Position Paper

Smoking and Lung Cancer: An Overview

Lawrence A. Loeb, Virginia L. Ernster, Kenneth E. Warner, John Abbotts, and John Laszlo

Abstract

This position paper summarizes the overwhelming evidence that tobacco smoking is the cause of 30 to 40% of deaths from cancer. The focus is on lung cancer because of the sheer magnitude of this disease in males and the likelihood of a similar epidemic in females. There are two categories of evidence that indicate smoking to be the major cause of human lung cancer. Without exception, epidemiological studies have demonstrated a consistent association between smoking and lung cancer in men and now suggest a similar association in women. Chemical analyses of cigarette smoke reveal a multitude of known mutagens and carcinogens. Moreover, these chemicals are absorbed, metabolized, and cause demonstrable genetic changes in smokers. Two consequences of smoking are evaluated. The results of treatment of lung cancer are not encouraging; despite vigorous therapy, the 5-year survival rate remains less than 10%. The social and economic costs of lung cancer and the smoking habit impinge on the productiveness of our society.

Position Statement

The findings of this paper were presented at the Seventy-Fifth Annual Meeting of the American Association for Cancer Research in May 1984. The following position statement was subsequently endorsed unanimously by the Association's Scientific and Public Affairs Committee, the Board of Directors, and the members present at the annual meeting:

The American Association for Cancer Research accepts the evidence gathered by cancer scientists as establishing that cigarette smoking is the major preventable cause of human lung cancer. We therefore go on record as advocating that the greatest cancer prevention measure that might be undertaken would be for people not to smoke. As interim steps toward this goal, we recommend the following actions be taken by the government and members of our society to reduce cigarette smoking:

1. Take legislative action to reduce "image advertising" and other types of promotional efforts designed to attract people to the practice of cigarette smoking.
2. Enact legislation designed to reduce the availability of cigarettes for children and young adults, particularly in school, military, and hospital settings. One measure would be to eliminate the tax-free status on cigarette sales in government installations.
3. Enact and enforce legislation that restricts smoking in public places.
4. Increase taxes on cigarettes and other tobacco products and use the proceeds for research, education, and treatment of the resulting diseases.
5. Eliminate federal support for the production and distribution of tobacco products.
6. Increase the effectiveness of warning labels on tobacco products.

General Introduction

The association of tobacco with cancer has been known for more than 50 years. However, the magnitude of this association has been firmly established relatively recently. In the 1950s, retrospective studies suggested a link between cigarette smoking and lung cancer (77). These observations were followed by a series of extensive prospective studies which documented the association of smoking not only with lung cancer but also with a significant increase in overall mortality. The publication of the Surgeon General's first Report on Smoking and Health in 1964 (73) led to a decline in cigarette smoking rates in the United States. However, there are still 53 million cigarette smokers in the United States, and some 30 million past smokers have quit. As a result of continued smoking, cancer of the lung now accounts for 30% of all cancer deaths in males in the United States. With the advent of increased smoking by females, the epidemic of lung cancer in women parallels that which commenced in men some 30 years ago. In many states in the United States, 1984 will be the year in which cancer of the lung will be for women a more frequent cause of death than cancer of the breast.

The following sections survey technical knowledge in four areas pertinent to smoking and lung cancer. The first section summarizes the epidemiological studies of cancer among both active and passive smokers. Particular emphasis is given to the increased rates of lung cancer in women. "Carcinogenesis" reports the identification of numerous mutagens and carcinogens in cigarette smoke and the metabolism and activity of these agents individually and in concert. "Clinical Aspects" reports on the dismal survival rate among lung cancer patients, concluding that prevention remains the most promising approach. The final section discusses the economic costs of tobacco smoking to individuals and society as a whole.

Epidemiology

Introduction

Lung cancer has been the leading cause of cancer death...
among American men since the early 1950s. Although it ranked only seventh among American women in 1950, lung cancer is about to surpass breast cancer to become the primary cause of cancer death in women as well as men. Mortality rates for this disease have increased from 4.9/100,000 in 1930 to 71.6/100,000 by 1980 among men and from 2.2 to 20.9/100,000 over the same period among women (Chart 1). However, the overall rate of increase is currently decelerating in men, while it is accelerating in women. In 1984, there will be an estimated 121,000 lung cancer deaths in the United States (85,000 in men and 36,000 in women), with lung cancer comprising 35% of all cancer deaths in men and 18% in women (Table 1). Because survival rates for lung cancer are poor compared with most other sites, the disease accounts for a higher percentage of all cancer deaths than of all incident cases of cancer (22% of newly diagnosed cases in men and 10% in women).

In recent years, the rate of increase in age-adjusted lung cancer rates among American men appears to be leveling off, and age-specific trends show actual declines in rates for men under age 50. In the future, as these younger cohorts move into the older age groups where most lung cancer occurs, we might expect a leveling off and eventual decline in lung cancer among men. In women, age-adjusted rates have continued to show dramatic increases. However, very recent age-specific incidence data show slight fluctuations in rates among women ages 35 to 44 years (Chart 2). A cohort analysis of age-specific lung cancer mortality rates shows a decline among women ages 35 to 39 who were born in 1938 to 1942 and among those ages 30 to 34 who were born in 1943 to 1947 compared with rates seen for those ages in earlier cohorts (77). Numbers in the younger age group are relatively small, however, which means that minor changes in rates from one year to the next should not be overinterpreted. In any event, age-adjusted lung cancer mortality rates for American women increased 337% between 1950 and 1980. The effect of lung cancer on overall changes in United States cancer mortality rates is shown in Table 2, by race and sex, for the period 1950 to 1977.

Mortality rates for lung cancer were higher among whites than among nonwhites until the mid-1960s. Since then, mortality rates for nonwhite males have surpassed those of white males, and female rates have been similar in whites and nonwhites. Average annual age-adjusted incidence rates during 1973 to 1977 were 76.4 and 110.0/100,000 in white and black males, respectively, and 21.8 and 24.3/100,000 in white and black females (86).
Trends in Cigarette Smoking

Adults. "The onset of widespread cigarette use among women lagged behind that of men by 25 to 30 years" (76). Estimates of the prevalence of cigarette smoking in the United States come from the National Health Interview Survey. In 1979, 36.9% of male respondents ages 17 years and over reported themselves to be regular cigarette smokers, compared with 28.2% of females (76). These figures represent declines for both sexes since 1965, when the first Health Interview Survey data were collected. At that time, 51.1% of men and 33.3% of women were reported to be regular cigarette smokers. From other surveys, it appears that smoking prevalence for men was slightly greater than 50% from the 1930s through the 1950s or 1960s and has since declined rather impressively to its present level (76). Among men who are in their fifth and sixth decades and women who are in their seventh and eighth decades and women who are in their fifth and sixth decades are those whose birth cohorts will experience the greatest lifetime exposure to cigarette smoking (19).

Knowing the proportion of adults who smoke, however, does not adequately describe smoking patterns. Age at initiation, number and type of cigarettes smoked, inhalation practices, and patterns by socioeconomic status are all important factors in understanding possible differences between men and women in studies that have examined the relationship between smoking and lung cancer.

The mean age at onset of regular cigarette smoking has been less than 20 years for cohorts of men born since before 1900, whereas in women the mean age of onset was 35 years in those born before 1900 and has declined steadily for subsequent cohorts. It was estimated to be age 15 or 16 for cohorts born between 1951 and 1960 (76). Thus, total lifetime exposure was potentially much greater for the later-born cohorts of women whose experience could not have been reflected in the early studies of smoking and lung cancer conducted in the 1950s and 1960s.

Data since 1965 also show that, while the prevalence of smoking has declined over time, the proportion of heavy smokers is increasing. Among women smokers, for example, only 13.7% smoked 25 or more cigarettes daily in 1965, and this proportion increased to 22.4% by 1979 (Chart 3). Data on inhalation practices among smokers for 1975 show that 30.3% of men and 16.4% of women who smoked reported that they "inhaled deeply into the chest," 58.5% of men and 50.7% of women "inhaled almost every puff," and 10.9% of men and 12.9% of women smoked their cigarettes "as far as possible" (75).

The market share of filter-tipped cigarettes (now greater than 90%) and the consumption of low-tar cigarettes have increased impressively in recent years, particularly among women. In 1970, only 9.5% of female smokers used brands with "tar" levels of less than 15 mg, and by 1979 this proportion was up to 38.5% (Chart 3). To some extent, then, the increase in average number of cigarettes smoked daily may be a function of decreasing tar levels over the same period, as smokers have compensated for switching to low-tar brands by smoking more cigarettes. (Further discussion of low-tar cigarettes is contained under "Carcinogenesis".)

In men, there is today a clear inverse relationship between socioeconomic status, defined by educational level or occupation, and lung cancer rates. Since at least the mid-1960s, men who are college graduates have been much less likely to smoke than are men with a high school education or less, and men in professional and managerial positions have had lower smoking rates than do blue-collar workers (75). In women, smoking rates have consistently been lowest among those with a grade school education or less, but between 1964 and 1975 marked changes occurred in the relationship between smoking and educational achievement at the levels beyond grade school attained by most of the population (75). In 1964, smoking prevalence was similar (35.0 to 36.5%) for women with some high school education, women who were high school graduates, women with some college, and college graduates. By 1975, smoking among female college graduates had declined to 21.1% and, although rates for women in the other educational levels had declined somewhat, they were similar and remained relatively high (31.9 to 33.2%).

This might be taken as evidence that nonsmoking, like so many other behaviors, is a "trickle-down" phenomenon, adopted first by members of the higher socioeconomic levels and eventually followed by the rest of society. Still, at least as of 1976, the occupational gradient seen in men was not mirrored in women, although women in the "professional, technical, and kindred" group appeared to have lower smoking rates than do those in all other major occupational groups (76). Only as more recent data become available will it be possible to know if the relationship between smoking and socioeconomic status in women will follow the patterns seen in men, much as adoption of cigarette smoking itself in women lagged behind that of men.

Teens. During the 1970s there was considerable concern about an epidemic of smoking among teenage girls in the United States. National survey data indicated that smoking prevalence had steadily increased in this group since the late 1960s. By 1979, although the overall proportion of female adolescents ages 12 to 18 years who smoked was down compared with 1974 figures, girls in the subgroup ages 17 to 18 years were smoking

![Chart 3. Trends in smoking prevalence, 1930s to present, United States males and females. --- prevalence of regular cigarette smoking among United States adults; ----, estimated percentage of adult regular smokers who smoked brands of <15 mg "tar"; ----, estimated percentage of adult smokers who smoked ≥25 cigarettes daily. Source: United States Surgeon General (76).](chart3.png)
at slightly higher rates than their counterparts in earlier surveys, and their smoking rates were by then higher than those for boys the same age (26.2 versus 19.3%, respectively) (76). Concerns about high smoking rates among teens stem from the fact that earlier initiation is associated with heavier smoking and with more difficulty in attempts to quit compared with later initiation.

Unfortunately, there are no current national data on the prevalence of teenage smoking to update the 1979 figures. The results of an ongoing annual survey of 18,000 high school seniors show that self-reported smoking peaked in 1977 to 1978, declined steadily through 1981, and then stayed on a plateau or rose slightly in 1982 (32). Among members of the class of 1982, 70.1% had smoked cigarettes at any time, 30.0% had smoked cigarettes within the 30 days prior to the survey, and 21.1% had smoked cigarettes daily within the past 30 days. Females were slightly more likely than males to smoke at least half a pack per day (14.7 versus 13.1%, respectively), and the sex difference was greater for occasional smoking. Since this survey is confined to high school seniors, it may not be generalizable to all older teenagers, inasmuch as those who drop out of school may smoke at higher rates. Studies have shown that girls who are college bound are less likely to smoke than girls who do not intend to go to college. In the 1982 survey of high school seniors, for example, only 8% of students who planned to go to college smoked half a pack or more daily compared with 21% of those who were not college bound.

A study conducted among 7th to 11th graders in three schools in the Minneapolis-St. Paul area in 1980 found that 39.6% of girls 15 to 16 years old reported themselves to be smoking at least a few times per month (50). This proportion is higher than figures reported for other studies, which may reflect (a) a more liberal definition of current smoking behavior, (b) the fact that students’ saliva and expired air samples were collected in the Minnesota study, which might have made them more likely to report themselves as smokers, or (c) that smoking rates in teenage girls are generally higher than recognized. Whichever estimate is correct, all are sufficiently high to elicit public health concern, given current knowledge of the health effects of smoking.

Epidemiological Studies of Smoking and Lung Cancer

The evidence for smoking as the primary cause of lung cancer comes from a large number of cohort (prospective) and case-control (retrospective) studies in humans, as well as from indirect studies that have monitored lung cancer patterns in populations in relationship to smoking habits. (Experimental evidence that cigarette smoke is carcinogenic is reviewed under “Carcinogenesis.”) The epidemiological data on smoking and lung cancer fulfill all of the generally accepted criteria for causal association, including the consistency of results across studies, the strength of the relationship, its specificity, the correct temporal sequence between exposure and disease, and the coherence of the association as evidenced by a dose-response relationship.

The epidemiological evidence on smoking and lung cancer has been extensively reviewed and updated in successive reports from the United States Surgeon General. In particular, the reader is referred to the initial report of 1964 (73), the report of 1971 (74), the summary report of 1979 (75), the 1980 report which focused on women (76), and the report of 1982 which was devoted entirely to cancer (77). The results of 8 prospective studies, all initiated in the 1950s and 1960s, show markedly increased risks of lung cancer in smokers compared with non-smokers (Table 3). Only 4 of the 8 studies included women; all found that the overall relative risk of lung cancer associated with smoking was consistently elevated across studies, although not as high as for men. More than 50 retrospective studies of smoking and lung cancer have been reported, again showing elevated risks of lung cancer for smokers compared with non-smokers, with lower risk ratios for females than males (15). It is generally agreed that among males the overall risk of lung cancer in smokers is about 10 times that of non-smokers.

An estimated 85 to 90% of lung cancer among American men is attributable to cigarette smoking. Given the lower relative risks for women and the lower prevalence of cigarette smoking, the overall proportion of female lung cancer associated with cigarette smoking has been lower than for men. However, previous calculations (15) have been based largely on the experience of women studied in the 1950s and 1960s, members of birth cohorts that began smoking later, smoked fewer cigarettes, and probably inhaled less than members of later-born female cohorts. As a result of heavier exposure among female smokers over time, the risk of lung cancer should approximate that of male smokers. Female cancer mortality rates today are only slightly lower than those of males 25 years ago, reflecting the lag in adoption of cigarette smoking by women and suggesting similar risks in both sexes (76). One recent case-control study found that the relative risk of female lung cancer associated with smoking was 8.9 (53). Using the smoking prevalence of 33% for American women in the mid-1960s, a relative risk of 6.9 would mean that about 66% of lung cancer in women could be attributable to cigarette smoking [following the method of Levin (43)]. Doll and Peto (11), in work cited in the 1982 report of the Surgeon General, estimate that 77.4% of lung cancer in women is the result of smoking. In fact, the difference in lung cancer mortality rates among American women between 1980 and 1950 (20.9 versus 4.7/100,000) is 78% of the 1980 rate. It could be argued that factors other than cigarette smoking may have contributed in small part to the difference; on the other hand, this estimate of population-attributable risk of 78% might be conservative since it assumes, erroneously, that none of the deaths in 1950 were due to cigarette smoking.

In addition to consistency and strength of results across many

<table>
<thead>
<tr>
<th>Population</th>
<th>Size</th>
<th>No. of deaths</th>
<th>Non-smokers</th>
<th>Cigarette smokers</th>
</tr>
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<tr>
<td>British physicians</td>
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<td>14.00</td>
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<tr>
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<tr>
<td>9-state study</td>
<td>78,000 males</td>
<td>331</td>
<td>1.00</td>
<td>14.20</td>
</tr>
<tr>
<td>California males in 9 occup.</td>
<td>188,000 males</td>
<td>448</td>
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<td>10.73</td>
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<tr>
<td></td>
<td>68,000 males</td>
<td>368</td>
<td>1.00</td>
<td>7.61</td>
</tr>
</tbody>
</table>

* Source: United States Surgeon General (77), p. 36.
studies of various designs and conducted in diverse geographic settings, the data on time trends in cigarette smoking and lung cancer described earlier provide strong evidence of a logical temporal relationship. Cairns illustrated this point well using British data on time trends in smoking and lung cancer (Chart 4). Allowing for a lag time of about 20 years, lung cancer rates followed and paralleled smoking prevalence patterns, first in men and later in women. As noted in the Surgeon General’s 1982 report on smoking and cancer:

When the prevalence of cigarette smoking by birth cohort is compared with the mortality experience by birth cohort, the relationship between cigarette smoking behavior and lung cancer mortality experience is extremely coherent. (77)

Although cigarette smoking is related to many respiratory and cardiovascular conditions, as well as to cancers of a number of sites, the specificity of the association with lung cancer is apparent in the markedly elevated relative risks for that disease. Evidence for a dose-response relationship is also strong, thereby satisfying the final criterion for causality, namely the coherence of the association. Across studies, risk increases with number of cigarettes smoked (Chart 5), with years smoked, with earlier age at onset of cigarette smoking, with degree of inhalation, with tar and nicotine content of cigarettes smoked, and with use of filtered compared with nonfiltered cigarettes, and risk decreases with number of years since smoking cessation. Finally, lung cancer mortality rates are strongly correlated with per capita cigarette consumption across countries (77), and special populations within the United States which proscribe cigarette use, notably Mormons and Seventh Day Adventists, have much lower lung cancer rates than do comparison populations that include smokers (77). British physicians, among whom smoking cessation rates have been high, have experienced marked declines in lung cancer mortality rates (10).

Passive Smoking and Lung Cancer

A number of studies have shown an association between illness in young children, particularly respiratory disease (pneumonia, bronchitis, asthma), and exposure to parents’ cigarette smoke. This relationship persists when social class, birth weight, and parental production of cough and phlegm are taken into account (75). In a 7-year prospective study, Tager et al. (70) found that exposure to maternal smoking was associated with decreased development of pulmonary function in children, as measured by forced expiratory volume in 1 sec. The investigators controlled for previous forced expiratory volume, age, height, change in height, and cigarette smoking habits of the children themselves. Similarly, in a study of spirometric measurements confined to subjects age 40 and older, Kauffman et al. (34) in France found that nonsmokers (of either sex) whose spouses smoked 10 g or more of tobacco daily had significantly lower forced midexpiratory flow rates (FEF25-75) than did those married to nonsmokers. Among women there was also a significant difference in forced expiratory volume in 1 sec, and a dose-response relationship to husband’s smoking was found for nonemployed women. Earlier, White and Froeb (83) reported on a study of the effect of long-term involuntary smoking on small airways function. They found that chronically exposed nonsmokers had lower forced mid- and end-expiratory flow rates (FEF25-75 and FEF75-85, respectively) than did nonexposed nonsmokers. Values for the former group were similar to those of light smokers.

Only relatively recently have studies been reported on the possible association of lung cancer with exposure to the cigarette smoking of others (passive or involuntary smoking) (Table 4). Based on his large prospective Japanese study, Hirayama (20) first reported that nonsmoking wives of smokers had elevated rates of lung cancer compared with nonsmoking women whose husbands did not smoke. Considerable attention focused on this potentially very important finding, including methodological criticisms (20). Hirayama (21) subsequently provided further data to show the consistency of his findings across subgroups. Trichopoulos et al. (71) in Greece and Correa et al. (7) in New Orleans have since published case-control studies that support the claim that lung cancer in nonsmokers is associated with exposure to smoking by spouses. In both studies, there was statistically significant evidence of a dose-response relationship, i.e., risk increased with degree of spouse’s cigarette smoking.

Several additional studies could be variously interpreted. Garfinkel (15), based on his analysis of data from the large prospect-
primary cause of cancer death in women. Age-adjusted lung cancer mortality rates for American women increased over 300% between 1950 and 1980. Seldom, if ever, has the correlation between any risk factor and disease been as strong, consistent, and extensive as that between cigarette smoking and lung cancer. Numerous cohort and case-control studies have shown markedly elevated relative risks for this disease in smokers compared with nonsmokers. This correlation makes lung cancer a largely preventable disease. It is estimated for the United States that 85 to 90% of lung cancer cases among men and around 70% or more in women is presently attributable to cigarette smoking.

Smoking prevalence among American men has declined since the mid-1950s, and the male lung cancer epidemic seen throughout this century shows signs of slowing down and eventually reversing, if downward trends can be projected into the future. For women, evidence of reduction in smoking came later, and the decline appears to be relatively minor. Among older teens, at least, girls are more likely to smoke than boys. Among women, lung cancer rates can only be expected to increase in the near future, as the female cohoists most heavily exposed to cigarette smoking pass through the older ages where lung cancer risk is greatest. A number of studies show that passive smoking affects lung function; although the evidence is not overwhelming, it is a cause for increasing concern that several recent studies suggest elevated risks of lung cancer among passive smokers.

The epidemiological evidence reviewed here on smoking as a risk factor has been limited primarily to lung cancer. The list of other smoking-related diseases is long, including, but not limited to, emphysema, bronchitis, coronary heart disease, and cancers of the larynx, oral cavity, kidney, pancreas, and bladder. Women who smoke share these disease risks with men but may also experience unique risks associated with oral contraceptive use and pregnancy. The risk of myocardial infarction is increased approximately 10-fold among birth control pill users who smoke compared with those who neither smoke nor use oral contraceptives, and pregnant women who smoke increase considerably their risk of spontaneous abortion, stillbirth, and other complications of pregnancy and labor, compared with nonsmokers (76). The Surgeon General estimates that, all causes together, over 340,000 deaths occur annually in this country as a result of cigarette smoking (75).

Carcinogenesis

Introduction

Once an unambiguous statistical association was established between smoking and lung cancer (73, 77), investigators began to ask which substances in cigarette smoke are carcinogenic and how they transform normal cells into malignant cells. The questions arose: What are the harmful constituents of cigarette smoke? Which are mutagenic and carcinogenic? Are they absorbed or metabolized, and how do they alter the genetic information of the cells? The answers to these questions have provided experimental evidence linking cigarette smoke with cancer, as well as providing new methodologies by which to identify and to quantitate carcinogens in tobacco smoke. This new knowledge allows one to monitor effects of a smoke-filled environment on nonsmokers and to examine the feasibility of designing less harmful cigarettes.

Table 4

<table>
<thead>
<tr>
<th>Author and date</th>
<th>Country</th>
<th>Study type and gender</th>
<th>Measure of exposure to smoking</th>
<th>Relative risk*</th>
</tr>
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<td>Cohort (women)</td>
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<td></td>
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<td>Correa et al. (1983)</td>
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<tr>
<td></td>
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<td>&gt;40 cigarettes</td>
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</tr>
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* Results are statistically significant at p < 0.05 unless otherwise indicated.

NS, not significant.

Lung cancer has been the leading cause of cancer death in the United States among men, and it will soon become the leading cause of cancer death in women. Age-adjusted lung cancer mortality rates for American women increased over 300% between 1950 and 1980. Seldom, if ever, has the correlation between any risk factor and disease been as strong, consistent, and extensive as that between cigarette smoking and lung cancer. Numerous cohort and case-control studies have shown markedly elevated relative risks for this disease in smokers compared with nonsmokers. This correlation makes lung cancer a largely preventable disease. It is estimated for the United States that 85 to 90% of lung cancer cases among men and around 70% or more in women is presently attributable to cigarette smoking.

Smoking prevalence among American men has declined since the mid-1950s, and the male lung cancer epidemic seen throughout this century shows signs of slowing down and eventually reversing, if downward trends can be projected into the future. For women, evidence of reduction in smoking came later, and the decline appears to be relatively minor. Among older teens, at least, girls are more likely to smoke than boys. Among women, lung cancer rates can only be expected to increase in the near future, as the female cohorts most heavily exposed to cigarette smoking pass through the older ages where lung cancer risk is greatest. A number of studies show that passive smoking affects lung function; although the evidence is not overwhelming, it is a cause for increasing concern that several recent studies suggest elevated risks of lung cancer among passive smokers.

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Constituents of Cigarette Smoke

The combustion of tobacco in cigarettes at temperatures up to 900° results in pyrolysis, oxidation, hydrogenation, decarboxylation, and dehydration of the tobacco constituents. The newly generated chemical species are gasified by distillation and sublimation or become adherent to small monodisperse particles. Over 3000 chemicals have been identified and quantitated in tobacco smoke obtained from smoke machines that operate under a set of uniform conditions (77). Early studies demonstrated that unfraccionated tobacco smoke was mutagenic in bacteria (35) and carcinogenic when applied to mouse skin (84). The important question is which of the many constituents are responsible for human cancer. Chemical separations alone were inadequate. What was required were different biological assays for carcinogenicities.

The Ames bacterial assay has been most extensively utilized to identify and to characterize environmental mutagens. Using this assay, tobacco smoke constituents have been analyzed for mutagenicity (35). The concept that substances can be putatively classified as carcinogens on the basis of enhanced mutagenesis in bacteria has been proven very useful. The assay measures the frequency of mutations that allow histidine-requiring bacteria to grow in the absence of histidine. The high sensitivity of this assay permits the detection of mutagenity of smoke obtained from the equivalent of 1/100 of a cigarette. A similar quantity of tobacco smoke can induce sex-linked recessive lethal mutations in Drosophila (8). Furthermore, exposure of human lymphocytes in vitro to tobacco smoke condensate obtained from 1/400 of a cigarette induces another mutagenic phenomenon, namely, SCEs (8). The malignant transforming activities of tobacco smoke tar has been demonstrated with normal fibroblasts in culture and after application to mouse skin and to hamster larynx (27).

Customarily, tobacco smoke is collected in 2 phases: as a volatile or gaseous phase; and as a tar or particulate phase. The latter is monodisperse, is approximately 0.4 μm in diameter, and is retained on a specified filter. The particulate phase is frequently extracted and fractionated into acid, neutral, and basic components (26), although other separation protocols have been utilized. In addition, there is an insoluble residue that contains known metal carcinogens, such as nickel and cadmium (69). After extensive purification by high-pressure liquid and gas chromatography, many of the components were identified by automated mass spectroscopy. A list of some of the major types of identified chemical carcinogens in cigarette smoke is given in Table 5. Unexpectedly, this simple chemical subfractionation also separates compounds exhibiting different biological activities.

The neutral fraction contains a variety of polynuclear aromatic hydrocarbons and exhibits most of the tumorigenic activity associated with cigarette smoke. Application of this fraction to the skin of mice, the ears of rabbits, or the larynx of hamsters results in both benign and malignant tumors (77). The known carcinogens in this fraction include benzo(a)pyrene and dibenz(a)anthracene, as well as chlorinated hydrocarbon insecticides. In agreement with studies on the metabolism of polynuclear aromatic hydrocarbons, mutagenicity by this fraction in Salmonella should and does require the addition of an S-9-activating enzyme system (14). Activating enzymes are predominantly found in liver but are present in many tissues, including human lung. It has been suggested frequently that the presence and specificity of activating systems in a tissue are important factors in determining the site of occurrence of cancers by different chemicals. Therefore, the activated carcinogens form covalent adducts with different cellular macromolecules. It is commonly believed that the binding to DNA is the primary initiating event in carcinogenesis by these agents. Bulky bound adducts block fork progression during DNA replication (30). On the basis of studies in bacteria, it has been postulated that stopping of DNA synthesis is a signal for the synthesis of error-prone replication factors that permit DNA synthesis to proceed past the bulky adducts and also promote mutagenesis at distant sites. The sum of mutagenic activities of individual components in the neutral fraction as measured in the Ames assay or as measured by the induction of SCEs in human lymphocytes is insufficient to account for the total mutagenic activity of this fraction prior to subfractionation (8). The implication is that mutagenicity and presumably carcinogenicity result from the concerted effects of multiple components.

The acidic fraction contains compounds that exhibit cocarcinogenic and tumor-promoting activity, as well as a number of potent mutagens. Cocarcinogens are operationally defined as weak carcinogens that enhance the potency of other carcinogens (78). Tumor promoters are reversible potentiators of carcinogenesis by other previously applied agents (initiators) but by themselves are not carcinogenic. The important fact that lung cancer incidence declines soon after cessation of smoking implies that major factor in the association between smoking and lung cancer is reversible and suggests a tumor-promoting activity. The molecular mechanism of tumor promotion is unknown; these compounds are not mutagenic but may serve to enhance the synthesis of growth factor, permitting the proliferation of already initiated cells. Two sets of epidemiological observations suggest that cocarcinogenesis or tumor promotion may be important properties of ingredients in cigarette smoke. The mortality ratio

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Major mutagens and carcinogens and related substances in tobacco smoke*</th>
<th>Amount in smoke from one cigarette</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Particulate phase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Neutral fraction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzo(a)pyrene</td>
<td>10–50 ng</td>
<td></td>
</tr>
<tr>
<td>Dibenzo(a)anthracene</td>
<td>40 ng</td>
<td></td>
</tr>
<tr>
<td>5-Methylchrysene</td>
<td>0.6 ng</td>
<td></td>
</tr>
<tr>
<td>Benzo[c]fluoranthene</td>
<td>50 ng</td>
<td></td>
</tr>
<tr>
<td>B. Basic fraction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine</td>
<td>0.06–2 ng</td>
<td></td>
</tr>
<tr>
<td>N-Nitrosonornicotine</td>
<td>0.2–3.7 μg</td>
<td></td>
</tr>
<tr>
<td>C. Acetic fraction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catechol</td>
<td>40–280 μg</td>
<td></td>
</tr>
<tr>
<td>D. Residue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nickel</td>
<td>0–3 μg</td>
<td></td>
</tr>
<tr>
<td>Cadmium</td>
<td>80 ng</td>
<td></td>
</tr>
<tr>
<td>Pb</td>
<td>0.03–1.0 μCi</td>
<td></td>
</tr>
<tr>
<td>II. Vapor phase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrazine</td>
<td>32 μg</td>
<td></td>
</tr>
<tr>
<td>Vinyl chloride</td>
<td>1–16 ng</td>
<td></td>
</tr>
<tr>
<td>Urethan</td>
<td>10–35 μg</td>
<td></td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>20–90 μg</td>
<td></td>
</tr>
<tr>
<td>Nitrogen oxides</td>
<td>16–600 μg</td>
<td></td>
</tr>
<tr>
<td>Nitrosodicycline</td>
<td>0.1–28 μg</td>
<td></td>
</tr>
</tbody>
</table>

* The abbreviations used are: SCE, sister chromatid exchange; COI, cost of illness.
from lung cancer in uranium miners who are smokers is 442 times greater than in control individuals. In several studies, this high incidence is significantly greater than that predicted on the basis of smoking (10-fold) or on the basis of uranium mining (5-fold) (77). An analogous situation is likely to exist with smokers from lung cancer in uranium miners who are smokers are also exposed to asbestos.

The potential carcinogenic activities of constituents in the basic fraction obtained from cigarette smoke are difficult to evaluate. Sugimura et al. (68) initially demonstrated that pyrolysis of proteins in fish results in the production of trypophan derivatives that are extraordinarily potent mutagens in the Ames assay. For example, methyl indoles, which are present in tobacco smoke, are 1000-fold more mutagenic than is benzo(a)pyrene (77). Similar compounds are found in the acidic fraction of tobacco tar. However, these potent mutagens may not be potent carcinogens (77).

The insoluble residue of cigarette smoke contains nickel, polonium, and other metals. Radioactive 210Po is present in the environment and is stored in the parenchyma of lungs. The accumulation of 210Po in lungs of cigarette smokers is estimated at 2.5 to 3.0 times greater than that in nonsmokers (18). Nevertheless, on the basis of the lack of an overwhelming incidence of lung cancer in uranium miners who do not smoke, but who are exposed to high concentrations of polonium, it seems unlikely that the trace amount of polonium in cigarette smoke is a major factor in causing lung cancer among the general population.

The volatile phase of cigarette smoke contains nickel carbonyl, hydrazine, vinyl chloride, and formaldehyde, as well as trace amounts of nitrosamines (77). Nickel is classified as a human carcinogen based on increased incidence of cancer in nickel-refinery workers, showing a 200- and 10-fold increase in nasal carcinoma and lung cancer, respectively (69). Nickel carbonyl has been shown to cause respiratory tumors in a variety of animals. The in vivo enhancement in infidelity of DNA synthesis by Ni2+ suggests that nickel causes mutations by promoting misincorporation at the level of DNA replication (66). Hydrazine is carcinogenic in mice and has been shown to alter the amino group on cytidine, as well as to introduce methyl groups into cellular DNA by unknown mechanisms (65). Vinyl chloride is activated by cytochrome P-450, resulting in the formation of an epoxide that reacts with adenine on DNA to form a carbon bridge across the N-1 and N-6 positions. The increased misincorporation by DNA polymerase in copying template containing vinyl chloride-modified nucleotides may account for mutagenicity by vinyl chloride (65). Despite the mutagenicity and carcinogenicity of these and other individual components, the lack of tumor formation in animals exposed to the volatile phase of cigarette smoke suggests that these carcinogens are not major causative agents of lung cancer in humans.

During the curing and burning of tobacco, a series of carboxylic amino acids are formed from nicotine and related alkaloids. Two of these tobacco-specific amino acids, N'-nitroso-nicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanolone, are exceptionally potent carcinogens. A single dose of 1 mg of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanolone is able to induce tumors of the lung, nasal cavity, and trachea in Syrian golden hamsters (25). In addition, tobacco smoke contains nitric oxide, which is known to cause endogenous N-nitrosation of proline (77). It is not currently possible to compare the amounts of nitrosamine formed from tobacco smoke to those which are formed endogenously, and thus it is difficult to assess the contribution of nitrosamines from smoke to the causation of human cancer. Furthermore, nitrosamines may be organ-specific carcinogens; e.g., N'-nitrosodimethylamine induces predominantly esophageal tumors in Fischer 344 rats when administered in drinking water. It has been suggested that the high concentration of nitrosamines in snuff is responsible for the associated oral cancers (23).

Absorption and Metabolism

The respiratory epithelium provides an extensive surface for the absorption of volatile chemicals and the entrapment of small particles. This epithelial surface, which lines the alveolar spaces and conducting airways in humans, totals 60 to 90 sq m. The monodisperse small particulates in the tobacco smoke aerosol easily penetrate into the deep regions of the human lung. That carcinogens in tobacco smoke are absorbed and metabolized is documented by their presence in the urine of smokers (55). That carcinogens in tobacco are mutagenic in vitro is documented by increased chromosomal aberrations in lymphocytes of smokers (51).

The urine of smokers has been analyzed for the presence of mutagens. On the average, mutagenic activity of urine from smokers is increased about 5- to 10-fold as compared with nonsmokers. In certain individuals, the increase in mutagenicity is as great as 100-fold, and in one individual this has been shown to result from the presence of 2-aminonaphthalene, a known human bladder carcinogen (6). Interestingly, the enhanced mutagenicity in urine from smokers is highest in the evening and lowest in the morning, implying that the mutagenic factors are rapidly metabolized. The requirement for metabolic activation in the Ames assay using urine from smokers does not necessarily imply that chemicals in the urine are excreted without having undergone metabolic activation. Since the S-9 extracts contain a variety of enzymes as well as microsomal activating enzymes, the mutagens might have been initially present as conjugated derivatives of previously activated carcinogens (e.g., glucuronides). The chemical form of mutagens during transport from the lung to distant organs is not known. The increased abnormalities and decreased mobility of sperm obtained from smokers provides additional evidence for the general metabolism of toxic tobacco constituents (80) but is not necessarily indicative of DNA damage. Changes in morphology and decreasing mobility could result from effects of tobacco smoking on sperm development. The fact that cigarette smoke is mutagenic in humans has been established by chromosomal analysis of lymphocytes from smokers and nonsmokers. In studies from different laboratories, a small but significant increase in SCEs in smokers has been demonstrated repeatedly (79). More substantial increases in the frequencies of several types of chromosomal aberrations have been observed in other extensive studies (51, 77). Considering the number of smokers in our society, even a relatively weak mutagenic effect could have substantial consequences on the total gene pool in the human population.

Overall Consideration

The above studies have presented the profile of known carcinogens in tobacco smoke. At present, there is no direct method
to assign priority to any of these substances as putative causal agents in human lung cancer. It is likely that individual components in cigarette smoke may be preferentially associated with human cancers at different sites. Moreover, the spectrum of chemicals present in smoke (initiators, complete carcinogens, promoters, cocarcinogens) suggests that the production of overt cancers may involve the concerted actions of several agents. Because of these considerations, elimination of single components from cigarette smoke would not be the key to the production of less harmful cigarettes.

Animal models have been inadequate for assessing the potentials of chemical carcinogens to produce lung cancer. Even though tobacco smoke condensates and the constituents separated therefrom have been shown to be carcinogenic after direct application in multiple tissues in animals, the results of inhalation studies have not been illuminating in determining which carcinogens cause lung cancer. The demonstration of bronchiogenic carcinoma in animals by inhalation of cigarette smoke has been at best sporadic. Most simply, animals are reluctant to inhale cigarette smoke, and anatomical considerations as well as shallow breathing protect many species from the ingress of particulate fractions into the bronchial tree. Nevertheless, long-term inhalation studies have produced benign and malignant laryngeal tumors in Syrian golden hamsters.

Carcinogenicity of Passive Smoking

Since there is no apparent threshold in the dose response between extent of smoking and the incidence of lung cancer, it is logical to inquire whether lung cancer in nonsmokers might result from exposure to smoke-filled environments. The chemical composition of sidestream smoke is similar to that of mainstream smoke. Of concern is the fact that sidestream smoke contains higher amounts of carcinogenic N-nitrosamines and smaller size particles (24). Smaller size particles stay suspended longer in air and more easily penetrate into the bronchial tree. This issue of passive smoking has come into public prominence because of the rights of nonsmoking individuals not to expose themselves to potent carcinogens and because of the publication of epidemiological studies that suggest an elevated incidence of cancer of the lung in nonsmoking spouses of smokers (see "Epidemiology"). Quantitation of absorption of cigarette smoke in individuals passively exposed has been achieved by measurements of urinary cotinine, a stable metabolite of nicotine. Of particular concern is exposure to high levels of environmental cigarette smoke in selected settings. Greenberg et al. (17) documented that urinary cotinine was significantly increased in infants as a result of exposure to caretakers who smoke. The combined epidemiological and chemical evidence suggest that the biological effects of passive exposure are real but that passive smoking is not the only cause of lung cancer in nonsmokers. Since the predominant type of lung tumor in nonsmoking females is bronchioladenocarcinoma, histological studies in nonsmoking spouses should provide a sensitive independent criterion for induction of other histological types of lung cancers that are normally associated with smoking.

Less Harmful Cigarettes

The major efforts to diminish the hazards associated with cigarette smoking have been directed at reducing the content of nicotine and tar in tobacco smoke. In fact, there is a 20% lower incidence of lung cancer in smokers of low-tar cigarettes compared with those who use high-tar cigarettes. The reductions in nicotine and tar have been achieved mainly by use of filters. Contrary to the general conception, there has not been a significant reduction in the nicotine and tar content of the cigarettes themselves. The changes in nicotine and tar have been demonstrated in the tobacco smoke obtained by machines that smoke cigarettes under standard conditions. Recently, Benowitz et al. (3) demonstrated that serum cotinine concentration is proportional to the number of cigarettes smoked and not to the machine-certified nicotine content of the smoke. This finding implies that smokers have modified their smoking techniques in order to maintain a desired level of serum nicotine, e.g., compression of filter, deeper inhalation, etc. This is not surprising, since many studies have suggested that nicotine is habituating. Nicotine itself, unfortunately, is the source of certain carcinogenic nitrosamines in smoke. Also, the nicotine and tar contents in cigarette smoke have been reduced in parallel; thus, as smokers compensate to increase nicotine intake, it is likely that they also increase tar intake. This is supported by studies on the genotoxicity of tobacco smoke; based on either mutagenicity in Salmonella or SCEs in human lymphocytes, the genotoxicity per mg of tar in tobacco smoke is similar in nonfiltered and filtered cigarettes (8). Also, the mutagenic effects detected by induced SCEs are the same in lymphocytes obtained from smokers of low- and high-tar cigarettes (28).

Based on the demonstrated human experiences and considering the multitude of mutagens and carcinogens in cigarettes, it seems unlikely that major reductions in lung cancer will be achieved by altering cigarette composition. In fact, it can be argued that efforts in this direction are counterproductive and time delaying and that they detract from the primary objective of reducing cancer mortality by reducing cigarette smoking.

Conclusion

Cigarette smoke contains many complete carcinogens, direct- and indirect-acting tumor initiators, tumor promoters, cocarcinogens, and mutagens. The mutagenicity of many constituents in tobacco smoke has been demonstrated in a variety of prokaryotic and eukaryotic test systems. The carcinogenicity of some of these mutagens has been demonstrated in animals; some of these compounds are already designated as human carcinogens. In smokers, these agents are absorbed by the lung epithelium and excreted in urine. Moreover, many of these chemicals cause mutagenic changes in human lymphocytes in vivo. Of particular concern are metabolites of nicotine itself, the major habituating agent in tobacco smoke. Some of these metabolites are potent animal carcinogens.

The characterization of chemical constituents in tobacco smoke has contributed to an analysis of 2 important recent issues, passive smoking and low-tar cigarettes. The chemical components of sidestream smoke are similar to those of mainstream smoke. Passively exposed individuals absorb cigarette smoke, as indicated by significantly higher levels of urinary cotinine. The combined epidemiological and chemical evidence suggest that the biological effects of passive exposure are real, but passive smoking is not the only cause of lung cancer in nonsmokers. Contrary to the general conception, there has not
been a significant reduction in the nicotine and tar content of cigarettes themselves. Even though the concentration of nicotine and tar has been reduced in the smoke of cigarettes, smokers have modified their smoking techniques in order to maintain a desired level of nicotine, the habituating agent. This has been documented by analysis of serum cotinine, a stable metabolite of nicotine.

Considering the multiplicity of mutagens and carcinogens in cigarette smoke and considering the evidence for their concerted interactions with body constituents, it is argued that reductions in individual components would not be an effective strategy for the reduction of cancer mortality. Curtailment of smoking is required.

CLINICAL ASPECTS OF LUNG CANCER

Introduction

The spectrum of medical concern about the problem of lung cancer is wide, ranging from prevention and early detection to staging and choice of treatment for patients with localized disease, to palliation and care of those who have advanced disease or are terminally ill. Since the overall 5-year survival of patients with lung cancer is only 5 to 8%, despite the fact that truly localized disease has a far better prognosis, the best way to have an impact on the problem obviously would be to prevent the occurrence of the disease. It is sobering to consider how limited has been the impact of health education and behavior modification given the fact that the great majority of lung cancers (about 85%) are potentially preventable.

In 1980, there were 75,535 deaths from lung cancer among men and 28,309 among women in the United States. The remarkable trends in both incidence and sex distribution are illustrated in Chart 1. There have been several studies comparing the characteristics of lung cancer in men and women as a function of smoking history: in one study of 2668 newly diagnosed patients with lung cancer, there were 134 cases among nonsmokers, 37 of 1919 (1.9%) in men and 97 of 749 (13%) in women (33). Adenocarcinoma was relatively more common among the patients who were nonsmokers, and especially among the nonsmoking women.

Prevention

Health maintenance programs should focus on preventable exposure to substances thought to be etiological in lung cancer. Although industrial exposure to asbestos, chromium, nickel, and polycyclic hydrocarbons is dangerous, together these hazards represent only a small fraction of the hazard associated with smoking. However, when present, such exposures seem to augment the hazards of smoking in the causation of lung neoplasia.

It has been estimated that between 2.5 and 4 of every 10 smokers will die because of the habit (from cancer, heart, lung disease, etc.) (56). Most habitual smoking begins in the teen years, apparently under the influence of peer social pressure. In describing the stages in the natural history of smoking (starting, continuing, stopping, resuming), Lichtenstein (46) pointed out that curiosity, rebelliousness, social pressure, confidence, and availability are recognizable factors in the initiation process. It should not be surprising that in the farmland of tobacco-pro-ducting states children often begin to smoke "behind the barn" when they are 9 to 11 years old. More surprising, perhaps, is the fact that parents even in urban areas will in many instances purchase cigarettes for their children. Some success has been achieved in delaying the onset of smoking by teaching children to resist peer pressure. Physicians are rarely involved in these programs; the opportunities lie with teachers, health educators, and voluntary societies (American Cancer Society, Lung Association) which make effective use of the mass media for this important purpose.

About one-third of adults in the United States are regular smokers. The need for effective means to facilitate cessation of smoking is receiving increasing attention, particularly since it can now be stated that the carcinogenic and cardiac risk factors are profoundly influenced by sustained abstinence (29). Epithelial injury and squamous metaplasia-dysplasia are reversible events. Nonetheless, it should be recognized that most smokers who stop do so on their own; intervention programs have not had a high rate of success, the rates of dropout and recidivism being very high. Since most "quit smoking" programs have only 6 to 12 months of follow-up, and they rely on self-reporting systems, it is difficult to arrive at a meaningful figure for the rate of success, although it may be no better than 20% in the traditional larger programs. Some transitional strategies have been thought to be helpful as treatment adjuncts, particularly when encouraged by physicians and the media and when part of more comprehensive programs. Low-tar cigarettes, and more recently nicotine chewing gum, have been recommended to lessen the degree of exposure (to carcinogens, not to carbon monoxide) and deal directly with the physiological dependence on nicotine, and to some extent with the need for oral gratification. (Some 10% of heavy smokers may become dependent on the gum, and it is thus not advised for those who are pregnant or who have peptic ulcers or cardiovascular disease.) Recent information, however, indicates that low-tar cigarettes do not in fact have the desired effect of lessening carcinogenic exposure for the smoker (see "Carcinogenesis"). Failure to develop a strategy for coping with psychological dependence is still a deficiency of all but the most professionally operated programs. The success rates of various types of smoking cessation methods are summarized in Table 6; the factors which determine success have been thoroughly reviewed by Shipley and Orleans (63). Well over 90% of physicians agree that it is their responsibility to set a good example for patients by not smoking cigarettes, and as a group they have had good success in smoking cessation. Yet two-thirds of smokers (>70% in the case of young women) say that their personal physician had not advised them about the dangers of smoking (59). Since physician advice can be quite effective when it is given, clearly there is much room for improvement here.

Early Detection Screening

Given the magnitude of the problem of lung cancer, it is tempting to think in terms of large screening programs to facilitate early detection of tumors while they are surgically curable. In designing such programs, however, it is essential to consider costs, feasibility, acceptability, and potential benefit. For all practical purposes, the only diagnostic techniques susceptible to mass screening are chest X-rays and sputum cytology. Since both are expensive, they could at best be applied to high-risk
SMOKING AND LUNG CANCER

Table 6
Smoking cessation methods: initial and long-term results*

<table>
<thead>
<tr>
<th>Treatment modality</th>
<th>Abstinence (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>After 1 yr</td>
</tr>
<tr>
<td>Quitting on one's own</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without any outside help</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With self-help programs (mail, phone)</td>
<td>67</td>
<td>16-20</td>
</tr>
<tr>
<td>Mass media and community programs</td>
<td>20-40</td>
<td>16 (8-15 mo)</td>
</tr>
<tr>
<td>Television clinics</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Community media campaigns</td>
<td>5-9</td>
<td></td>
</tr>
<tr>
<td>Physician advice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phrenics</td>
<td>5-10</td>
<td></td>
</tr>
<tr>
<td>Chronic respiratory illness or at risk for coronary heart disease</td>
<td>20-30</td>
<td></td>
</tr>
<tr>
<td>Post-myocardial infarct</td>
<td></td>
<td>50-60</td>
</tr>
<tr>
<td>Quit clinics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voluntary health organizations (5-day plans, ACS, ALA, AHF)</td>
<td>60</td>
<td>16-22</td>
</tr>
<tr>
<td>Commercial quit clinics (Smokenders, Schick, Smokewatchers)</td>
<td>70</td>
<td>35-40 (7)</td>
</tr>
<tr>
<td>Medical sector clinics (Kaiser, Toronto Health Department)</td>
<td>62</td>
<td>42</td>
</tr>
<tr>
<td>Majority psychological/behavioral treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypnosis, behavior modification, psychotherapy</td>
<td>20-30</td>
<td></td>
</tr>
<tr>
<td>Abstinent participants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All participants</td>
<td>15-25</td>
<td></td>
</tr>
<tr>
<td>Promising behavioral approaches</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid smoking plus</td>
<td>70-100</td>
<td>40 (6 mo)</td>
</tr>
<tr>
<td>Normal-paced smoking plus</td>
<td>60</td>
<td>30 (6 mo)</td>
</tr>
<tr>
<td>Smoke-holding/rapid puffing plus</td>
<td>70</td>
<td>50 (3-6 mo)</td>
</tr>
<tr>
<td>Broad spectrum with smoke aversion</td>
<td>70-100</td>
<td>30-40 (6 mo)</td>
</tr>
</tbody>
</table>

* Source: C. S. Orleans (52).


categories, according to the World Health Organization classification system (Table 7). However, more than 95% fall into the 4 major types of epidermoid or squamous, small (oat) cell, adenocarcinoma, and large cell carcinoma. Although the relative frequency of these types varies considerably at different reporting centers, the proportion of epidermoid cancers is about 35 to 40% of the total, adenocarcinomas make up about 30% (20% small cell and 10% large cell). Although large and small cell cancers occur in similar proportions in males and females, adenocarcinoma is relatively more prevalent in females, while squamous cell cancers are more prevalent in males. Regardless of histological type, the staging of lung cancer is virtually identical in females and in males, with 23% in females and 22% in males being localized and 51% (in both) presenting with distant disease.*

Clinical evaluation of a patient suspected of having lung cancer can be time consuming and expensive; thus, it may be useful to emphasize some of the basic principles so that undue delay and expense are held to a minimum. Writing about this subject, Koh and Prout (37) begin with the observation that "the pragmatic and efficient approach to treating lung cancer starts with a healthy respect for the dismal natural history of the disease." Part of this grim history is the low overall 5-year survival (5 to 8%). Life expectancy for patients with inoperable disease is only 3 to 9 months, depending on extent of disease and performance status (31, 40), and one-third of patients who have curative resection will have evidence of residual or distant disease within 1 month after surgery. Expected survival is related to extent of disease at the time of presentation, and more than 80% of
patients present with Stage III disease, based on unfavorable characteristics of the local tumor (T3), mediastinal node involvement (N1), or distant metastases (M1). Although women with localized disease may have slightly greater survival rates than do men with localized disease, survival when there is distant disease at the time of presentation is identical for men and women, 50% being dead by 6 months (Chart 6). This type of information dictates that a tissue diagnosis and assessment for operability should be obtained expeditiously.

A node biopsy is generally recommended as the initial procedure for patients with abnormal chest X-rays and palpable supraclavicular nodes. This procedure carries with it minimal morbidity, serves to establish a positive diagnosis in over 80% of patients, and excludes resectability of the lung lesion. Thoracentesis and cytological examination of pleural effusions can establish a diagnosis of cancer in 50% of cases and, when combined with Cope needle biopsy, can yield a diagnosis of cancer in 90% of patients. When there is no obvious metastatic lesion to biopsy, as in asymptomatic patients, a series of 5 outpatient early morning sputum cytologies will often establish the diagnosis. In expert hands, the accuracy of cytological diagnosis from sputum is just about as high as with fixed tissue sections. Bronchoscopy with brushings, biopsy, and washings yields a diagnosis in about 80% of patients who do not have peripheral tumors. Percutaneous transthoracic needle biopsy under radiological monitoring is being increasingly used as a definitive procedure for diagnosing a lung mass, although some morbidity, such as pneumothorax, is seen in about 25% of patients (60).

Evaluation of extent of disease (staging) and operability should go on simultaneously. Discussion of the value of various types of X-rays and scans (brain, bone, liver) is beyond the scope of this article, but these have been reviewed recently (37). In a VA cooperative group study of more than 5000 patients who had inoperable lung cancer (all histological types), there were 3 major prognostic factors, initial Karnofsky performance status, extent of disease, and weight loss during the previous 6 months (67). At least performance status and a history of weight loss are easy and inexpensive to obtain. Indeed, Feinstein (13) pointed out earlier that of all the tests that we use, the clinical symptoms relating to lung cancer may be the best prognosticator, the longest survival being obtained in asymptomatic individuals. In addition, patients who truly have Stage I lesions [tumor-nodes-metastases (TNM) classes of T1N0M0, T1N1M0, T1N1M1, and T2N0M0] currently have an expected 5-year survival of around 70% with surgical resection alone. There are occasional recurrences even after 5 years, but as far as we know, none after 10 years. Indeed, meticulous sampling of hilar and mediastinal nodes identified a series of pathological Stage I cancers in whom the 5-year survival was 90% (49).

Overall treatment options and therapeutic results have been reviewed succinctly recently (12). Some 60% of patients (all histological types) staged as having localized cancer are operated upon as the primary treatment (41). Many patients are explored with the intent of curative resection but are found to be irresectable; others have the lung removed but are discovered to have regional spread. For the latter group, it seems instinctively reasonable to use adjuvant chemotherapy after the bulk of the tumor has been removed, but unfortunately, this has not been found to be effective and only adds immediate morbidity to what for a time would be a life of good quality (62). Perhaps this lack of success should not be surprising, given the paucity of drugs capable of causing biologically meaningful remissions in the measurable lesions of lung cancer (other than small cell cancer).

Because it is rare that complete remissions can be achieved with the use of individual drugs, there have been many attempts at using drug combinations, even at very high doses with autologous marrow rescue. From time to time, considerable enthusiasm has arisen for various combinations and schedules of chemotherapy because partial tumor regressions can be obtained with these, but it is unfortunately the case that survival has not been prolonged with chemotherapy. Nonetheless, this continues to be a very important area for research since we have yet to find potent or relatively selective agents. The sole exception to this state of affairs is in chemotherapy for small cell (or oat cell) cancer of limited extent, where good (partial plus complete) remissions can be achieved regularly (80 to 90%) by the use of multiple drugs given during the initial course of therapy, often in conjunction with radiation. Chemotherapy has resulted in prolongation of survival, most notably for those patients whose disease is localized to the chest; lasting remissions are much less frequent in patients with extensive disease. Ironically, however, the overall survival of untreated patients with small cell cancer is so poor that chemotherapy only lengthens it to approximately the same level seen with other histological forms of lung cancer.

Although there are some long-term survivors (5 to 10%) and even rare cures, the disease usually recurs, and it is unlikely that a second remission would be obtained after additional chemotherapy, even with drugs that were not used during the initial induction therapy. A great deal of current research is aimed at enriching the important fraction of long-term survivors by the use of radiation therapy, very-high-dose chemotherapy, and other therapeutic maneuvers.

Radiation therapy is the other mainstay of lung cancer therapy. There is no doubt that it is an important means for palliating troublesome problems such as bronchial, superior venal caval, or nervous system compression; pulmonary bleeding; or pain from bone involvement. There is doubt (at least in the mind of this reviewer) that it contributes in a major way to prolongation...
SMOKING AND LUNG CANCER

of survival when it is used as definitive primary therapy. Kjaer (36) has published a thorough review of the literature on this subject. Whether radiotherapy treatment prolongs life is a question that may be debated, but the data seem to indicate that, if survival is enhanced, the effect is only modest (although perhaps not insignificant, given the large numbers of patients affected).

Immunotherapy has been used for the treatment of lung cancer with at least some enthusiasm. Initial studies involving the post-operative intrapleural administration of Bacillus Calmette-Guerin were highly encouraging. However, controlled studies have not substantiated the benefit of this approach. The concept of enhanced immune killing is still attractive in principle, particularly following surgical resection, and there are numerous new immunomodulating agents for this purpose, but they have yet to be studied.

Conclusion

Overall 5-year survival figures for patients with lung cancer are not only among the lowest for any type of cancer, but also these have not improved appreciably over the past 2 to 3 decades despite new techniques of surgery, chemotherapy, and radiation therapy. We conclude that prevention remains the most promising approach. Yet the larger smoking prevention and cessation programs have had only limited success to date. There are highly successful cessation programs, but they have not been widely accessible to American smokers. Ineffective health education of young people, peer pressure, tobacco availability, and psychological dependence are all parts of the problem. Health professionals could become much more effective by becoming increasingly active as health educators.

Early detection, while intuitively appealing, has not yet been proven effective in reducing mortality from lung cancer, even in high-risk populations. The studies to date have not focused on women who are smokers. Cost-effective clinical evaluation of patients suspected of having lung cancer can be achieved with prompt cytological diagnosis (node biopsy, sputum, needle biopsy) and an expeditious search for causes of inoperability.

With regard to treatment techniques, true Stage I lung cancers (non-small cell type) are potentially curable with surgical resection. The use of adjuvant chemotherapy to treat patients with residual microscopic disease has thus far been unsuccessful. Combination chemotherapy can produce remissions in the majority of patients with small cell cancer and yields some long-term survivors (5 to 10%), but only up to the level of the other common histological types. Combination chemotherapy may cause transient tumor regressions in a non-small cell cancer. However, survival advantage has never been demonstrated, and very aggressive treatment with currently available drugs may even be counterproductive. Radiation therapy can be a useful adjunct in treatment of patients with small cell cancer (involved field, brain prophylaxis). Radiation therapy is useful in palliation (compression, pain, etc.) of patients with various types of lung cancer, but the benefits of radiation as primary therapy for prolonging survival have not been convincingly demonstrated.

More effective prevention, early detection, and treatment are of tremendous public health importance in the United States. Whether there are unique biological features in women with lung cancer remains to be determined. Since efforts at early detection and treatment have failed to substantially reduce lung cancer mortality, we conclude that primary prevention through control of cigarette smoking represents the major hope for a disease of great health and economic consequences.

THE ECONOMICS OF SMOKING AND LUNG CANCER

Introduction

In an era of high and rapidly escalating health care costs, an inevitable dimension of concern with a disease is its economic impact. In 1983, Americans spent over $350 billion on health care, in excess of $1500 per man, woman, and child. The typical American had to work more than a month simply to pay for health care, to cover the insurance premiums, out-of-pocket payments, and taxes that finance our health care system. These costs do not reflect the productivity losses associated with disease that are also borne by the society. Cancer, our nation's most feared disease, ranks third behind diseases of the circulatory system and injuries as the major contributors to the total cost of illness. Accounting for some 25% of all cancers, lung cancer alone commands a significant share of the nation's health resources.

Because they are avoidable by modification of life-style, the costs of behavior-related diseases are of particular interest to the health policy community. The implicit logic in analyzing the costs of such illnesses is that these costs can be prevented and thereby represent savings to the society. The argument is that disease prevention and health promotion can serve as significant mechanisms for containing health care costs. This is the rationale underlying much of the current "promotion of health promotion." As we shall see, however, the contemporary view of disease prevention qua cost containment is imperfect.

Cigarette smoking has been preeminent among the unhealthy behaviors subjected to economic scrutiny. The costs of smoking-related disease have been the subject of at least a dozen studies dating from 1968. The interests of the analysts have varied widely and in some instances there have been logically incomparable. Nevertheless, there is enough uniformity in basic methodological approaches to draw some confident qualitative conclusions, and the best of the studies provide reasonable quantitative estimates of the kinds of costs the analysts have been investigating. On the question of the total social costs of smoking-related illness, for example, the most recent and thorough estimate of annual health care costs and productivity losses associated with smoking places the figure at $42.2 billion in 1980 dollars. An earlier, frequently cited study estimated the cost in 1976 dollars to be $27.54 billion (47), a figure that translates roughly to $40 billion in 1980 dollars. Working from this earlier study, Kristein (39) recently estimated the aggregate annual medical costs and productivity losses at $47.59 billion, also in 1980 dollars. In 1984 dollars, these figures translate into a cost of from $55 to $60 billion.

The consistency of these estimates should not be interpreted

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as implying a definitive answer to the question, "How much does smoking-related disease cost our society?" These studies share a commitment to "human capital" evaluation of the indirect costs of smoking-related illness and to the same basic methodology originally applied by Rice (58) and recently explicated by Hodgson (22). In essence, the human capital method values the indirect, or nonmedical, costs as the productivity losses attributable to the morbidity and premature mortality produced by the relevant illnesses. The technique is a conceptually sound approach to valuing livelihood; it does not, however, estimate the value of life, as it has so often been misinterpreted. As a result, it fails to account for certain important costs. Most notable are the difficult (or impossible) to quantify costs of the pain and suffering of the immediate victims of disease and their friends and families. No cost estimation technique adequately accounts for these costs; most ignore them altogether, at best acknowledging them qualitatively but leaving them out of any formal quantitative analysis. Yet as Abt (1) has demonstrated, a reasonable case can be made that, could they be quantified, these costs might exceed considerably those which are readily and commonly estimated. Abt suggested that in the case of cancer, the true social costs might be an order of magnitude greater than the costs that are generally measured.

This significant limitation in COI estimation is not the only one. Both quantifiable direct and indirect costs are commonly ignored in COI studies, due in part to the difficulty (or cost) of identifying and quantifying them and in part to the belief that they are not quantitatively important in the overall picture. Examples include the costs of home modification for a disabled victim of an illness and the time and other costs of family members' provision of care.

Social Costs of Smoking-induced Lung Cancer

Within the past year, 2 studies have emerged that have examined the costs of smoking-induced lung cancer directly. Rice and Hodgson's analysis of the economic costs of smoking-related disease uses an assessment of the total economic cost of illness combined with attributable risk methodology. From this work and their recent work on the costs of cancer, it is possible to construct an estimate of the cost of smoking-induced lung cancer in 1980. Medical expenditures on all lung cancers in men totaled $1.003 billion that year, with $595 million spent on care of women with lung cancer. Rice and Hodgson estimate the portion of male lung cancer attributable to smoking at 76.5% and that of female lung cancer at 45.5%. Thus, medical expenditures on smoking-induced lung cancers are estimated at $1.038 billion. The productivity losses attributed to smoking-induced lung cancer deaths are valued at $5.876 billion. A proportionate share of the total morbidity cost implies some $446 million. Thus, the total economic cost of smoking-induced lung cancer is estimated at $7.36 billion, or better than 17% of the entire cost of smoking-related illness. In 1984 dollars, this cost would be about $10 billion. As we discuss below, these figures may considerably underestimate the true economic costs.

Manipulation of the data provided by Rice and Hodgson permits estimation of the costs of smoking-induced lung cancer in women, and in working-age women alone. We complete that exercise here but alert the reader at the outset that, immediately following the estimates, we will discuss reasons that we believe these figures represent a substantial underestimation of today's true economic costs of smoking-induced lung cancer in women.

As noted above, 1980 medical expenditures on women with lung cancer totaled $595 million. If the attributable risk fraction of 0.455 is applied to this figure, medical expenditures on smoking-induced lung cancers in women were $270.73 million. Rice and Hodgson estimated the productivity losses associated with the deaths of these female victims at $1.329 billion. (It is standard practice in COI studies to impute dollar values to unpaid labor. The most common imputed value is for the household services of women in their own homes [22].) If the morbidity productivity losses represent a similar share, they totaled $76.44 million. All told, the economic costs of smoking-induced lung cancer in women are estimated at $1.68 billion ($2.2 billion in 1984 dollars), just under a quarter of the total costs of smoking-induced lung cancer. The reasons that the female share of the total is relatively small are: (a) the smaller number of women contracting lung cancer; (b) the lower attributable risk fraction; and (c) the fact that, as measured by wage rates, women's labor is valued less than men's in today's labor market.

The vast majority of the economic loss attributable to smoking-induced lung cancer in women in 1980 was associated with the illness and deaths of relatively young women. Three-quarters of 1980 medical expenditures on female victims of lung cancer were for women under the age of 65. In the case of smoking-induced cancer, this amounts to $200 million. By contrast, only 55% of expenditures on lung cancer care for men is for men under 65. Since productivity losses result predominantly from the illness and deaths of people under the age of 65, we (arbitrarily) credit 95% of the mortality and morbidity costs to the women under age 65. Thus, we estimate the 1980 productivity losses of women under 65 at $1.335 billion. This gives total economic costs of smoking-induced lung cancer in these women of $1.536 billion ($2 billion in 1984 dollars), better than 90% of the total for all women. Thus, in 1980, the costs of smoking-induced lung cancer in women under age 65 alone constituted better than 3.6% of the total economic costs of smoking-related disease.

Above, we suggested that calculations such as these considerably underestimate today's true economic costs of smoking-induced lung cancer in women. The principal reason is the major deficiency in COI studies. No accounting is made for the nonquantifiable but undeniably large costs of pain and suffering. A second and straightforward reason is the inflation that has occurred since 1980. Between 1980 and 1984, the general price level has risen by close to 30%, and medical prices have increased even more. The impact of inflation was illustrated above in several instances in which we translated 1980 cost estimates into their approximate 1984 dollar value.

Each of these arguments applies to the cost of lung cancer in men as well. Two additional factors, however, apply uniquely to the case of women. The first, as noted under "Epidemiology," is that the rate of lung cancer in women has been rising exceptionally rapidly. Thus, estimates based on the Rice and Hodgson analysis would underestimate today's costs by a substantial fraction simply due to the increase in the number of lung cancer deaths.

The second factor applying uniquely to women is the probable gross underestimation of attributable risk. All of the data on which estimates of attributable risk are based date from several decades ago. Men's smoking patterns had arrived at a plateau...
of illness. Smoking ultimately consumes a significant share of the fairly substantial percentage, the qualitative message is unaltered: smoking contributes a substantial share of the total costs of smoking-induced illness and the costs associated with them will have to be increased by one-third.

Consideration of all of these factors together demonstrates the limitations of a specific COI estimate. All COI figures underestimate the true costs of illness by omitting the social costs of pain and suffering. Further, any single-year estimate necessarily fails to portray the situation in later (or earlier) years; i.e., to represent the measurable costs of a disease problem at present, earlier estimates must be updated to reflect inflation and changes in prevalence, at minimum. In the instance of the measurable costs of smoking-induced lung cancer in women, for example, to characterize the current situation, one would have to increase the figures derived from Rice and Hodgson's work by more than 100%.

Having demonstrated the rather ephemeral quality of COI estimates, we should emphasize a sturdier characteristic. Whether an estimate is off by 10, 50, or even 150%, a solid COI calculation does provide a good "ballpark" estimate, lending context, perhaps best characterized as qualitative, to a discussion of the social consequences of a disease or behavior. In the present instance, the cost-of-smoking literature tells us that we are dealing with a substantial economic issue as well as a major health problem. In the United States, the COI figure places smoking's adverse economic consequences at an amount larger than the direct value of the cigarettes sold (about $23 billion in 1980). Thus, the health outcomes of smoking can be thought of as an "industry" larger than the cigarette business itself. A full accounting of the latter would include the indirect economic contribution of cigarette sales, bringing the total value of cigarette production and distribution to some $58 billion (82). This contribution to the gross national product, however, could be realized if the same resources were devoted to alternative uses. The costs of smoking-induced illness include many irreplaceable resources.

Another more common and perhaps more meaningful perspective on the economic costs of smoking-related disease is that these account for 8.6% of the total national costs of illness. Looking only at direct expenditures, smoking-related health care consumes 75 cents of every $1 spent on medical services. Again, even if the estimates of the costs of smoking are off by a fairly substantial percentage, the qualitative message is unaltered: smoking ultimately consumes a significant share of the resources this nation devotes to health care. Smoking-induced lung cancer, the portion of a single cancer attributable to a single behavior, alone is responsible for 1.5% of the total national cost of illness.

**Individual Costs of Smoking-induced Lung Cancer**

Each year, the number of new cases of lung cancer exceeds the number of deaths by about 10 to 20%, and many of the new cases are included among the deaths. Assuming 80,000 smoking-induced new lung cancer cases a year, and if, again arbitrarily, one-third of the new cases died during the same year, this would mean a prevalence during the year of about 122,500 cases of smoking-induced lung cancers. Dividing this total into the total social cost of $7.36 billion implies an average economic burden of some $60,000 per case. The 1980 medical expenditures per case would have totaled some $8,500; therefore, the bulk of the cost is in lost productivity, and primarily in losses due to mortality. A similar analysis for women translates into an average burden of $73,000, including $61,000 in productivity losses and $12,000 in medical expenditures. The larger figures for women probably reflect the younger age distribution of female victims of lung cancer.

The above figures constitute crude estimates of the cost per victim. Oster et al. (54) offer a different perspective in a recent study in which they translate risks of smoking-related illnesses into expected values of lifetime costs. They categorize smokers by age, sex, and extent of smoking habit (light smoking defined as less than 1 pack/day, moderate as 1 to 2 packs, and heavy as more than 2). Each figure in the resultant table gives the expected value of the costs of a given smoking-related disease: lung cancer, coronary heart disease, or emphysema. The value represents the lifetime health care costs and productivity losses associated with the relevant disease, multiplied by the probability that the smoker will contract the illness. For lung cancer, costs range from a high of $9055 (in 1980 dollars) for a male heavy smoker 40 to 44 years of age to a low of $210 for a female light smoker 75 to 79 years of age.

In all age-smoking-status categories, women have lower expected costs than men, reflecting the lower wage rates paid to women and the lower attributable risk factor for lung cancer. As with Rice and Hodgson, Oster et al. rely on the available but old data to estimate attributable risk. Their figure for men (82.8%) is somewhat higher than Rice and Hodgson's and, we believe, more reasonable. Their figure for women (43.1%), however, is slightly lower. The calculations of Oster et al. of expected costs for women go as high as $3078 for the 40- to 44-year-old heavy smoker. For heavy smokers under the age of 65, costs range from $2142 to $3078 (compared with $4391 to $9055 for men). For moderate women smokers under 65, costs range from $1399 to $2011 ($3450 to $7114 for men). For light smokers, the range is $685 to $985 ($2025 to $4175 for men).

The study by Oster et al. is unique in "personalizing" the economic risk of smoking. The study seems to be directed at convincing people that one reason they should quit smoking, or never start, is that smoking may ultimately prove quite costly to them in terms of the medical costs they will experience and the earnings they will not realize. Adding in heart disease and chronic obstructive lung disease, these costs reach a maximum of $61,304 for 35- to 39-year-old male heavy smokers. Nevertheless, the reality is that most of these costs are quite impersonal; they will not be borne by the individual smoker. In the United States, most of the medical care costs will be paid by third-party insurers, both private and public (especially Medicare). The productivity losses have an air of unreality in that the vast majority
of them, mortality losses, will be "experienced" by the disease victim only after he or she is deceased. For the individual with a family, these potential losses do have some meaning, but certainly not a value comparable to their totals, since life insurance will "defray" some of the losses within the family and social programs will replace others. In short, the costs are real and will be experienced by the society, but except for a small fraction of them, their personal relevance is missing. The most individually meaningful cost of smoking is the $10,000 to $20,000 the average smoker can expect to spend buying cigarettes over a lifetime of smoking. Ultimately, this concern may be replaced by another individually relevant economic concern, as employers increasingly restrict hiring to nonsmokers. In short, it is the tangible pocketbook costs of smoking that matter most to smokers. By comparison, the costs of lung cancer are quite abstract.

Costs of Smoking-induced Lung Cancer: Other Perspectives

Thus far, we have examined the costs of smoking-related lung cancer from the social and individual perspectives. As we just suggested, the costs have an abstract quality to them. They are real, but in their diffuseness they lack the kind of urgency that their simple magnitudes might suggest. From at least 3 other viewpoints, however, the costs of smoking-related disease may seem more tangible, more relevant to self-interested decision making. These perspectives are those of businesses, government, and private insurance companies. To the extent that illness imposes economic burdens directly on these organizations, they will have economic incentives to pay attention.

Perhaps the most obvious of these is government, for with so much smoking-related illness occurring in senior citizens, Medicare bears the financial burden of much smoking-related health care in the United States. This has been recognized recently in a recommendation by the Advisory Commission on Social Security that cigarette excise taxes be raised and revenues earmarked for the Medicare trust fund. To date, the scholarly literature includes no analyses of which we are aware that examine the costs of smoking-related illness to government. Simple manipulation of cost of cancer data permits a rough estimate of the financial implications of smoking-induced lung cancer for Medicare. The National Center for Health Statistics data show just over $600 million having been spent on medical care for lung cancer victims in 1980 (excluding nursing home care). If smoking-induced cancer accounts for 75% of this total, the federal government will bear the major share of a $450 million health care bill. It seems likely that the government’s share will equal at least two-thirds of this, or $300 million.

Is this enough money to warrant governmental concern? Three hundred million dollars is only a small fraction of government expenditures for health care, but in an environment of budgetary duress one might think that 9-digit figures would merit attention. Unfortunately, the existence of a large health care bill need not translate into the prospect for a substantial financial savings, even if the specific health problem in question can be overcome. We will discuss this most important point in the next section of the paper. Before turning to business’s interest, however, we note in passing that government has interests that extend beyond liability for health-care costs including, for example, the lost tax revenues associated with lost productivity.

Business is an obvious focal point for interest in the costs of smoking. Recently, Kristein (39) has produced an analysis of the costs of smoking to business and the short-run benefits of employees’ giving up smoking. Reviewing smoking’s impact on the major cost centers in a business, including health, life, and disability insurance, absenteeism, productivity, occupational health, and passive smoking by nonsmoking employees, Kristein concludes that smoking costs employers between $336 and $501 in 1980 dollars. The analysis finesses an issue discussed in the next section of this paper.

Unfortunately, Kristein’s article does not lend itself readily to a disease-specific assessment of the costs of smoking. In an introductory table on the total economic costs of smoking, based on Luce and Schweitzer’s (47) work, Kristein estimates the social cost of smoking-related neoplasms at 16% of the total. If lung cancers account for three-quarters of the neoplasms and are representative in terms of their costs, then roughly 12% of smoking’s social costs are attributable to lung cancer. (This figure compares with our estimate, deriving from the Rice and Hodgson analysis, that lung cancers account for 17% of the total costs of smoking.) If, further, lung cancer bears responsibility for a proportionate share of the costs of smoking to employers, Kristein’s figures imply a lung-cancer-only annual cost of $40 to $72 per smoker. This crude calculation should be interpreted only as providing a qualitative impression of the economic burden that smoking imposes on employers.

Assessment of the role that smoking-induced lung cancers will play in the costs of health insurance should be a fairly straightforward matter. It seems implausible that these costs have not been examined, but we are not familiar with relevant analyses in the scholarly literature.

Gross versus Net Cost

In the contemporary political and economic environment, assessment of the costs of smoking-related illness has 2 purposes. One is a genuine desire to understand the economic dimension of the social consequences of cigarette smoking. The other is a political motivation. Proponents of the nonsmoking cause want dramatic cost figures to persuade legislators and the public that smoking is exacting too great a price to be tolerated.

Conceptually these purposes are wholly separable; in practice, the line distinguishing them occasionally is crossed. The latter seems to be particularly true in the current effort to encourage businesses to adopt smoking prevention and other health promotion programs. Many proponents of health promotion predicate their advocacy on the notion that the program in question will save money for the business. That is, the health promotion effort can be viewed as any other business investment, where the financial bottom line is the critical deciding variable.

Presentation of the aggregate social costs of smoking-related illness, as done in this paper, often implies a similar theme; namely, smoking is economically burdensome to our society and its reduction would be economically beneficial. The former can be true at the same time that the latter is not. The reduction of smoking undoubtedly would benefit the society (or individual business) in many dimensions, including many economic dimensions. The costs of diseases like lung cancer would fall over time, business productivity would increase, and so forth. But the very success of a smoking prevention effort would contribute to new social costs in the future. Specifically, a significant reduction
in the prevalence of smoking could add many tens of thousands
of the elderly population, thereby creating need for expanded
social support programs. Both businesses and government
would have to deal with the additional retirement support needs
of this group, through pension programs and Social Security,
and the substantial medical care needs of the elderly would
impose additional burdens on health care insurance budgets,
again private and public.

The magnitude of such later costs has only recently become
the subject of analysis. Gori and Richter (16) introduced the issue
in an article entitled, "The Macroeconomics of Disease Prevention
in the United States." Leu and Schaub (42) recently com-
pared the magnitude of national health care costs in the actual
Swiss economy since the late 1800s with that which would have
accrued in the total absence of smoking. Although their study
must be regarded as a preliminary attempt to resolve the quan-
titative issue, Leu and Schaub arrive at a conclusion that is
probably qualitatively sound and important. Total health care
costs in the nonsmoking society are not very different from those
of the smoking society. There is one critical difference between
the societies, however. There are more people, living longer and
healthier lives, in the nonsmoking society. Thus, measured solely
in terms of health care costs, reduction in smoking may not
prove to be cost-saving in the aggregate, although it may rep-
resent a cost-effective means of improving health.

Kristein (39) criticizes the Gori-Richter/Leu-Schaub view of the
matter as Malthusian, ignoring a variety of possible responses
of a society to its population's aging. Nevertheless, the funda-
mental point cannot and should not be ignored. We should look
to disease prevention/health promotion efforts as a means of
improving the quality of life, rather than necessarily as reducing
its cost.

Conclusion

The measurable costs of cigarette smoking total well in excess
of $80 billion per year. Smokers spend some $27 billion on
cigarettes, and the rest, $55 to $60 billion, reflects society's
medical care costs and productivity losses attributable to smok-
ing-induced disease.

Lung cancer induced by smoking imposes a substantial cost
on our society, the largest portion of which cannot be measured
in dollars and cents, the pain and suffering of cancer victims and
their friends and loved ones. The economic costs traditionally
evaluated, the direct costs of medical care and indirect costs
associated with productivity losses, constitute the major share
of the measurable costs but not all of them. Such costs as the
modification of patients' living environments and the provision of
(unpaid) care by family members (sometimes associated with the
loss of earned income) are not included. Limitations such as
these emphasize the qualitative nature of quantitative estimates
of the economic costs of illness. Smoking-induced lung cancer,
these studies tell us, is expensive. It exacts an enormous toll in
the utilization of resources that we would prefer to be devoting
to scores of alternative uses. Its measurable costs are in the
vicinity of 10 billion dollars annually, and its unmeasured costs
may well equal or exceed this amount.

The economic costs of smoking-induced lung cancer in women
are rising particularly rapidly as the epidemic of women's lung
cancer grows and as women's wages rise in the marketplace. A
disproportionate number of female lung cancer victims are under
65 years of age (compared with male victims), so the economic
burden of smoking escalates even more rapidly as the market
begins to value women's and men's labor on a more equal
footing.

The economic benefit to be derived from reductions in smok-
ing-induced lung cancer is not simply the opposite side of the
cost record. Cessation of smoking will diminish the quitter's risk
of lung cancer, but years will have to pass before the quitter's
risk approaches that of the never-smoker. Thus, for several
years, smoking-induced lung cancer will continue to exact a toll
even from the population of quitters. Furthermore, the very
success of smoking prevention efforts will result in new economic
costs to support the people who will live longer lives as a result
of their decisions to quit smoking or not to start in the first place.
The abolition of smoking-induced lung cancer might not save
this nation $10 billion in resources each year. It would, however,
create the enviable situation of redirecting those resources from
caring for the ravaged victims of cancer to enhancing the quality
of life for tens of thousands of "new" senior citizens.

How can a reduction in smoking-induced lung cancer be
achieved? A general discussion of smoking-control policies lies
outside the boundaries of this article. Nevertheless, it seems
appropriate in an examination of the economics of smoking-
induced lung cancer to note that there is a wide variety of
economic tools that can reduce smoking and its associated
burden. These range from society-wide restrictions on the pro-
motion of cigarettes (a $1.5 billion per year enterprise) to com-
pany-specific weekly salary bonuses for nonsmoking employees
(81).

Perhaps the most accessible social tool is the raising of
cigarette excise taxes, cigarette-specific taxes levied by the
federal government, taxes in all of the states, and scores of local
units of government. Research demonstrates that, by raising
prices, taxes discourage cigarette consumption. This effect is
particularly strong among teenagers, whose smoking initiation
decisions will define adult smoking prevalence patterns 10 to 20
years later. Also encouraging is the finding that the principal
response to price increases involves the decision not to smoke,
rather than a reduction in the daily consumption of continuing
smokers (44, 45). Taxation has the added virtue of being an
instance in which government can do well by doing good, be-
cause accompanying decreases in smoking will be increases in
tax revenues.

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SMOKING AND LUNG CANCER


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