The epidemiology of lung cancer

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Summary
Lung cancer is the most frequent cancer worldwide, accounting for about 12% of all new cancer diagnoses in the two sexes combined. During the 1950s and 1960s clear evidence emerged that smoking was the cause of striking lung cancer increases. Risk of lung cancer increases approximately with the fourth power of duration of smoking and the square of the number of cigarettes smoked daily. Between 1990 and 1994, lung cancer mortality rates showed first decreases in the US and several European countries, including Italy, in men although not in women. Marked shifts are, however, taking place in the incidence of different histologic types. Adenocarcinoma, which had always been the predominant type in women and non-smokers, is increasingly associated with tobacco smoking. Since the 1950s steady rises in the incidence of adenocarcinoma of the lung have been observed in many developed countries. Increases are similar in the two sexes and have followed a clear cohort pattern, paralleling changes in smoking habits and cigarette design more than diagnostic advances. Low-yield filter cigarettes tend to be inhaled more deeply than high-yield cigarettes in order to satisfy a craving for nicotine. The peripheral part of the lung, where most adenocarcinomas arise, is thus exposed to a disproportionately higher amount of smoke carcinogens. The hazards of light and ultra-light cigarettes tend to be underestimated, whereas the only safe cigarette is the non-smoked one.

Key words: adenocarcinoma of the lung, incidence, low-yield cigarettes, lung cancer, trends

Introduction
Early this century lung cancer was a rare disease; it is now the most frequent cancer worldwide, accounting for about 12% of all new cancer diagnoses in the two sexes combined, 18% in men [1]. The epidemic of lung cancer was first noted in males in the US and a number of European countries during the 1940s. By the early 1950s, epidemiological studies using case-control approaches had provided strong evidence that cigarette smoking was the predominant cause of the disease [2-4]. During the 1950s and 1960s prospective studies confirmed the findings of case-control studies, and epidemiological and toxicological evidence supported the conclusion that smoking was the major cause of lung cancer [5].

Factors determining risk in cigarette smokers include the duration of smoking, number of cigarettes smoked and type of cigarettes smoked [6, 7]. The analysis of data from the study of British doctors by Doll and Peto [8] indicated that risk increased approximately with the fourth power of duration of smoking and the square of the number of cigarettes smoked daily. However, above 20 cigarettes per day the risk increased somewhat less steeply, because less smoke is inhaled from each cigarette by men with a high daily consumption than by men with a lower consumption [9].

These relationships indicate that interpretations of age-specific trends of lung cancer rates should be made in the context of both age-related patterns of starting to smoke and amount smoked. In fact, the hazards of very prolonged tobacco use (i.e., in cohorts of men who started at a very early age) seem now greater than was thought to be the case 20 years ago. Lung cancer death rate ratios (smoker: non-smoker) in the two American Cancer Society million-person prospective studies have risen from the 1960s to the 1980s from 12 to 22 in men and from 3 to 11 in females [10]. Differences in the time smoking spread in the population accounts also, for instance, for the persistence of more elevated mortality rates for lung cancer in northern Italy, despite the higher prevalence, in the last decade, of smokers in the south than in the north of the country [11].

Factors that determine the susceptibility of individual smokers have not yet been adequately characterized. The results of association, family, and twin studies suggested, however, that hereditary factors are involved in the initiation and maintenance of tobacco use [12]. Despite increasing negative attitudes about smoking and intensified public campaigns and legislation against smoking, cigarette smoking among adults in the US has remained about 25% during the 1990s (although it had declined from 42% in the previous 25 years). The approximate 1/4 of adult population who are current smokers may represent a hard core of individuals who are genetically predisposed to smoke tobacco and/or to indulge to other drugs (alcohol, cocaine, and amphetamine). Moreover, dietary habits (most notably, low vegetable and fruit intake level) and some occupational and environmental
exposures (e.g., polycyclic aromatic hydrocarbons, arsenic, asbestos, chromium, nickel, and, as indoor pollutants, radon and passive smoking) can contribute to lung cancer risk in smokers [13].

Recent trends

After several decades of increase, some downward trends are recently emerging for lung cancer mortality in several developed countries. In the US, between 1990 and 1994, deaths decreased 1.4% per year in men, although they continued to increase among women [14]. Also in Italy lung cancer mortality rates, age-standardized on the basis of the world standard population, declined in men by 9%, from 60.3 in 1987–1989 to 54.6/100,000 in 1994 (−9%). Conversely, female mortality rates have increased slightly from 7.2 to 7.7/100,000 in 1992, to remain stable thereafter [15].

Lung cancer includes a wide range of malignant neoplasms [16]. The major histologic subtypes are squamous-cell carcinoma, adenocarcinoma, and small-cell carcinoma. Whether a lung cancer is small-cell carcinoma or non-small-cell carcinoma is generally the most important question asked to pathologists, on account of major differences in therapeutic approaches. From the point of view of etiology and time trends, however, adenocarcinoma of the lung has shown in the last three decades the most interesting changes. In fact, recent trends in developed countries vary according to histologic types(s). In Varese province, northern Italy, declines (males) or stabilization (females) for squamous-cell carcinoma and tapering increases for small-cell carcinoma (males) took place between 1976 and 1992 [17]. In contrast, adenocarcinoma incidence rates increased more than two-fold in men and women thus approaching, in 1991–1992, in the two sexes combined, squamous-cell carcinoma rates.

Population-based data from other countries already showed similar changes in lung cancer histologic pattern. In the US, data from the National Cancer Institute’s Surveillance, Epidemiology and End Results (SEER) Program for 1973–1994 [16, 18] showed that the incidence of adenocarcinoma had surpassed in the mid-1980s that squamous-cell carcinoma for all sexes and races combined. In white males the rates for squamous-cell and small-cell carcinoma declined after peaks in 1981 and 1986, respectively [18]. In the Netherlands the highest incidence for squamous-cell carcinoma in males was reached in 1978, while for adenocarcinoma the first decline appeared after 1985 [19]. A rising trend in female lung cancer incidence up to the late 1980s was found for each successive cohort and for every histologic type [19]. In the Vaud Canton, Switzerland, adenocarcinoma has been the only histologic type to increase substantially (about 2.5-fold) from 1974 to 1994 in both sexes. Conversely, rates for squamous-cell carcinoma incidence dropped in males, though not in females, in the last quinquennium. In young Swiss adults (i.e., 35–44 years) in 1990–1994 incidence rates of adenocarcinoma were similar in men and women and exceeded about three-fold those of squamous-cell carcinoma [20].

Rates of major histologic types in the 1990s

The figure shows age-standardized incidence rates by major lung cancer histologic type in different developed countries. In Italy, 13 areas contributed incidence data for the early 1990s (Ferrara, Florence, Genoa, Latina, Macerata, Modena, Parma, Ragusa, Romagna, Torino, Trieste, Varese, and Veneto), with a population of about eight million [21]. Nordic country data are based on nation-wide registration systems from Denmark, Finland, Norway and Sweden with a total population of about 23 million. The US SEER Program covers a population of about 19 million from five States (Connecticut, Iowa, New Mexico, Utah, and Hawaii) and four metropolitan areas (San Francisco, Detroit, Atlanta, and Seattle). Japanese data are based on six different areas (Hiroshima, Mijagi, Nagasaki, Osaka, Saga, and Yamagata) with a total population of approximately 16 million.

Even in developed countries, it is clear that the proportion of non microscopically verified lung cancer is not negligible, particularly in Japan (28%) and Italy (25%). Apart from vast variations in total lung cancer incidence, some interesting differences in the relative importance of major histologic types can be noticed. The rate ratio between squamous-cell carcinomas and adenocarcinomas was everywhere greater in men than in women, but also varied by country. In males, it was over 1.5 in Nordic countries and Italy, but around 1.0 in Japan and the US. In females, it was around 0.5 in western countries but 0.2 in Japan [21]. As discussed below, these differences in the relative importance of adenocarcinoma reflect a difference in the extent and the time that various populations have been involved in the spread of smoking habits and replacement of non-filter cigarettes with low-yield filter-tip ones [22].
Changes in smoking habits

Adenocarcinoma has always represented the majority of lung carcinomas among nonsmokers of both genders [23, 24] and increases, as a proportion, with increasing duration of smoking cessation [25]. This may be because non-tobacco lung carcinogens (e.g., environmental pollutants) are more deeply inhaled and reach the peripheral regions of the lung where adenocarcinomas generally arise [26].

Between the mid-1950s and the mid-1980s, filter-tip cigarettes largely replaced unfiltered cigarettes, and sales-weighted averages in the yields of tar and nicotine in the US [22] and most other developed countries [27], have declined approximately three-fold. The consumption of cigars, pipe tobacco, and handrolled cigarettes was still higher than that of manufactured cigarettes in several European countries (e.g., Switzerland) before World War II, but it quickly diminished thereafter [28]. Although the use of filter tips and the decrease in tar yield have contributed to the observed downward trends of squamous-cell and small-cell carcinomas (i.e., the lung carcinoma types most strongly associated with cigarette smoking [24, 29, 30], especially among men, the fall in nicotine yield may have had a more complex outcome.

To satisfy a craving for nicotine, a smoker of low-yield filtered cigarettes tends to compensate by increasing the number and depth of puffs. Therefore, the bronchiolo-alveolar regions and the smaller bronchi, which lack protective epithelium [18], are exposed to disproportionately higher amounts of certain smoke constituents, including smaller corpuscular carcinogens, volatile aldehydes, polynuclear aromatic hydrocarbons, aromatic amines, and N-nitrosamines [22]. As a consequence, adenocarcinomas have become more frequent.

Market shifts from black tobacco to blended or bright tobacco are also likely to have played a role in changing adenocarcinoma incidence in European countries [30] because alkaline smoke of black cigarettes, like the smoke of pipe and cigars, cannot be deeply inhaled.

Conclusions

Diagnostic advances may have contributed to the disproportionate increase of adenocarcinoma. Flexible bronchoscopy, introduced in the late 1960s, and fine-needle aspiration, computerized tomography, and improved stains for mucin, all introduced in the late 1980s, made it easier to assess peripheral adenocarcinoma [10]. However, these diagnostic advances would be expected to cause discrete 'period' increases and a disproportionate rise in incidence among the elderly, who would mostly have been excluded from invasive examinations in the past. Conversely, the steady increase in lung adenocarcinoma since the 1950s followed a clear birth cohort pattern, paralleling changes in smoking more than diagnostic advances [10]. In fact, cigarette smoking has become more strongly associated with lung adenocarcinoma in the last decades, with relative risks in the two subsequent American Cancer Society prospective studies, rising from 4.6 to 19.0 in men and from 1.5 to 8.1 in women [10]. It is thus of great importance that smokers are not induced to believe that smoking-related hazards can be avoided by switching to 'light' or 'ultra-light' cigarettes.

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References


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