The Changing Epidemiology of Smoking and Lung Cancer Histology

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In 1950, the first large-scale epidemiological studies demonstrated that lung cancer is causatively associated with cigarette smoking, a finding subsequently confirmed by the Royal College of Physicians in London, the U.S. Surgeon General, and the World Health Organization. Although cigarette consumption has gradually decreased in the United States from a high of about 3800 cigarettes per adult per year in 1965 to about 2800 cigarettes in 1993, death from lung cancer has reached a high among males at the rate of 74.9/100,000/year and among females at the rate of 28.5. However, in the younger cohorts, the lung cancer death rate is decreasing in both men and women. In this overview we discuss the steeper increase during recent decades of lung adenocarcinoma incidence compared with squamous cell carcinoma of the lung. In 1950, the ratio of these two major types of lung cancer in males was about 1:18; today it is about 1:1.2–1.4. This overview discusses two concepts that are regarded as contributors to this change in the histological types of lung cancer. One factor is the decrease in average nicotine and tar delivery of cigarettes from about 2.7 and 38 mg in 1955 to 1.0 and 13.5 mg in 1993, respectively. Other major factors for the reduced emission of smoke relate to changes in the composition of the cigarette tobacco blend and general acceptance of cigarettes with filter tips; the latter constitute 97% of all cigarettes currently sold. However, smokers of low-yield cigarettes compensate for the low delivery of nicotine by inhaling the smoke more deeply and by smoking more intensely; such smokers may be taking up to 5 puffs/min with puff volumes up to 55 ml. Under these conditions, the peripheral lung is exposed to increased amounts of smoke carcinogens that are suspected to lead to lung adenocarcinoma. Among the important changes in the composition of the tobacco blend of the U.S. cigarette is a significant increase in nitrate content (0.5% to 1.2–1.5%), which raises the yields of nitrogen oxides and N-nitroamines in the smoke. Furthermore, the more intense smoking by the consumers of low-yield cigarettes increases N-nitroamines in the smoke 2–3-fold. Among the N-nitroamines is 4-(methylamino)-1-(3-pyridyl)-1-butanone (NNK), a powerful lung carcinogen in animals that is exclusively formed from nicotine. This organ-specific tobacco-specific nitrosamine (TSNA) induces adenocarcinoma of the lung. All of these factors, the more intense smoking, the deeper inhalation of the smoke, and the increased yields of N-nitroamines in the smoke of low-yield cigarettes, are considered major contributors to the drastic increase in lung adenocarcinoma among cigarette smokers in recent years. This overview also discusses the differences in the major lung cancer types in female compared with male smokers as well as the likely underlying factors for increased lung cancer risk among African Americans compared with that among white Americans. Although the only sure way to prevent smoking-related diseases is growing up the tobacco habit, there must be a measure of protection for those who cannot accomplish this. Therefore, setting upper permissible limits of tar levels for the smoke of U.S. cigarettes, similar to strategies already taken in Western Europe, should be considered. — Environ Health Perspect 103(Suppl 8):143–148 (1995)

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Introduction

The age-adjusted death rate of lung cancer in the United States has more than doubled during the past two decades (1). Although this statistic is well known to public health officials, it masks an important underlying trend in the changing histopathology of lung cancer. Using data from the national Surveillance, Epidemiology and End Results (SEER) Registries, Devesa et al. (2) showed that for a segment accounting for 7% of the U.S. population, the rates of certain histologic types of cancer increased much more rapidly than those of other lung cancer cell types and that these rate increases differed between men and women. From 1969 to 1971 to 1984 to 1986, the incidence of lung adenocarcinoma in the United States increased by 111% in white men and by 151% in black men. In contrast, the rates for squamous cell carcinoma increased by only 25 and 50%, respectively. However, among women, the rates for both adenocarcinoma and squamous cell cancer increased by similar percentages. Adenocarcinoma rates increased by 220% among white women and 221% among black women, and the incidence of squamous cell carcinoma increased by 156 and 209%, respectively.

These changes have also been observed in hospital-based studies. In 1950, the first large-scale case-control study of cigarette smoking and lung cancer in the United States found that adenocarcinoma comprised approximately 5% of lung cancers among men (3). In more recent case-control studies, we reported that 40% of all lung cancer cases had a diagnosis of adenocarcinoma (4). This is well in line with several reports about changes in the ratio of squamous cell carcinoma to adenocarcinoma in male cigarette smokers (5–8).

Although lung cancer is the most common type of cancer in the United States for both men and women, the reasons for these temporal patterns in lung cancer histology remain unknown. Insight into these temporal trends can be gained by examining changes in the composition of cigarette smoke due to product modification as well as changes in smoking habits. While lung
cancer incidence rates have been increasing rapidly, the chemical composition of cigarettes consumed in the United States has changed dramatically. The sales-weighted average tar and nicotine yields of all cigarette types, which are based on standardized machine smoking, have declined approximately 60% over the past several decades (9). Changes in the composition and makeup of U.S. cigarettes have resulted in low-tar and low-nicotine cigarettes. Epidemiological studies have shown that the long-term smoker who smokes filter-tipped cigarettes exclusively has a 30 to 50% reduction of risk for lung cancer (10).

The tar yield of a cigarette reflects many parameters, including the type of tobacco, the porosity of the cigarette paper, and the presence of a filter with or without perforations. Tar is that component of mainstream tobacco smoke that is retained on a glass filter, minus nicotine and minus water (11). Tar contains a number of compounds that are lung carcinogens (12,13). When machine smoked under standard laboratory conditions, U.S. nonfilter cigarettes have tar yields between 16 and 27 mg/cigarette; filter cigarettes have tar yields below 20 mg/cigarette (14).

Although lower tar yields would appear to be less harmful to smokers because of the reduced concentration of mainstream smoke carcinogens, the altered chemical composition of the smoke of low-yield cigarettes may actually have a potentiating effect in terms of the risk of adenocarcinoma. Two ideas have been suggested to explain the more pronounced increase in adenocarcinoma relative to that of squamous cell cancer. One concept suggests that adenocarcinoma of the lung occurs because of the organ-specific, carcinogenic N-nitrosamines formed by nitrosation of nicotine and other minor alkaloids during processing of tobacco and during smoking (15,16). During the past four decades, the sales-weighted average tar and nicotine yields of U.S. cigarettes have decreased from about 38 and 2.7 mg to 13.5 and 1.0 mg, respectively (9). These yields are based on standardized machine smoking conditions of 1 puff/min, a puff volume of 35 ml, and a puff duration of 2 sec (11). However, to satisfy their nicotine dependency, many smokers of low-yield filter cigarettes smoke more intensely, taking up to 5 puffs/min, with a puff volume of up to 55 ml (17–20). When one uses a smoking machine but employs these “human smoking parameters,” the smoke yields increase 2- to 3-fold for tar, nicotine, carbon monoxide, and the carcinogenic tobacco-specific nitrosamine (TSNA) (21–23). In addition, the smoker of low-yield cigarettes has the tendency to inhale more deeply (24). Consequently, the peripheral lung of the smoker of low-yield filter cigarettes is exposed to relatively higher doses of smoke, including polynuclear aromatic hydrocarbons (PAHs) as well as carcinogenic TSNA such as 4-(methylnitrosamo)-1-(3-pyridyl)-1-butanone (NNK); this is of concern because NNK is a systemic carcinogen that induces lung adenocarcinomas in laboratory animals independent of the site of application (25). In further support of the concept of systemic lung carcinogenesis as an important contributor to changes in lung cancer histology, the tobacco blend of U.S. cigarettes has increased in nitrate content from about 0.5 to 1.3–1.5%, causing concomitant higher yields of NNK in the smoke (16). The systemic carcinogen hypothesis holds that more intensive smoking of filter cigarettes and the increased smoke yields of the organ-specific carcinogenic N-nitrosamines, especially that of NNK, are major contributors to the higher incidence of lung adenocarcinoma in smokers, and especially in male smokers. It is also important to note that the percentage of all cigarettes smoked in the United States that were filter-tipped was 19% in 1955, 51% in 1960, 80% in 1970, 92% in 1980, and more than 97% in 1992 (26).

As an alternative or additional explanation, the “airborne carcinogen hypothesis” suggests that the significant reduction in cigarette tar yield that has occurred over the past four decades has caused smokers to draw greater puff volumes (18). With increasing puff volume, smoke particles are inhaled into the lung with greater velocity. This forced inhalation of the smoke aerosol opens the alveoli widely and facilitates the rapid saturation with nicotine (27). The secondary and tertiary bronchi of the lung and the alveolar region also lack the defenses present in the major bronchi (i.e., ciliated epithelium and mucus-secreting cells). Therefore, the peripheral bronchi are less resistant to the toxic and carcinogenic constituents of cigarette smoke. This could be one reason that the rate of adenocarcinoma among women did not increase as steeply as that among men. Clearly, most women who smoke have not been exposed to the same levels and types of habituating agents, toxins, and carcinogens that were emitted by the high-tar, high-nicotine cigarettes of former decades but instead have been exposed to the quantitatively different constituents of the smoke of filter-tipped cigarettes. This concept is supported by the observation that 35.5% of male lung cancer patients who were interviewed during 1977 to 1978 smoked nonfilter cigarettes exclusively, while at that time only 13.3% of the female cases reported use of nonfilter cigarettes. In 1993, these figures were 19.4% for men and only 7.2% for women, respectively.

The idea that deeper inhalation causes primarily adenocarcinomas in the distant parts of the lung is supported by data showing that most lung neoplasms among smokers of pipes and cigars are squamous cell carcinomas arising from the major bronchi (28). Cigars and pipes generate alkaline smoke with significant amounts of unprotonated nicotine that are rapidly absorbed through the oral mucosa, thus quickly satisfying any craving for nicotine. Therefore, in contrast to smokers of low-yield cigarettes, cigar and pipe smokers either do not inhale the smoke very deeply, or not at all (29).

Historically, most long-term smokers in the United States have smoked nonfilter cigarettes during their lifetimes but have switched to filter cigarettes in more recent years. Relatively few smokers have smoked filter cigarettes exclusively. And, until recently, very few people in the United States have smoked low-tar filter cigarettes-only (<14 mg tar). The effects of these low-tar cigarettes in relation to lung cancer are unknown. Some studies have shown that smoking of filter cigarettes that yield medium levels of tar is not as strongly related to lung cancer as the smoking of higher yield nonfilter cigarettes (10,30–32). Yet it is imperative to continue epidemiologic and laboratory studies to delineate the effects of the low-yield cigarette with respect to incidence and type of lung cancer. If it were proven that smoking cigarettes with low tar yield is less strongly associated with lung cancer than smoking cigarettes with higher tar yield, such proof would constitute a scientific basis for legislation that calls for an upper permissible tar level for all cigarettes produced. One step in this direction has already been taken in the European Common Market Community in 1993 (33).

However, it is possible that smoking the low-yield cigarette actually increases the risk of adenocarcinoma of the lung compared with smoking cigarettes of medium yield. As previously discussed, the smoke of low-yield cigarettes often is inhaled more deeply into the peripheral
lungs than smoke of high-yield cigarettes. The peripheral bronchioles have limited cilia and other defense mechanisms. Thus, any expected reduction due to the low tar emission from such cigarettes may be offset by deeper inhalation and the consequences thereof. Indirect epidemiologic evidence supports this hypothesis. Bronchioalveolar carcinoma (BAC) has been a rare tumor suspected to be unrelated to cigarette smoking. However, a recent study documented a clear dose–response relationship between BAC and years of cigarette smoking (34).

Some data from a long-standing case-control study conducted from 1977 to 1994 support these ideas (4). Table 1 reveals that although the risk of squamous cell carcinoma is reduced among the relatively few smokers who only smoked filter cigarettes during their lifetimes when compared with the risk of other smokers, smoking low-tar cigarettes is not associated with a reduced risk of adenocarcinoma.

Future epidemiologic studies will enable us to estimate the effects of lifetime smoking of low-tar cigarettes on lung cancer risk. This is possible, because the market share of filter cigarettes of all cigarettes sold has been steadily increasing from 0.56% since World War II to 97% in 1992 (26) and persons born in the United States after 1944 constitute the first cohort that have smoked predominantly filter cigarettes (35). These smokers are now reaching the age when lung cancer occurs relatively often.

### Gender Differences in Lung Cancer Risk

Since 1950, adenocarcinoma of the lung has always been relatively more common in women than in men (13,36–38). Furthermore, the distribution of neoplasms of other cell types such as squamous cell carcinoma and small cell carcinoma is different among women. Table 2 compares lung cancer histology in the SEER population registries (39). It is evident that squamous cell carcinoma is relatively more common in men, whereas adenocarcinoma and bronchioalveolar carcinoma are relatively more common in women.

Even among nonsmokers, there are gender differences in lung cancer epidemiology. An evaluation of the worldwide epidemiologic patterns of lung cancer among 1325 nonsmoking women showed that 50 to 80% had adenocarcinoma (40). Nonsmoking lung cancer patients under 50 years of age are relatively more likely to be men than women (41). However, the percentage of all nonsmoking lung cancer patients in our database is much higher for women than for men (10 vs 3%, respectively). These findings imply that there may be a differential effect of smoking on lung cancer for men and women or that some endocrine factor may modify this association. Some recent evidence supports this concept (35).

For example, men and women may differ in their susceptibility to the insults of tobacco smoke. This could reflect a difference related to the manner of smoking or an independent effect due to hormonal or other factors. In recent studies, the relative risks for lung cancer in women exceeded those for men for given levels of smoking intensity. Risch et al. (42) reported that the odds ratio for lung cancer among male smokers increased from 5.2 for 1 to 30 pack-years to 22.6 for >60 pack years. In female smokers, the corresponding odds ratios were 7.3 and 81.9, respectively. Our own findings suggest that gender differences are greater for squamous cell cancer than for adenocarcinoma (43). The likelihood of gender differences in lung cancer risk is supported by the greater proportion of adenocarcinoma in women, the finding of estrogen steroid receptors in lung tumor tissues (44–48), and epidemiologic studies relating hormonal factors to the development of lung cancer (49,50). In addition, studies have shown that sex hormones increase the incidence of pulmonary neoplasms in laboratory animals (51).

A report by Adami et al. (50) shows a 30% increased rate of lung cancer in Swedish women who took estrogen replacement therapy. Our own recent observations suggest that this increased risk is associated with adenocarcinoma of the lung only. Women who took estrogen replacement therapy (ERT) had a significantly elevated risk (relative risk [RR] 1.7; 95% confidence interval [CI], 1.0–2.8) for adenocarcinoma (52). In contrast, no association was found between ERT and the risk for squamous cell carcinoma (53). Since millions of American women take estrogens to alleviate postmenopausal symptoms and prevent osteoporosis, the widespread use of the drugs must be assessed. In addition, low body weight increases the risk of adenocarcinoma (54,55) and may modify the risk associated with ERT. Other hormonal factors may also play a role in the development of lung cancer. Studies by Gao et al. (49) found that Chinese women with short menstrual cycles had a 3-fold increased risk of lung cancer. Taioli et al. (52) failed to confirm this finding, although cycle length is subject to recall bias (56).

Along related lines, the association between body mass index (BMI) and the risk of squamous cell carcinoma and adenocarcinoma has been examined in several studies. We found that low body mass 5 years prior to diagnosis was significantly related to the risk of lung cancer in women (55). Because BMI is also highly related to levels of smoking, the risk of BMI was determined separately for different levels of smoking. Our results were consistent for all levels of smoking. When examining this

### Table 1. Age-adjusted odds ratios for squamous cell carcinoma and adenocarcinoma among current cigarette smokers, 1977–1994.

| Type of cancer          | Males (%) | OR     | 95% CI | Females (%) | OR     | 95% CI |
|------------------------|-----------|--------|--------|-------------|--------|--------|
| Squamous cell carcinoma| (n=699)   | 8.2    | 1.00   | 17.3        | 22.0   | 1.00   |
| Lifetime filter        |           | 13.0   | 0.68–1.73 | 18.1 | 1.79 | 1.18–2.71 |
| Switched 21+ years ago | 18.5      | 1.77   | 1.08–2.97 | 18.5 | 2.32 | 1.38–3.90 |
| Switched 10–20 years ago| 31.7     | 1.85   | 1.19–2.89 | 28.3 | 1.46 | 0.91–2.35 |
| Switched 1–5 years ago | 20.0      | 2.10   | 1.27–3.48 | 17.5 | 2.15 | 1.16–3.98 |
| Lifetime nonfilter     | 21.7      | 1.91   | 1.19–3.06 | 11.8 | 3.02 | 1.80–5.72 |
| Adenocarcinoma         | (n=715)   | 12.0   | 1.00   | 27.6 | 1.00 | 1.00   |
| Lifetime filter        |           | 15.0   | 0.69–2.73 | 18.1 | 1.79 | 1.18–2.71 |
| Switched 21+ years ago | 16.0      | 1.09   | 0.69–2.00 | 32.2 | 1.36 | 0.94–1.94 |
| Switched 10–20 years ago| 34.6      | 1.36   | 0.93–2.00 | 32.2 | 1.36 | 0.94–1.94 |
| Switched 1–5 years ago | 18.5      | 1.14   | 0.78–1.79 | 16.5 | 1.40 | 0.89–2.60 |
| Lifetime nonfilter     | 18.9      | 1.24   | 0.81–1.90 | 5.6  | 1.27 | 0.70–2.32 |

*Referent group. **Switched means switched from nonfilter to filter.

### Table 2. Distribution of lung cancer histology, SEER Program, 1983 to 1987.

| Cell Type          | Males, % | Females, % |
|--------------------|----------|------------|
| Squamous cell      | 31.2     | 19.0       |
| Small cell         | 16.6     | 20.2       |
| Large cell         | 9.3      | 8.9        |
| Adenocarcinoma     | 22.7     | 29.7       |
| Bronchioalveolar   | 2.5      | 4.6        |
| Carcinoma          |          |            |
| Other              | 16.7     | 17.6       |
relationship by histologic tumor type, low body mass was more strongly related to the risk of adenocarcinoma than to that for squamous cell carcinoma (55).

Racial Differences in Lung Cancer Risk

The lung cancer mortality rate for black men is 33% higher than that for white men (39), yet black men smoke fewer cigarettes per day than white men (57). However, 40.6% of the population of black men smoke cigarettes, while only 32.1% of the white male population smoke cigarettes (58, 59). Lung cancer mortality rates are similar for black and white women. Ecologic studies of censustract data and cancer rates suggest that the racial differences in cancer rates may largely be due to socioeconomic status (60). However, other studies have shown that poor people smoke less (61). The higher lung cancer rates among black men may also be at least partially related to differences in diet and occupational exposures. Specific dietary differences are thought to include a higher intake of fat from fried meats and lower consumption of vegetables among blacks (62).

There are few data on the relative effects of cigarette smoke in blacks compared with whites even though one study based on small numbers suggests that blacks have a greater risk of lung cancer than whites for a given level of smoking (43). Host factors may also explain racial/ethnic differences in lung cancer incidence. Ethnic differences in the metabolism of drugs and other xenobiotics have been known for some time (63). Differences in nicotine metabolism are reflected by the higher serum levels of cotinine in black smokers than in white smokers (64). A recent study using urinary biomarkers of the tobacco-specific lung carcinogen NNK showed white smokers to have a higher ratio of the detoxified metabolite of NNK relative to the activated metabolite than black smokers (65). It is unknown whether the observed racial differences in metabolism imply a genetic mechanism. There is no clear evidence of genetic differences in P450 isozymes (66).

Conclusion

Further research in lung cancer epidemiology should focus on determining the causes of the steeper increase and current prevalence of adenocarcinoma relative to squamous cell carcinoma, evaluating gender differences in the risk of lung cancer, and conducting biochemical–epidemiologic studies to verify whether racial/ethnic differences in metabolism of tobacco carcinogens are due to a genetic predisposition or other modifiers. In addition, it is necessary to monitor the chemical composition and biological activities of cigarette smoke. Since cigarette smoking is the major cause of human cancer, any changes in the makeup of the tobacco product and inhalation patterns have a direct impact on cancer mortality in this country. It is disconcerting that only a limited number of research scientists in the United States are actively pursuing the epidemiologic and experimental leads described in this paper.

In theory, reducing the incidence of lung cancer in the United States can be accomplished simply by lowering the prevalence of cigarette smoking. The national goals for the year 2000 include a 15% adult smoking rate. However, after three decades of declining smoking rates, smoking levels in adults have remained constant at about 25 to 27% since 1990 (37, 67). Reducing this rate further appears to be an optimistic goal at this point. However, recent epidemiologic findings have suggested that the morbidity and mortality from lung cancer can be reduced by targeting certain segments of the population that may be at higher risk for lung cancer than other segments (38). Clearly, if the goal of significantly reducing the incidence of cancer is to be met by the year 2000, what is done or left undone with respect to determining lung cancer etiology and prevention will determine our success or failure. If certain segments of the population are at higher risk of lung cancer than other groups, cancer prevention programs need to be especially targeted toward these groups.

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