [for year 1984].* Federal Trade Commission, Washington, D.C., 1985.

Federal Trade Commission. *Report of "Tar", Nicotine and Carbon Monoxide of the Smoke of 370 varieties of domestic cigarettes [for year 1988].* Federal Trade Commission, Washington, D.C., 1990.

Federal Trade Commission. *Report on Tar, Nicotine, and Carbon Monoxide Content of the Smoke of 534 Varieties of Domestic Cigarettes [for year 1990].* Federal Trade Commission, Washington D.C., 1992.

Federal Trade Commission. *Report on Tar, Nicotine, and Carbon Monoxide Content of the Smoke of 1262 Varieties of Domestic Cigarettes [for year 1996].* Federal Trade Commission, Washington D.C., 1999.

Garfinkel, L. Changes in the cigarette consumption of smokers in relation to changes in tar/nicotine content of cigarettes smoked. *American Journal of Public Health* 69:1274-1276, 1979.

Garfinkel, L. Changes in number of cigarettes smoked compared to changes in tar and nicotine content over a 13-year period. A Safe Cigarette? *Banbury Report 3, Proceedings of a Meeting Held at the Banbury Center, Cold Spring Harbor Laboratory, NY, Oct. 14–16, 1979*. Gori, G.B., Bock, F.G. (Editors.). Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1980.

Gillis C.R., Hole, D.J., Boyle, P. Cigarette smoking and male lung cancer in an area of very high incidence. I: Report of a case-control study in the West of Scotland. *Journal of Epidemiology and Community Health* 42:38-43, 1988.

Giovino, G.A., Tomar, S.L., Reddy, M.N., Peddicord, J.P., Zhu, B.P., Escobedo, L.G., Eriksen, M.P. Attitudes, knowledge, and beliefs about low-yield cigarettes among adolescents and adults. *The FTC Cigarette Test Method for Determining Tar, Nicotine, and Carbon Monoxide Yields of U.S. Cigarettes. Report of the NCI Expert Committee*. Smoking and Tobacco Control Monograph No. 7. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, NIH Publication No. 96-4028, 1996.

Goodman, B. to Meyer, L.F. September 17, 1975. Memo by Barboro Goodman. Marlboro-Marlboro Lights study delivery data. Bates No. 2021544486.

Goodman, B. to Meyer, L.F. October 21, 1982. Memo by Barboro Goodman. Effect of reduced dilution on tar delivery to a smoker. Phillip Morris Archive Document I.D. No. 1003415278/5280.

Green, S.J. Research conference held at Hilton Head Island S.C., September 24-30, 1968. University of California San Francisco Tobacco Archive Document I.D. 1112.01, 1968.

Haddock, CK; Talcott, GW; Klesges, RC; Lando, H. An examination of cigarette brand switching to reduce health risks. *Annals of Behavioral Medicine* 21:128-134, 1999.

Hammond, E.C., Horn, D. Smoking and Death Rates—A report on 44 months of follow-up of 187,783 men. II. Death rates by cause. *Journal of the American Medical Association* 166:1294-1308, 1958.

Hammond, E.C., Garfinkel, L. Changes in cigarette smoking. *Journal of the National Cancer Institute* 32:49, 1964.

Hammond, E.C. Smoking in relation to the death rates of one million men and women. *National Cancer Institute Monograph* 19:127-204, 1966.

Hammond, E.C. The long term benefits of reducing tar and nicotine in cigarettes. *A Safe Cigarette? Banbury Report 3, Proceedings of a Meeting Held at the Banbury Center, Cold Spring Harbor Laboratory, NY, Oct. 14–16, 1979*. Gori, G.B., Bock, F.G. (Editors.). Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1980.

Hammond, E.C., Garfinkel L., Seidman, H., Lew, E.A. Some recent findings concerning cigarette smoking. *Origins of Human Cancer. Book A: Incidence of Cancer in Humans*. Cold Springs Harbor Conferences on Cell Proliferation, Volume 4. 1977.

Hammond, E.C., Garfinkel, L., Seideman, H., Lew, E.A. "Tar" and nicotine content of cigarette smoke in relation to death rates. *Environmental Research* 12:263-274, 1976.

Harris, J. Cigarette smoking among successive birth cohorts of men and women in the United States during 1900–1980. *Journal of the National Cancer Institute* 71:473-479, 1983.

Hawthorne, V.M., Fry, J.S. Smoking and health: The association between smoking behavior, total mortality, and cardiorespiratory disease in West Central Scotland. *Journal of Epidemiology and Community Health* 32:260-266, 1978.

Hecht, S.S. Biochemistry, biology, and carcinogenicity of tobacco-specific N-nitrosamines. *Chemical Research in Toxicology* 11:559-603, 1998.

Higenbottam, T., Shipley, M.J., Rose, G. Cigarettes, lung cancer, and coronary heart disease: The effects of inhalation and tar yield. *Journal of Epidemiology and Community Health* 36:113-117, 1982.

Hoffmann, D., Hoffmann, I. The changing cigarette, 1950–1995. *Journal of Toxicology and Environmental Health* 50:307-364, 1997.

Holmes, J.C., Hardcastle, J.E., Mitchel, R.I. Determination of particle size and electric charge distribution in cigarette smoke. *Tobacco Science* 3:148-153, 1959.

Imperial Tobacco Limited. Research & Development Division, Progress report July 1993-December 1993. Bates No. 402415194-402415196. Available at www.tobaccopapers.org/documents/psc8.pdf.

International Committee on Radiation Protection, Task Group in Lung Dynamics. Deposition and retention models for internal dosimetry of the human respiratory tract. *Health Physics* 12:173-207, 1966.

Jarvis, M.J., Boreham, R., Primatesta, P., Feyerabend, C., Bryant, A. Nicotine yield from machine-smoked cigarettes and nicotine intakes in smokers: Evidence from a representative population survey. *Journal of the National Cancer Institute* 93:134-138, 2001.

Jöckel, K.H., Ahrens, W., Wichmann, H.E., Becher, H., Bolm-Audorff, U., Jahn, I., Molik, B., Greiser, E., Timm, J. Occupational and environmental hazards associated with lung cancer. *International Journal of Epidemiology* 21:202-213, 1992.

Johnston, L.D., O'Malley, P.M., Bachman, J.G. Cigarette use and smokeless tobacco use decline substantially among teens. University of Michigan News and Information Services: Ann Arbor, MI. [On-line], 2000. Available: www.monitoringthefuture.org; accessed 1/16/01.

Kabat, G.C. Aspects of the epidemiology of lung cancer in smokers and nonsmokers in the United States. *Lung Cancer* 15:1-20, 1996.

Kaufman, D.W., Palmer, J.R., Rosenberg, L., Stolley, P; Warshauer, E., Shapiro, S. Tar content of cigarettes in relation to lung cancer. *American Journal of Epidemiology* 129:703-711, 1989.

Khuder, S.A., Dayal, H.H., Mutgi, A.B., Willey, J.C., Dayal, G. Effect of cigarette smoking on major histological types of lung cancer in men. Lung *Cancer* 22:15-21, 1998.

Kieth, C.H. Particle size studies on tobacco smoke. *Beitrage zur Tabakforschung International* 11:123-131, 1982.

Kieth, C.H., Derrick, J.C. Measurement of the particle size distribution and concentration of cigarette smoke by the "conifuge." *Journal of Colloid Science* 15:340-356, 1960.

Krzyzanowski, M., Sherrill, D.L., Paoletti, P., Lebowitz, M.D. Relationship of respiratory symptoms and pulmonary function to tar, nicotine, and carbon monoxide yield of cigarettes. *American Review of Respiratory Disease* 143:306-311, 1991.

Kuller, L.H. Ockene, J.K., Meilahn, E., Wentworth, D.N., Svendsen, KH., Neaton, J.D. Cigarette smoking and mortality. Cigarette smoking and mortality. MRFIT Research Group. *Preventive Medicine* 20:638-654, 1991.

Lange, P., Nyboe, J., Appleyard, M., Jensen, G., Schnohr, P. Relationship of the type of tobacco and inhalation pattern to pulmonary and total mortality. *European Respiratory Journal* 5:1111-1117, 1992.

Lee, P.N., Garfinkel, L. Mortality and type of cigarette smoked. *Journal of Epidemiology and Community Health* 35:16-22, 1981.

Levi, F., Franceschi, S., La Vecchia, C., Randimbson, L., Te, V. Lung carcinoma trends by histological type in Valud and Neuchatel, Switzerland, 1974–1994. *Cancer* 79:906-914, 1997.

Lubin, J.H., Blot, W.J., Berrino, F., Flamant, R., Gillis, C.R., Kunze, M., Schmahl, D., Visco, G. Patterns of lung cancer risk according to type of cigarette smoked. *International Journal of Cancer* 33:569-576, 1984.

Lubin, J.H. Modifying risk of developing lung cancer by changing habits of cigarette smoking. *British Medical Journal* 288:1953-56, 1984a.

Lubin, J.H. [letter-response] *British Medical Journal* 289:921, 1984b.

Mannino, D.M., Ford, E., Giovino, G.A, Thun, M. Lung cancer mortality rates in birth cohorts in the United States from 1960 to 1994. *Lung Cancer* 31(2-3):91-99, 2001.

Matos, E., Vilensky, M., Boffetta, P., Kogevinas, M. Lung cancer and smoking: A case-control study in Buenos Aires, Argentina. *Lung Cancer* 21:155-163, 1998.

Maxwell, J. C., Jr. *Historical Sales Trends in the Cigarette Industry, a Statistical Summary Covering 69 Years (1925-93)*. 1994. Richmond, VA, Wheat, First Securities, Inc.

McClusker, K., Hiller, F.C., Wilson, J.D., Mazumder, M.K., Bone R. Aerodynamic sizing of tobacco smoke particulate from commercial cigarettes. *Archives of Environmental Health* 38:215-218, 1983.

Miller, L.M., Monahan, J. The search for "safer" cigarettes. *The Reader's Digest* 38:37-45, 1959.

Mitchell, R.I. Second phase report on the determination of particle size in cigarette smoke. Report to Philip Morris Inc. Battelle Memorial Institute. October 30, 1958. Bates No. 1001905717.

Moolgavkar, S.H, Dewanji, A., Luebeck, G. Cigarette smoking and lung cancer: Reanalysis of the British Doctor's Data. *Journal of the National Cancer Institute* 81:415-420, 1989.

Morie, G.P., Sloan, C.H., Peck, V.G. Study of cigarette smoke filtration by means of the scanning electron microscope. *Beitrage zur Tabakforschung International* 7:99-104, 1973.

National Cancer Institute. *Cancer Mortality in the United States: 1959–1977*. NCI Monograph 59. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute, NIH Publication No. 82-2435. 1982.

National Cancer Institute. *The FTC Cigarette Test Method for Determining Tar, Nicotine, and Carbon Monoxide Yields of U.S. Cigarettes. Report of the NCI Expert Committee*. Smoking and Tobacco Control Monograph No. 7. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, NIH Publication No. 96-4028, 1996.

Negri, E., Franzosi, M.G., La Vecchia, C., Santoro, L., Nobili, A., Tognoni, G. Tar yield of cigarettes and risk of acute myocardial infarction. *British Medical Journal* 306:1567-1569, 1993.

Office for National Statistics (ONS). Statistics on Smoking: England. 1976–1996. *Statistical Bulletin* 1998/25, July 1998.

Palmer, J., Rosenberg, L., Shapiro, S. Low yield cigarettes and the risk of nonfatal myocardial infarction in women. *New England Journal of Medicine* 320:1569-1573, 1989.

Parish, S., Collins, R., Peto, R., Youngman, L., Barton, J., Jayne, K., Clarke, R., Appleby, P., Lyon, V., Cederholm-Williams, S., et al. Cigarette smoking, tar yields, and non-fatal myocardial infarction: 14,000 cases and 32,000 controls in the United Kingdom. The International Studies of Infarct Survival (ISIS) Collaborators. *British Medical Journal (Clin Res Ed)* 311[7003], 471-477, 1995.

Pathak, D.R., Samet, J.M., Humble, C.G., Skipper, B.J. Determinants of lung cancer risk in cigarette smokers in New Mexico. *Journal of the National Cancer Institute* 76:597-604, 1986.

Peel, D.M., Riddick, M.G., Edwards, M.E., Gentry, J.S., Nestor, T.B. *Formation of Tobacco Specific Nitrosamines in Flue-Cured Tobacco*. Presented at the 53rd Tobacco Science Research Conference. Montreal, Quebec, Canada. September 12–15, 1999.

Pepples, E. Industry response to cigarette/health controversy. February 4, 1976. University of California San Francisco Tobacco Archive Document I.D. 2205.01.

Petitti, D.B., Friedman, G.D. Cardiovascular and other diseases in smokers of low-yield cigarettes. *Journal of Chronic Diseases* 38:581-588, 1985.

Peto, R. Influence of dose and duration of smoking on lung cancer rates. *Tobacco: A Major International Health Hazard*. Zaridze, D.G., Peto, R. (Editors.). Lyons, France: International Agency for Research on Cancer, 1986.

Peto, R., Darby, S., Deo, H., Silcocks, P., Whitley, E., Doll, R. Smoking, smoking cessation, and lung cancer in the U.K. since 1950: Combination of national statistics with two case-control studies. *British Medical Journal* 321:323-329, 2000.

Pezzotto, S.M., Mahuad, R., Bay, M.L., Morini, J.C., Poletto, L. Variation in smoking-related lung cancer risk factors by cell type among men in Argentina: A case-control study. *Cancer Causes and Control* 4:231-237, 1993.

Pillsbury, H.C. Review of the Federal Trade Commission Method for determining cigarette tar and nicotine yield. *The FTC Cigarette Test Method for Determining Tar, Nicotine, and Carbon Monoxide Yields of U.S. Cigarettes. Report of the NCI Expert Committee*. Smoking and Tobacco Control Monograph No. 7. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, NIH Publication No. 96-4028, 1996.

Powell, J.T., Edwards, R.J., Worrell, P.C., Franks, P.J., Greenhalgh, R.M., Poulter, N.R. Risk factors associated with the development of peripheral arterial disease in smokers: A case-control study. *Atherosclerosis* 129:41-48, 1997.

Rimington, J. The effect of filters on the incidence of lung cancer in cigarette smokers. *Environmental Research* 24:162-166, 1981.

Royal College of Physicians. *Smoking and Health. Summary and Report of the Royal College of Physicians of London on Smoking in Relation to Cancer of the Lung and Other Diseases*. New York: Pitman Publishing Corp, 1962.

Russo, A., Crosignani, P., Francheschi, S., Berrino, F. Changes in lung cancer histological types in Varese cancer registry, Italy 1976–1992. *European Journal of Cancer* 33:1643-1647, 1997.

S-Plus 2000. Guide to Statistics. Data Analysis Products Division, MathSoft, Inc. Seattle, WA. June, 1999.

Shanks, T.G. Reduction in disease risks after quitting smoking. Presentation APHA. Chicago, IL. November 10, 1999.

Shiffman, S. Tobacco "chippers"—Individual differences in tobacco dependence. *Psychopharmacology (Berlin)* 97:539-547, 1989.

Sidney, S., Tekawa, I.S., Friedman, G.D. A prospective study of cigarette tar yield and lung cancer. *Cancer Causes and Control* 4:3-10, 1993.

Sparrow, D., Stefos, T., Bosse, R., Weiss, S.T. The relationship of tar content to decline in pulmonary function in cigarette smokers. *American Review of Respiratory Disease* 127:56-58, 1983.

Stellman, S.D., Muscat, J.E., Thompson, S., Hoffmann, D., Wynder, E.L. Risk of squamous cell carcinoma and adenocarcinoma of the lung in relation to lifetime filter cigarette smoking. *Cancer* 80(3):382-388, 1997.

Stevens, R., Moolgavkar, S. Estimation of relative risk from vital data: smoking and cancers of the lung and bladder. *Journal of the National Cancer Institute* 63:1351-1357, 1979.

Stevens, R., Moolgavkar, S. A cohort analysis of lung cancer and smoking in British males. *American Journal of Epidemiology* 119:624-641, 1984.

Swartz, J.B. Use of a multistage model to predict time trends in smoking induced lung cancer. *Journal of Epidemiology and Community Health* 46:311-315, 1992.

Tang, J.L., Morris, J.K., Wald, N.J., Hole, D., Shipley, M., Tunstall-Pedoe, H. Mortality in relation to tar yield of cigarettes: A prospective study of four cohorts. *British Medical Journal* 311:1530-1533, 1995.

Teague, C. Research planning memorandum on a new type of cigarette delivering a satisfying amount of nicotine with a reduced "tar"-to-nicotine ratio. March 28, 1972. Engle Plantiffs Exhibit No. 0111.

Thun, M.J., Heath, C.W. Changes in mortality from smoking in two American Cancer Society prospective studies since 1959. *Preventive Medicine* 26:422-426. 1997.

Thun, M.J., Lally, C.A., Flannery, J.T., Calle, E.E., Flanders, W.D., Heath, C.W. Cigarette smoking and changes in the histopathology of lung cancer. *Journal of the National Cancer Institute* 89:1580-1586, 1997a.

Thun, M., Myersm D., Day-Lallym C., Myers, D.G., Calle, E., Flanders, W.D., Zhu, B.P., Namboodiri, M., Heath, Jr, C. Trends in tobacco smoking and mortality from cigarette use in cancer prevention studies I (1959 through 1965) and II (1982 through 1988). *Changes in Cigarette-Related Disease Risks and Their Implications for Prevention and Control*. Smoking and Tobacco Control Monograph No. 8. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, NIH Publication No. 97-4213, 1997b.

Tobacco Advisory Group (of the Royal College of Physicians). *Nicotine Addiction in Britain*. Royal College of Physicians of London, 2000.

Todd, G.F., Hunt, B.M., Lambert, P.M. Four cardiorespiratory symptoms as predictors of mortality. *Journal of Epidemiology and Community Health* 32:267-274, 1978.

Townsend, J. Smoking and lung cancer: A cohort study of men and women in England and Wales 1935–70. *Journal of the Royal Statistical Society* A141[pt 1]:95-107, 1978.

Tolley, H.D., Crane, L., Shipley, N. Smoking prevalence and lung cancer death rates. *Strategies to Control Tobacco Use in the United States: A Blueprint for Public Health Action in the 1990s*. Smoking and Tobacco Control Monograph No. 1. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, Publication No. [PHS] 92-3316, 1991.

Travis, W.D., Travis, L.B., Devesa, S.S. Lung cancer. *Cancer* 75:191-202, 1995.

U.S. Bureau of the Census. U.S. population estimates by age, sex, race. Washington, D.C., 2000 Available from ww.census.gov/population/www/estimates/nat_80s_detail.html and nat_90s_detail.

U.S. Congress. Hearings before the Consumer Subcommittee of the Committee on Commerce. Senate, 90th Congress, August 23, 24, 1967.

U.S. Department of Health, Education, and Welfare. *The Health Consequences of Smoking: A Report to the Surgeon General*. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, Office on Smoking and Health. DHEW Publication No. (HSM) 71-7513, 1971.

U.S. Department of Health, Education, and Welfare. *Smoking and Health. A Report of the Surgeon General*. U.S. Department of Health, Education, and Welfare, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health. DHEW Publication No. (PHS) 79-50066, 1979.

U.S. Department of Health and Human Services. *The Health Consequences of Smoking: The Changing Cigarette. A Report of the Surgeon General*. U.S. Department of Health and Human Services, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health. DHHS Publication No. 81-50156, 1981.

U.S. Department of Health and Human Services. *The Health Consequences of Smoking: Nicotine Addiction. A Report of the Surgeon General*. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, Center for Health Promotion and Education, 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*. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, DHHS Publication No. (CDC) 90-8416, 1990.

U.S. Department of Health and Human Services. *Preventing Tobacco Use Among Young People: A Report of the Surgeon General*. 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. *Tobacco Use Among U.S. Racial/Ethnic Minority Groups: A Report of the Surgeon General*. 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, 1998.

Vutuc, C., Kunze, M. Lung cancer risk in women in relation to tar yields of cigarettes. *Preventive Medicine* 11:713-716, 1982.

Vutuc, C., Kunze, M. Tar yields if cigarettes and male lung cancer risk. *Journal of the National Cancer Institute* 71:435-437, 1983.

Wakeham, H to Cullman, H. March 24, 1961. Memo by H. Wakeman. Trends in tar and nicotine deliveries over the last 5 years. Bates No. 1000861953.

Warner, KE. Tobacco industry response to public health concern: A content analysis of cigarette ads. *Health Education Quarterly* 12:115-27, 1985.

Wald, N., Nicolaides-Bouman, A. (Editors.). *UK Smoking Statistics*. 2nd Edition. Oxford, UK: Oxford University Press, 1991.

Wilcox, H.B., Schoenberg, J.B., Mason, T.J., Bill, J.S., Stemhagen, A. Smoking and lung cancer: Risk as a function of cigarette tar content. *Preventive Medicine* 17:263-272, 1988.

Wingo, P.A, Ries, L.A.G., Giovino, G.A., Miller, D.S., Rosenberg, H.M., Shopland D.R., Thun, M.J., Edwards, B.K. Annual report to the nation on the status of cancer, 1973–1996, with a special section on lung cancer and tobacco smoking. *Journal of the National Cancer Institute* 91:675-690, 1999.

Withey, C.H., Papacosta, A.O., Swan, A.V., Fitzsimons, B.A., Ellard, G.A., Burney, P.G., Colley, J.R., Holland, W.W. Respiratory effects of lowering tar and nicotine levels of cigarettes smoked by young male middle tar smokers. II. Results of a randomised controlled trial. *Journal of Epidemiology and Community Health* 46(3):281-285, 1992.

Whittemore, A.S. Effect of cigarette smoking in epidemiological studies of lung cancer. *Statistics in Medicine* 7:223-238, 1988.

World Health Organization. *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death* (7th Ed. Rev. of the *International Lists of Diseases and Causes of Death*, adapted 1955). Vol. 1. Geneva: World Health Organization, 1957.

Wynder, E.L., Graham, E.A. Tobacco smoking as a possible etiologic factor in bronchogenic carcinoma. A study of six hundred and eighty-four proved cases. *Journal of the American Medical Association* 143:329-336, 1950.

Wynder, E.L., Graham, E.A., Croninger, A.B. Experimental production of carcinoma with cigarette tar. *Cancer Research* 13:855-864, 1953.

Wynder, E.L., Kabat, G.C. The effect of low-yield cigarette smoking on lung cancer risk. *Cancer* 62:1223-1230, 1988.

Wynder, E.L., Mabuchi, K., Beattie, E.J., Jr. The epidemiology of lung cancer: Recent trends. *Journal of the American Medical Association* 213:2221-2228, 1970.

Wynder, E.L., Stellman, S.D. Impact of long-term filter cigarette usage on lung and larynx cancer risk: A case–control study. *Journal of the National Cancer Institute* 62:471-477, 1979.