

Original Paper

Changes in Lung Cancer Histological Types in Varese Cancer Registry, Italy 1976–1992

A. Russo,¹ P. Crosignani,² S. Franceschi¹ and F. Berrino²

¹Servizio di Epidemiologia, Centro di Riferimento Oncologico, Via Pedemontana, Occ., 33081 Aviano, (PN); and ²Divisione di Epidemiologia, Istituto Nazionale dei Tumori, Via Venezian, 1, 20122 Milan, Italy

Shifts in histological tumour type distribution, chiefly an increase in adenocarcinoma, have been reported to accompany changes in lung cancer incidence in the last two decades in the United States and several other developed countries. To elucidate this phenomenon further, we analysed population-based lung cancer incidence rates in the period 1976–1992 from the Varese province, an area with 788 000 inhabitants in Northern Italy. Rates were age-standardised on the world standard population. Overall, lung cancer had stopped increasing in males since the late 1980s, and had started declining in middle-aged men. Conversely, upward trends persisted in females up to 1991–1992. Although it decreased from 13 to 9, the male-to-female incidence ratio was, in 1991–1992 still substantially higher than in the U.S. and North Europe. Specific trends emerged according to histological type(s), with declines (males) or stabilisation (females) for squamous-cell carcinoma and gradual increases for small-cell carcinoma in males. Adenocarcinoma was the only lung cancer type whose incidence rates increased similarly (2.5-fold) in males and females thus approaching, in 1991–1992, in the two sexes combined, the rate for squamous-cell carcinoma. Although advances in diagnostic techniques may have played a role, the absolute and relative increases in the adenocarcinoma rate reflect changes in cigarette manufacture (i.e. spread of filter tips and low-nicotine low-tar cigarettes) and the decrease in smokers. © 1997 Elsevier Science Ltd.

Key words: lung cancer, histologic type, cancer registry, incidence, trends, cigarettes, tar level, nicotine level

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INTRODUCTION

LUNG CANCER is the most common cancer site in males [1] and the leading cause of cancer mortality worldwide [2]. The main reason for the large increases in lung cancer mortality over the past decades lies in the increasing effects of tobacco smoking, first among males and later among females [2,3]. In several developed countries, including Italy, the male epidemic of lung cancer reached its peak in the 1980s, and thereafter started declining, especially in middle-aged men [2,3].

At around the same time, shifts in the distribution of major lung cancer histological types, most notably relative and absolute increases in adenocarcinoma, were reported in

the United States [4–7], Europe [8,9] and Asia [10,11]. These changes are essential in order to assess, with the due latency period, the impact of changes in smoking habits (i.e. smoking cessation and shifts towards low-tar, low-nicotine filter cigarettes).

To elucidate this issue further, we examined incidence trends of lung cancer by histologic type(s) from 1976–1992 incidence data of the Varese Cancer Registry, in Northern Italy, an area where cigarette consumption was the heaviest in Italy in the 1950s [12]. In fact, the Varese province shows among the highest lung cancer rates worldwide in males (82.3 per 100 000, world standardised), but not in females (8.2 per 100 000) [1].

MATERIALS AND METHODS

The present analysis is based on the datafiles of the Lombardy Cancer Registry, which includes information

Correspondence to S. Franceschi.

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Table 1. Number of cases of lung cancer and age-adjusted (world population) incidence rates per 100 000 by calendar period, histological type(s), and sex, Varese, Italy, 1976–1992

	Calendar period								
	1976–1980		1981–1985		1986–1990		1991–1992		
Histological type(s)	No.	Rate	No.	Rate	No.	Rate	No.	Rate	% change‡
Males									
Squamous cell carcinoma	579	24.7	888	37.7	879	37.3	305	31.9	–15
Small cell carcinoma	123	5.2	265	11.4	316	13.5	147	15.9	+39
Adenocarcinoma	181	7.7	298	12.8	463	20.2	212	23.3	+82
Other and NOS*† cancer	315	13.0	218	8.8	213	8.9	98	9.7	+10
Non-microscopically confirmed	515	20.8	330	13.2	290	11.4	101	9.9	–25
All	1713	71.4	1999	83.9	2161	91.4	863	90.7	+8
Females									
Squamous cell carcinoma	30	0.9	53	1.5	60	1.6	22	1.5	0
Small cell carcinoma	15	0.5	35	1.0	38	1.2	20	1.6	+60
Adenocarcinoma	49	1.7	69	2.1	104	3.3	56	4.2	+100
Other and NOS*† cancer	25	0.6	38	1.1	38	1.0	22	1.6	+45
Non-microscopically confirmed	66	1.8	51	1.2	78	1.6	30	1.7	+42
All	185	5.5	246	6.6	318	8.7	150	10.6	+61

*NOS, not otherwise specified. †Including non-epithelial neoplasms and unclassified cancers. ‡Represent percentage change between the periods 1981–85 and 1991–92.

concerning incident cases of malignant neoplasm in the province of Varese, with a population, according to the 1981 census, of approximately 788 000 [13]. All public and private hospitals and pathological laboratories of the province are asked to report to the registry all new or past cases of cancer. The completeness of reporting is checked against all death certificates of the province, whether cancer is mentioned or not, and the hospital discharge records of the whole Lombardy region and nearby Piedmont region. Information collected by the registry includes general demographic characteristics of the patient (age, sex, municipality of residence), site and histological type of the tumour according to the standard International Classification of Diseases for Oncology (ICD-O) [14] and time of diagnostic confirmation.

The present series comprised 7635 incident lung cancer primaries (6736 males and 899 females) registered from 1976 to 1992 in the resident population (Table 1). Cancers were grouped into the following histologic types, based on the morphological characteristics of the tumour [14]: squamous cell carcinoma (M: 8070–73); small cell carcinoma (M: 8041–45); adenocarcinoma, including bronchiolo-alveolar carcinoma (M: 8140, 8200–01, 8221, 8230, 8250–51, 8260, 8310, 8323, 8430, 8450, 8480–81, 8490, 8550, 8560); other carcinomas, including large cell and undifferentiated carcinoma, and not otherwise specified (NOS) carcinomas (M: 8010–12, 8020–21, 8030–33), malignant carcinoid (M: 8240–42) and non-epithelial neoplasms. For 1461 lung tumours (1236 males and 225 females), no microscopic confirmation was available. This percentage decreased from 31% in 1976–1980 to 13% in 1991–1992.

Age-specific and age-standardised (world standard population [1]) incidence rates were computed for major histologic types (i.e. squamous cell, small cell, adenocarcinoma, and 'other and Nos' lung cancer, including those lacking microscopical confirmation) and all lung cancers by calendar period (1976–1980, 1981–1985, 1986–1990, 1991–1992). In addition, for squamous cell and small cell carcinomas (males only) and adenocarcinoma (both sexes), age-specific rates for 35–44, 45–54, 55–64, 65–74 and 75–89 years of age were plotted against the central year of the birth cohort. The points corresponding to the same age

group were joined to provide more clearly spaced graphs. Thus, the cohort effect can be read in the ordinate.

RESULTS

Table 1 shows numbers and age-standardised incidence rates per 100 000 by calendar period, histologic type(s) and sex. The percentage change of rates from 1981–1985 to 1991–1992 are also given, in order to avoid the high proportion of non-microscopically confirmed tumours in 1976–1980. Overall, squamous cell carcinoma was the most frequent histologic type in males (39%), followed by adenocarcinoma (17%), and small cell carcinoma (13%). In females, corresponding percentages differed substantially for squamous cell (18%) and adenocarcinoma (31%), but not small cell carcinoma (12%). The present cancer series also comprised 967 other or NOS cancers, including 9 non-epithelial neoplasms and 46 unclassified lung cancers.

Rates of squamous cell carcinoma at all ages increased in males from 1976–1980 to 1981–1985, then plateaued around 37 per 100 000, to decline thereafter. Conversely, incidence rates of small cell carcinoma and adenocarcinoma increased approximately 3-fold from 5.2 to 15.9 and from 7.7 to 23.3 per 100 000, respectively. Rates for other and NOS cancers declined from 1976–1980 to the subsequent quinquennium, and then were approximately stable. In females, the incidence of all histological types showed upward trends. The incidence of squamous cell carcinoma, however, rose by 67% from 1976–1980 to the subsequent quinquennium, then stabilised. On account of the relatively small numbers, only the increase in adenocarcinoma was significant in females. In the last period (1991–1992), the male-to-female incidence ratio was 21 for squamous cell carcinoma, 10 for small cell carcinoma, and 6 for adenocarcinoma. Overall, the ratio decreased from 13 to 9 from 1976–1980 to 1991–1992. Rates of non-microscopically confirmed tumours of the lung diminished in males, but were approximately stable among females. Overall, the incidence of lung cancer in males increased by 28% from 1976–1980 to 1986–1990 and remained at around that level in 1991–1992. In females, overall rates nearly doubled (Table 1).

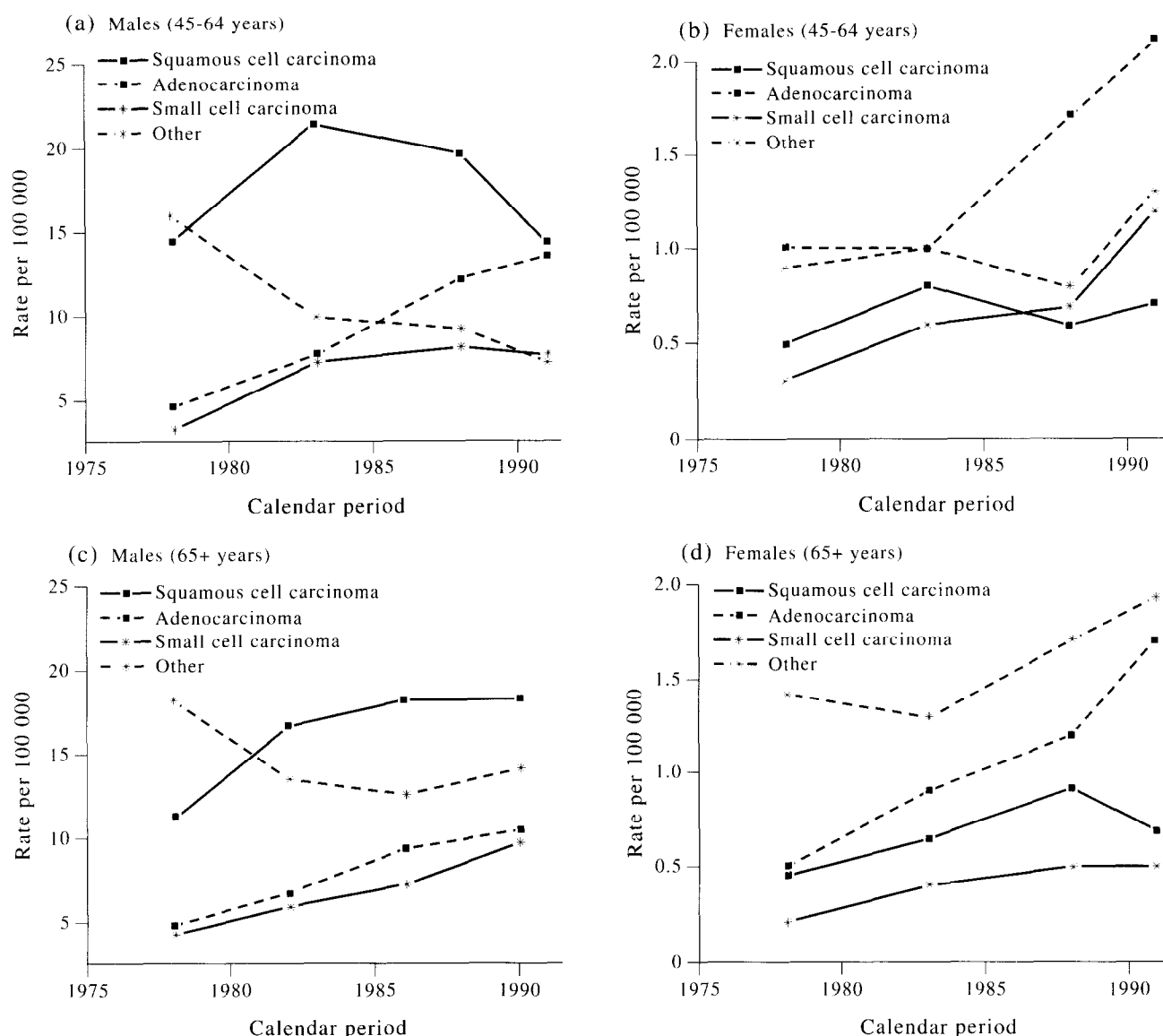


Figure 1. Trends in age-standardised (world standard population) incidence rates per 100 000 for lung carcinoma in 45-65 and ≥ 65 year age groups by sex and histologic type. Varese Province, Italy, 1976-1992.

Age-standardised incidence rates of lung carcinoma by histological type(s) in the two sexes in middle age (45-64 years) and in the elderly (≥ 65 years) are shown in Figure 1. Rates in the 35-44 year age group are not displayed because of the low numbers involved (138 men and 30 women for the whole study period). A decline in squamous cell carcinoma incidence rates since 1981-1985 was marked in middle-aged men, among whom small cell carcinoma showed a plateau for the same years. The incidence rate of adenocarcinoma tripled, reaching that of squamous cell carcinoma in 1991-1992 (i.e. 14 per 100 000). In elderly men, there was an increase in the incidence of all tumour types over the study period, with the exception of small cell carcinoma, the incidence of which declined from 1976-1980 to 1981-1985, and then plateaued. Middle-aged and elderly females showed gradual increases, but in 1991-1992, the first decline in the incidence rates for squamous cell carcinoma was seen. Large increases in adenocarcinoma emerged in both age groups. However, in elderly women due to the persistence of a high proportion of non-microscopically con-

firmed tumours, the 'other' category still exceeded specific histological type(s) (Figure 1).

Age-specific incidence rates of major histological type(s) (i.e. squamous cell carcinoma, small cell carcinoma and adenocarcinoma) were also examined by median year of birth of each cohort of males (Figure 2). Rates for squamous cell carcinoma peaked in the 1910-1920 cohorts, but declined thereafter, most markedly in those born after 1930. Rates of small cell carcinoma exhibited steeper increases than squamous cell carcinoma, up to the 1920-1930 cohorts, but fell similarly thereafter. Conversely, age-specific rates for adenocarcinoma in males increased at least up to the 1930-1940 cohorts and, possibly, tended to stabilise thereafter. Rates for 'other' lung cancers steadily and steeply declined for each male cohort born from 1910 onward (not shown).

In females only adenocarcinoma was sufficiently frequent to assess cohort effects. Age-specific rates for this histological type resembled those in males, with increases in successive birth cohorts at least up to the 1950 cohort (Figure 3).

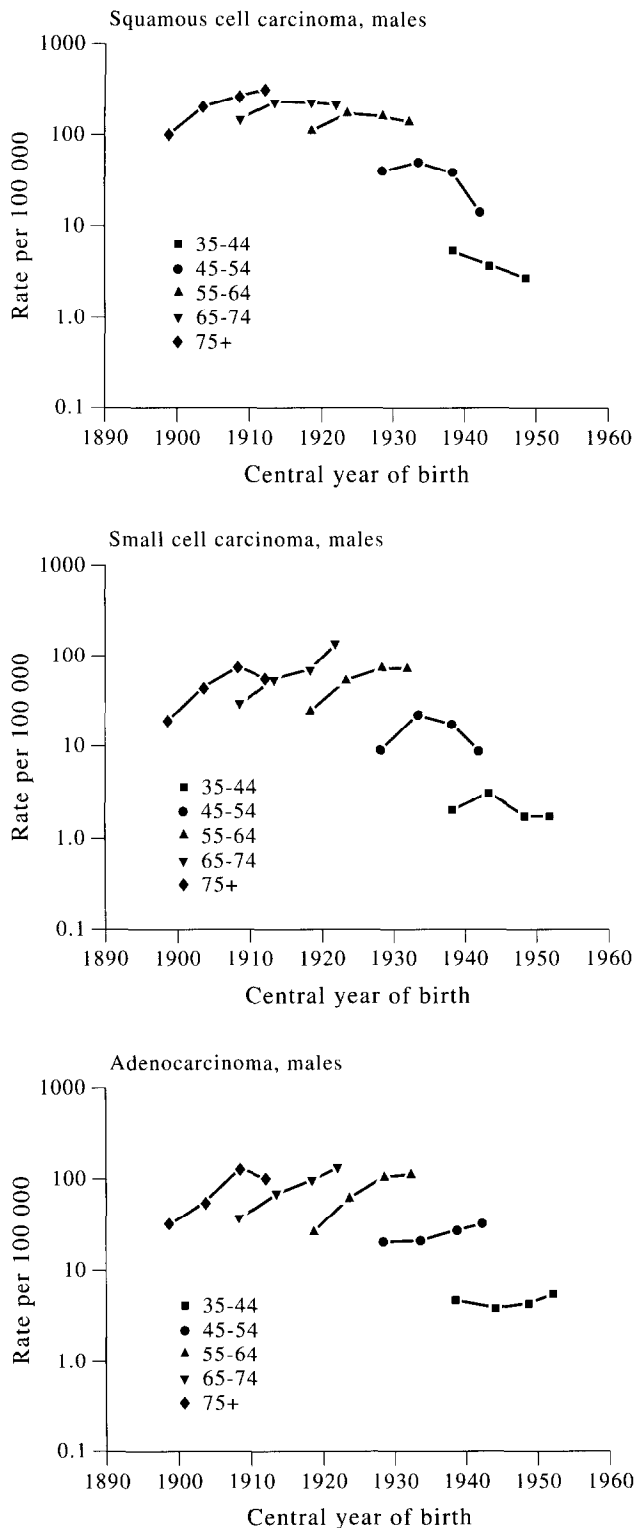


Figure 2. Crude age-specific incidence rates (35–44, 45–54, 55–64, 65–74 and 75–89 years) of lung carcinoma by histologic type and central year of birth in males. Varese Province, Italy, 1976–1992.

DISCUSSION

The present study showed that in the Varese province, as in several developed countries [2], the incidence of lung cancer overall has stopped increasing in males since the late 1980s, and had started declining in middle-aged men. Conversely, upward trends persisted in females up to 1991–

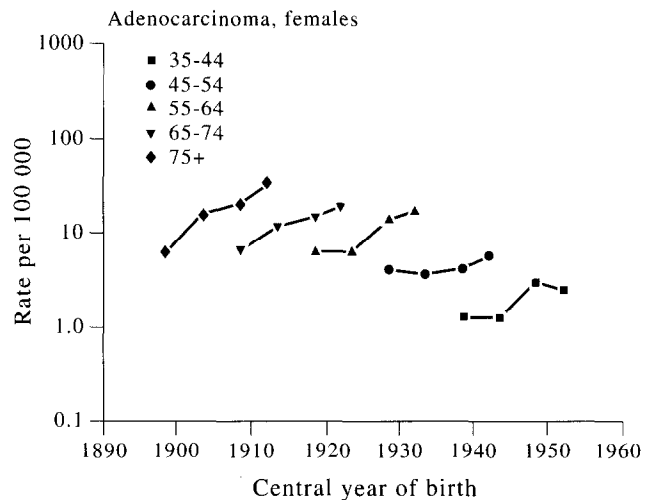


Figure 3. Crude age-specific incidence rates (35–44, 45–54, 55–64, 65–74 and 75–89 years) of adenocarcinoma of the lung by central year of birth in females. Varese Province, Italy, 1976–1992.

1992. Although it fell from 13 to 9, the male-to-female incidence ratio was still in 1991–1992 substantially higher than in the U.S. and North Europe [1]. Specific trends emerged, however, according to histological type(s), with declines (males) or stabilisation (females) for squamous cell carcinoma and gradual increases for small cell carcinoma in males. Adenocarcinoma was the only lung cancer type whose incidence rates increased similarly (more than 2-fold) in males and females, thus approaching, in 1991–1992, in the two sexes combined, that of squamous cell carcinoma.

Population-based data from other countries have already shown similar changes in lung cancer histologic pattern. In the U.S., data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program for 1973–1994 [6, 7] showed that the incidence of adenocarcinoma in the mid-1980s had surpassed that for squamous cell carcinoma for all sexes and races combined. In Caucasian males, the rates for squamous cell and small cell carcinoma declined after peaks in 1981 and 1986, respectively [7]. 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 [8]. A rising trend in female lung cancer incidence up to the late 1980s was found for each successive cohort and for every histological type [8]. In the Vaud canton, Switzerland, adenocarcinoma has been the only histological type to increase substantially (approximately 2.5-fold) from 1974 to 1994 in both sexes. In young Swiss adults (i.e. 35–44 years) in 1990–1994, incidence rates of adenocarcinoma were similar in men and women [9].

The increase of adenocarcinoma in the Varese province in the last two decades is not attributable to chance, since it is highly significant in both sexes and consistent with trends elsewhere in developed countries. Part of the increase may be attributable to changes in histopathological criteria and advances in diagnostic techniques. Modification of the definition of adenocarcinoma to include solid adenocarcinoma with mucus production in the revised World Health Organization classification of 1981 appears to have had a small effect [15]. However, most lung cancers are histologically heterogeneous and discrepancies can arise, for

instance, between the classification of small bronchoscopic biopsy specimens and the pathological diagnosis in subsequent resection specimens [16]. Most of all, the spread of the flexible bronchoscope and the use of the transthoracic aspiration needle biopsy in the last two decades have greatly improved access to the peripheral parenchyma of the lung, where most adenocarcinomas arise [16].

The present study has some weaknesses including a relatively small number of cancers in women and, most notably, the high proportion of non-microscopically confirmed tumours in the earliest period. Such a proportion is higher than that reported in similar studies from SEER (10%) [6] and Switzerland (8%) [9], although it decreased from 31% of all cancers of the lung in 1976–1980 to 17% in 1981–1985, remaining fairly stable thereafter. Furthermore, the distribution of non-microscopically confirmed tumours by location (i.e. 13% at trachea and bronchi and 87% at pulmonary lobi) was more similar to that of all lung cancers (14% and 86%) than to the specific distribution of adenocarcinoma (7% and 93%, respectively). Also, age-specific incidence rates by birth cohort were distinct, with, for instance, stable rates for non-microscopically confirmed tumours in the patients 75 years or older, but concurrent upward trends for adenocarcinoma.

This shift in lung cancer histologic type must reflect changes in smoking patterns in northern Italy. A clear downward trend in self-reported smoking prevalence among Italian men was observed between 1949 (71%) and 1986–1987 (41%), although the decline was certainly inflated by the increasing tendency to underreport smoking [3, 17]. Conversely, progressive increases in smoking prevalence were seen in women, at least up to 1983 [3, 17]. In 1980, among North Italian men, 51% were current smokers while 11% were former smokers. Corresponding percentages in women were 19% and 2% [3]. Adenocarcinoma of the lung represents the majority of lung cancers in non-smokers of both sexes [18] and increases, as a proportion, with increasing duration of smoking cessation [19, 20].

Furthermore, since the 1970s, the sale-weighted average tar yield of Italian cigarettes has fallen (approximately 17 mg per cigarette in 1983–1984 [3]), albeit somewhat more slowly than in the U.S. and North Europe [21]. Filter tips and lower tar levels have contributed to the observed downward trend in squamous and small cell carcinomas [2]. Conversely, low-tar, low-nicotine cigarettes allow (and induce the need for) deeper inhalation. Thus, the bronchioalveolar regions and the smaller bronchi, where adenocarcinoma generally arises and which lack protective epithelium [16], can be exposed to higher amounts of certain smoke constituents, most notably smaller corpuscular and volatile carcinogens [21].

In conclusion, despite classification difficulties, the study of incidence trends of specific histologic types in the two sexes and different populations provides important clues on the impact of smoking trends and the mechanisms of lung carcinogenesis.

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