Lung cancer epidemiology and risk factors in Asia and Africa

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SUMMARY

In industrialised countries, lung cancer is the most common form of cancer among males and it is growing among females. For both sexes, rates reflect smoking behaviours. The pattern appears to be different in Asia, particularly in China, where lung cancer rates in men reflect high smoking rates but high rates among non-smoking women appear to be related to other factors. The incidence of lung cancer is low in most African countries, but it is increasing. In addition to tobacco smoking, a number of etiological factors have been identified for lung cancer: indoor exposure to environmental tobacco smoke, cooking oil vapour, coal burning, or radon, outdoor air pollution and occupational exposure to asbestos and other carcinogens. Recent studies have shown that dietary factors may be important, with high consumption of vegetables and fruits being protective while preserved food and fatty food are harmful, and certain infections such as Mycobacterium tuberculosis, human papilloma virus and Microsporum canis are associated with a high risk of lung cancer. Among non-smokers, the probable role of genetic predisposition in lung cancer by increasing the individual’s susceptibility to environmental carcinogens is currently being studied actively. As the single most important cause for lung cancer is tobacco smoke and, with increased sales, a major epidemic is predicted for both Asia and Africa, all health care professions, government health authorities and national and international health organisations must join in a concerted effort against tobacco.

KEY WORDS: lung cancer; Asia; Africa

EPIDEMIOLOGY

Global cancer mortality and incidence

In 2000, the global burden of disease project estimated that cancer accounted for over 7 million deaths or 13% of total mortality, preceded by cardiovascular diseases, infectious and parasitic diseases.1 Cancer mortality as a proportion of total mortality differed substantially by region, from less than 5% in Africa to about 30% in Australia and New Zealand. Global cancer mortality rates among males and females were on average 128.2 and 104.6 per 100 000 population, respectively. Lung cancer was the leading cause of cancer deaths in the world, accounting for 17% of all cancer mortality, followed by cancers of the stomach, liver, colon and rectum and breast. There was a significant variation in the distribution of site-specific mortality by region. In industrialised countries such as in North America, lung, colorectal and prostate cancers are most common in males and breast, lung and colorectal cancers in females, in descending order.1 In Africa, prostate, liver and mouth and oropharynx in males and cervical, breast and liver in females are the most common cancer sites.1

In 2000, more than 10 million new cancer cases occurred worldwide. The global cancer incidence rates among males and females were on average 169 and 171/100 000, respectively.1 The distribution of cancer incidence was similar to mortality—lung cancer was the most common cancer world wide, accounting for 13% of total cancers, followed by cancers of the stomach, liver, colon and rectum and breast (Figure). The variations in the distribution of site-specific new cases of cancer by region were also similar to those observed in mortality.

Lung cancer mortality and incidence in Asia and Africa

In 2000, there were 1 211 000 deaths from cancer of the trachea, bronchus and lung globally. The rate in males was 28.8/100 000 and in females 10.8/100 000, with considerable regional variation. Within Asia, age-standardised mortality rates from lung cancer were highest in China and lowest in the South Pacific Islands, with rates of 29.1 and 13.8/100 000, respectively, in males and 14.5 and 7.7/100 000 in females. Age-standardised mortality from lung cancer is low in the two African regions (north and south), at 7.9 and

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11.5/100,000, respectively, in males and 3.2 and 5.3/100,000, in females. In the same year, there were 1,305,000 new cases from cancer of the trachea, bronchus and lung worldwide. The global age-standardised incidence rates for lung cancer were respectively 30.9 and 11.9/100,000 for males and females. The regional variations in lung cancer incidence were similar to those of mortality.

Trends in lung cancer mortality and incidence rates in Asia and in Africa

In many industrialised countries, lung cancer mortality has declined since the 1980s. Relatively few cancer registries in developing countries can provide incidence series spanning 15 years or more. The trends described below were from existing data and cannot be generalised to all developing countries. Parkins carried out a review of lung cancer in developing countries between the 1960s and the late 1980s utilising datasets not only from the World Health Organization (WHO) but also a number of other sources. In developing countries, lung cancer is primarily a problem of males, accounting for more than three-quarters of cases. The rates in females are low in all populations, except for those of Chinese origin. Chinese women have relatively high rates of lung cancer, especially adenocarcinoma, compared with other ethnic groups. In females, lung cancer incidence and mortality have increased during recent decades by 4.8% per year among the Chinese in Hong Kong and Singapore, but remained the same in other countries. The age-specific trends in incidence or mortality showed marked cohort effects that can be linked to specific prevalence of cigarette smoking. A more recent report from China shows a progressive increase in lung cancer rates in the past decade, mostly in men (Table 1). In South Korea, the age-adjusted mortality rates from lung cancer increased from 3.7 in 1980 to 17.8/100,000 in 1994 in males and from 1.4 to 7.0/100,000 in females; the projected average annual age-adjusted mortality rates in 2000–2004 were 65.4 and 15.1/100,000 for males and females, respectively.

The age-standardised rates of lung cancer in Kampala, Uganda, increased in men, rising from 0.5/100,000 in 1954–1960 to 1.0/100,000 in 1989–1991; these rates were low, however. In Bulawayo, Zimbabwe, lung cancer incidence in men was very high in the mid 1960s (43.8/100,000), but declined in the following decade. It is not clear how well these changes could be explained by patterns of smoking, as data are not available. Smoking in Africa is generally thought to be low, but changes are occurring rapidly. In Bulawayo, for example, by the early 1990s, 50% of males were current smokers, although the average consumption was low.

Histological types of lung cancer

Before 1980, the predominant cell type in lung cancer worldwide was squamous cell carcinoma. Since the 1980s there has been a gradual increase in the incidence of adenocarcinoma, with a corresponding decrease in squamous cell cancer in many countries. The same changing pattern is observed in Asia. In Taiwan, a study of over 10,000 cases over the period 1970–1993 showed that the incidence of squamous carcinoma decreased from 46.4% to 36.2% in men, whereas adenocarcinoma increased from 30% to 36% in men and from 50.7% to 64.8% in women, such that adenocarcinoma has now become the most common cell type. A similar pattern was found in Singapore, Korea, Hong Kong and Japan.

This changing histological pattern is ill-understood, and is probably multifactorial due to the increased use of adenocarcinoma-specific stains for diagnosis, the introduction of ‘light’ or ‘mild’ cigarettes or the changing composition and filtering of cigarettes, resulting in an increase of volatile nitrosamines depositing in the more distal bronchioles, while the older make of cigarette emitted particulates containing polycyclic aromatic hydrocarbons depositing on proximal bronchi associated with squamous cell cancers, and possibly other changes in environmental factors.

There is a dearth of data from Africa. Published...
reports often date back to the 1960s to 1970s. Two more recent studies in 1990s, both from Nigeria, have found squamous cell carcinoma to be most common in males, but adenocarcinoma predominated in females.16,17

RISK FACTORS ASSOCIATED WITH LUNG CANCER

Active tobacco smoking

Lung cancer was rare before the 20th century. The first epidemiological study on the relationship between tobacco and lung cancer was published as early as 1939 by several German physicians.18 This was followed by the study of British doctors by Doll and Hill19 after the Second World War and the large prospective study of Hammond in the United States,20 revealing tobacco as the culprit for lung cancer. The evidence linking tobacco smoking and lung cancer is beyond dispute. Tobacco smoke is a complex mixture of over 4000 different chemicals, of which over 40 compounds have been evaluated by the International Agency for Research on Cancer (IARC) in animals as carcinogens. Polycyclic aromatic hydrocarbons in tobacco smoke have been shown to induce tumours of the lung in animals.21–23

Major prospective studies have consistently demonstrated that the relative risk of lung cancer in smokers is closely related to the numbers of cigarettes smoked daily and the duration of smoking in a dose-response manner,24–26 with the duration of smoking four times more important than the number of cigarettes per day.26 On the other hand, there is a progressive reduction in the risk after stopping smoking, with the risk ratio decreasing from 12 to 19 in the initial 1–4 years after quitting to about 2 after 15 years.27

About 85% of all lung cancer is due to tobacco. In 2000, the estimated global annual lung cancer incidence was about 1.24 million, thus 935 000 lung cancer deaths were caused by tobacco.28 As cigarette consumption was about 3 trillion per year, it was estimated that one case of lung cancer arose from every 3 million cigarettes smoked.28

The pattern of cigarette smoking changed globally between 1970–1972 and 1990–1992. It is slowly decreasing in the industrialised world, at a rate of 1% annually, and rising in developing countries, at a rate of 2%. With declining sales in industrialised countries, international tobacco companies are directing aggressive marketing campaigns in developing countries in both Asia and Africa, targeting not only men but also women and young boys.29 Table 2 shows the prevalence of smoking in adults and young adults by sex in selected Asian and African countries and in the US and UK in the 1990s. In both adults and young adults, the prevalence of smoking in men in many Asian and African countries now exceeds those of the US and

<table>
<thead>
<tr>
<th>Country/region year</th>
<th>Prevalence in adults</th>
<th>Prevalence in young adults</th>
<th>Per capita cigarette consumption (unit)</th>
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<tr>
<td></td>
<td>Age, years</td>
<td>Male</td>
<td>Female</td>
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<td>15–45</td>
<td>64.7 (ur)</td>
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<td>China 1996</td>
<td>15–69</td>
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<td>15+</td>
<td>27.1</td>
<td>2.9</td>
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<td>India 1985–1986</td>
<td>25–64</td>
<td>45.0</td>
<td>7.0</td>
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<tr>
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<td>15+</td>
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<td>NA</td>
<td>NA</td>
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<tr>
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<td>18+</td>
<td>49.2</td>
<td>3.5</td>
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<td>20+</td>
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<tr>
<td>Zimbabwe 1993</td>
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<td>18+</td>
<td>27.6</td>
<td>22.1</td>
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<td>United Kingdom 1996–1997</td>
<td>16+</td>
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* Data from reference 30.
ur = urban; ru = rural; NA = not available.
the UK.\textsuperscript{30} Compared to the US and the UK, the prevalence of smoking in adult women is lower in Asian and African countries; however, in some Asian countries, the prevalence in young women is higher.

In China, the estimated consumption of cigarettes per adult increased by 260\% between 1970–1972 and 1990–1992. The rates of smoking were high in both the urban and rural areas in men, with rates of 60\% and 64\% and of 15\% and 9\% in women, respectively.\textsuperscript{31} In Africa, the overall consumption of tobacco was estimated to be 600 cigarettes per adult per year in 1990–1992, about one third of the consumption of countries in the Organisation for Economic Co-operation and Development in the same period.\textsuperscript{30} However, tobacco consumption is growing at a faster rate in Africa than in any other part of the world, rising by 2.4\% between 1985 and 1990 and expected to rise to 3.2\% between 1995 and 2000, compared to other developing countries, where the increase was expected to be 2.7\% in the same period. The increased rate in lung cancer in African countries is a reflection of the growth of tobacco use.

Lung cancer in Natal, South Africa, increased sixfold in men and fivefold in women between 1971 and 1982.\textsuperscript{32} In South-Western Zimbabwe, a study of cancer patients between 1963 and 1977 found that tobacco smoking \(>15 \text{ g/day}\) was associated with increased risk of lung cancer (odds ratio [OR] 5.2, 95\% confidence interval [CI] 3.5–7.7) in males compared to non-smokers.\textsuperscript{33} Among black South Africans, smoking \(>15 \text{ g/day}\) increased the risk for lung cancer, with an OR of 23.9 (95\%CI 9.5–60.3) in males, and an OR of 50.9 (95\%CI 12.6–204.6) in females,\textsuperscript{34} while in the Northern Province of South Africa, the risk of lung cancer was increased by 12 times (95\%CI 6.5–22.3).\textsuperscript{35}

It is expected that in the next 20 years the incidence of lung cancer will increase substantially in both Asian and African countries.

\textit{Environmental tobacco smoke (ETS)}

ETS consists of sidestream smoke and the exhaled smoke of the smoker. The two differ in composition, and some carcinogens such as benzo(a)pyrene, nitrates, and \(^{210}\text{Po}\) are present in higher concentration in sidestream smoke.\textsuperscript{36} Sidestream smoke, with its appreciable amount of gaseous components, penetrates into the peripheral parts of the lung causing peripheral lung cancers, particularly adenocarcinoma, among non-smokers.\textsuperscript{37} ETS is now classified as a class A carcinogen, responsible for 20\% of lung cancers in non-smokers.\textsuperscript{36,39}

The first major epidemiological study on ETS and lung cancer was published in 1981, from Japan,\textsuperscript{40} reporting that age-adjusted lung cancer mortality rates were lowest for wives of non-smokers, intermediate for wives of light or ex-smokers and highest for wives of heavy smokers. Since then, numerous studies have confirmed this association. A meta-analysis of 35 case-control and five cohort studies showed that the relative risk (RR) of lung cancer among non-smoking women ever exposed to ETS by their husbands was 1.20 (95\%CI 1.13–1.92), and that for ever being exposed to ETS at work was 1.16 (95\%CI 1.05–1.28).\textsuperscript{41} Seventeen of the 49 studies were from Asia (seven from mainland China, five from Japan, four from Hong Kong and one from Taiwan). Additional studies from Asia have been published recently, demonstrating the high risk of lung cancer in those with exposure to ETS in childhood.\textsuperscript{42,43} Because of the low prevalence of smoking in Asian women, any misclassification bias should be small, and the Asian evidence for a causal relationship between ETS and lung cancer is particularly strong.\textsuperscript{44}

No study of the relationship between ETS exposure and lung cancer in an African country appears to have been published.

\textit{Indoor air pollution}

The incidence of lung cancer in Chinese women is high in different parts of the world (Table 1). The majority (about 90\% in Taiwan, 75\% in Shanghai and 60\% in Shenyang and Hong Kong) are non-smokers, in contrast to white women in industrialised countries. A number of environmental factors other than ETS, including cooking oil vapours, indoor coal burning and diet, have been studied and are discussed below. It should be pointed out that most of these studies were carried out on non-smoking women, without adjustment for ETS exposure.

\textit{Cooking oil vapours}

Large epidemiological studies from Shanghai,\textsuperscript{45} Gansu\textsuperscript{46} and Shenyang,\textsuperscript{47} in mainland China and Taiwan,\textsuperscript{48} have all shown that exposure to cooking oil fumes at high temperature (wok cooking) with inadequate fume extraction is a significant risk factor for lung cancer in non-smoking Chinese housewives, with risk ratios of 1.4, 1.67, 3.79 and 3.2–12.2, respectively, in the four studies. Volatile substances generated from vegetable oils such as rapeseed and soyabean under such conditions have been found to be genotoxic.\textsuperscript{49,50} Linolic acid in rapeseed oil is probably the cause of mutagenicity at high temperature when it is oxidised to produce pyrolysates.\textsuperscript{51} Extracts of fumes from safflower oil, vegetable oil and corn oil were found to contain benzo(a)pyrene, benzo(a)anthracene and dibenz(a,h)anthracene.\textsuperscript{52}

\textit{Indoor coal burning}

Burning of smoky coal for heating and cooking in unventilated homes in China has been implicated as a risk factor, particularly for non-smoking housewives. In rural Xuanwei county, where lung cancer is unusually common in women, a good correlation between
indoor air benzo(a)/pyrene concentration (as an index of indoor coal burning pollution) and high lung cancer mortality rates \((r = 0.778, P < 0.01)\), particularly from adenocarcinoma, was found.\(^{53}\) Subsequent studies from Guangzhou in southern China (coal burning for cooking) and Harbin and Shenyang in north-east China (coal burning for cooking and heating) all confirmed that household coal burning is a significant risk factor, with a risk ratio of 1.5–2.2, increasing to 18.7 (adjusted for personal smoking) when exposure was more than 30 years.\(^{47}\)

**Indoor radon**

Indoor radon comes from the soil, building materials and groundwater from drilled wells. In the US, it has been estimated that indoor radon may cause between 6000 and 36 000 lung cancer deaths per year.\(^{54}\) The US Environmental Protection Agency has recommended that the annual average concentration for houses should not exceed 4pCi/l (148 Bq/m\(^3\)).\(^{55}\) A recent meta-analysis of eight epidemiological studies from five countries (each enrolling a minimum of 200 case subjects and measuring houses for radon concentrations) gave an estimated RR of 1.14 (95%CI 1.0–1.3) at 150 Bq/m\(^3\).\(^{56}\)

Case-control studies performed in countries in the Asia Pacific region showed contradictory results.\(^{16,57}\) In China, neither the High Background Radiation Research Group\(^{58}\) nor Blot et al.\(^{59}\) found a correlation between radiation levels and lung cancer, although a third Chinese study in the Geijiu area in Yunnan Province demonstrated a positive correlation between lung cancer mortality and indoor radon levels >100 Bq/m\(^3\) in a dose-response fashion.\(^{60}\) A study in three towns in Rajasthan, India, estimated that the lifetime risk of lung cancer due to indoor radon exposure for the total population of the study area was 0.67\%, and that the mean relative loss of life expectancy was between 0.12\% and 0.20\% in the three towns.\(^{61}\) A case-control study in the Saraphi district of northern Thailand confirmed the enhancing effect between high indoor radon concentrations and smoking in causing lung cancer.\(^{62}\)

**Others**

Incense burning at home by housewives is common in Chinese families, especially in older generations in rural areas. Chinese incense smoke contains carcinogens, including 3,4-benzopyrene.\(^{63}\) Studies in Hong Kong and Taiwan,\(^{64–66}\) however, showed a reduced risk for lung cancer between incense smoke in non-smoking housewives due to the confounding effect of dietary factors,\(^{65}\) as incense burning among Chinese is representative of a traditional lifestyle, associated with a more vegetarian diet (i.e., with less meat and less chili consumption), which is a protective factor for lung cancer.

Other indoor pollutions, such as exposure to mosquito coil smoke and kerosene stove cooking, have also been studied in Chinese, with negative results.\(^{67,68}\)

There have been very few studies of indoor environmental exposures and lung cancer in Africa. Among black South Africans, the use of paraffin (kerosene) fuel for heating was associated with an increased risk for lung cancer in males, but interestingly not in females, although the number of cancer subjects in this study was very small.\(^{14}\)

**Outdoor air pollution**

Known carcinogens, including gaseous and particulate organic compounds (e.g., benzo(a)pyrene, benzene, dimethylnitrosamine), inorganic particles (e.g., arsenic, asbestos, cadmium, chromium, nickel) and radionuclides (e.g., radium, radon, thoron), are detected in ambient air, particularly in urban areas. A number of studies have examined the relationship between air pollution, especially on diesel exhaust and lung cancer, and most studies have shown risk ratios ranging from 1.2 to 1.8; however, the effect of smoking has not been adjusted for in most of these studies.\(^{69}\) The IARC has categorised diesel engine exhaust as a probable carcinogen.\(^{70}\)

In Asia, a large 5-year cohort study in three residential areas of Shanghai with different levels of air pollution did not show any effect of ambient air pollution on the risk of lung cancer among non-smokers.\(^{71,72}\) However, women living within 200 m of factories in Shenyang, China, had a significantly higher risk of lung cancer, after adjusting for smoking and other risk factors.\(^{73}\) Another case-control study in Taiwan showed that women living in municipalities with high levels of petrochemical industrial pollution had a significantly higher risk of lung cancer than women living in municipalities with low levels of petrochemical pollution.\(^{74}\)

Non-occupational exposure to talc and amosite/crocidolite and its association with lung cancer risk in women in urban areas of Japan has been studied by Yamada et al.\(^{75}\) A significantly higher level of ferruginous and uncoated fibres was found in urban lung cancer cases than urban non-lung cancer cases. These fibres are mainly amosite/crocidolite, with some fibrous talc.

In the Northern Province of South Africa, a moderate level of environmental exposure to asbestos in the current residence or since birth was associated with increased risk of lung cancer (OR 2.1, 95\%CI 1–4.4 and OR 2.9, 95\%CI 1.2–6.7, adjusted for personal smoking) in males, while in females, heavy environmental exposure to asbestos in current residence also increased the risk of lung cancer (OR 5.4, 95\%CI 1.3–22.5, adjusted for personal smoking).\(^{35}\)

With the current industrialisation and modernisation in Asia, the problem of outdoor air pollution and lung cancer should be closely monitored.
**Occupational exposure**

Occupational exposure to many agents is known to cause lung cancers, particularly in smokers, accounting for about 5% to 20% of all lung cancers.76

**Asbestos**

All asbestos mineral types are known to be associated with an increased risk of lung cancer.77 The recognition of its carcinogenicity has led to bans on the importation of amphibole asbestos into many European Union (EU) countries, beginning with Sweden in 1975. By the early 1980s, most industrialised countries, including Japan, had instituted such bans. As the global market shrank for amphibole asbestos, its major South African producers sought new markets for their useful but very hazardous minerals. In 1993, South Africa was still exporting amphibole asbestos to 21 countries, mostly in Asia, although production ceased a few years later.78 Chrysotile is currently the main asbestos mineral traded globally, mostly originating in Canada, Russia or Brazil. Many EU countries also support a ban on chrysotile.

In Asia, fewer details of statistics and studies on occupational lung cancer are available. A historical cohort mortality study of ship repair workers in a US Navy shipyard in Japan, with a follow-up period of 1947–1974,79 showed that laggers who had handled asbestos materials directly had a significantly raised standardised mortality rate (SMR) of 2.75 for lung cancer, whereas boiler repairers, who had less direct exposure, showed no elevation of the SMR of lung cancer overall. A retrospective cohort study (1972–1981) of occupational lung cancer in asbestos (chrysotile) factories in China showed a risk ratio of lung cancer in factory workers of 5.32, with a dose-response relationship and a synergistic effect with cigarette smoking.80

**Silica**

Although crystalline silica was recently classified as a human carcinogen by the IARC, controversy still exists over this issue, partly because of the difficulty of resolving the confounding factors of smoking, exposure to mixed dust and background radiation in workers. In Asia, a number of studies examining the association between occupational silica exposure and lung cancer have been performed, with conflicting results. Studies suggesting a positive association included those from Japan81,82 and China83,84 and they showed an overall dose-related excess risk of about two-fold. On the other hand, studies from Shanghai85 and Hong Kong86 concluded that smoking was the main factor for lung cancer in these workers, and that silica did not contribute independently.

The level of exposure to dust and alpha radiation and the risk of lung cancer in South African gold miners have been investigated in several epidemiological studies. The first mortality study of 3971 white miners, followed from 1970 for 9 years, reported an RR of 1.8 (95% CI 0.94–3.31), adjusted for smoking, for one unit of 10 000 particle years.87 The follow-up period was extended to 20 years, and an RR of 1.08 (95% CI 0.94–1.2) was reported.88 A second mortality study involving a cohort of 2260 white gold miners followed from 1970 to 1986 showed an association between lung cancer deaths and cumulative dust exposure (RR 1.023, 95% CI 1.005–1.042, adjusted for smoking).89 A nested case-control study was carried out on this second cohort and the risk of lung cancer was associated with cumulative dust exposure, duration of underground mining, presence of silicosis and tobacco smoking.90

Sugar cane farmers and sugar mill workers in India are exposed to fibres of biogenic amorphous silica (BAS) formed from silica absorbed from the soil and deposited on the leaves of the sugar cane crop, or crystalline silica formed as a result of conversion of BAS to cristobalite at high temperatures. These farmers had an increased risk of lung cancer (OR 1.92).91

**Other occupational exposures**

An increased risk of lung cancer has been found among textile workers and woodworkers in India, although this increase in risk was not statistically significant.92,93 A large cohort study of 74000 benzene-exposed workers (in coating applications, rubber, chemical and shoe production) in 12 cities in China showed significant dose-related increases in deaths due to lung cancer and haematopoietic malignancies.94

The role of occupational exposure in lung cancer in Africa has been relatively well studied compared with other risk factors. Among black South Africans, a history of exposure to potentially toxic substances was associated with an increased risk for lung cancer that was significant in males but non-significant in females.94 In South-Western Zimbabwe, copper and nickel mining was associated with a significantly increased risk for lung cancer.13

**Diet**

Epidemiological studies from the West have suggested that a higher intake of fruit and vegetables is protective against the risk of lung cancer, but randomised controlled clinical trials using high doses of beta carotene and vitamin A failed to show a reduced risk for lung cancer.95–97 The lack of demonstrable benefit or even an adverse outcome of increased risk of lung cancer in smokers who participated in these trials would contradict the epidemiological observations and suggest that there are nutrients other than beta carotene and vitamin A in fruits and vegetables that may inhibit carcinogenesis. On the other hand, dietary fat, particularly saturated fat consumption, is associated with an increased risk of lung cancer.

Case-control studies in Chinese women in Shanghai98 and Harbin99 in the mainland of China, Hong Kong100 and Taiwan101 have all shown similar findings,
namely a protective effect associated with high consumption of fruits, leafy green vegetables and food sources rich in vitamin A. This protective effect is mostly seen for lung cancer of the adenocarcinoma type. On the other hand, cured meats (Chinese sausage, pressed duck and cured pork, all specialties of Cantonese cuisine), deep-fried cooking, chili and alcohol increased the risk of lung cancer. Studies in Chiang Mai Province of Northern Thailand and K sola in south India all showed similar findings.

In Japan, preserved foods formed a large part of the diet before refrigerators were widely used; these contain N-nitroso compounds or their precursors with mutagenicity. Miso (preserved, fermented soybean paste) soup and pickles (excluding salted fish) were found to be associated with an increased risk, and frequent intake of soybeans and tofu (soybean curd) a decreased risk (tofu being especially protective against squamous cell cancer) of lung cancer, confirming the deleterious effects of preserved foods and protective effects of soyfoods rich in isoflavones.

London et al., in a follow up study of a cohort of 18,000 Chinese men in Shanghai from 1986 to 1997, found that isothiocyanates reduced lung cancer risk, and that the risk reduction was strongest among persons genetically deficient in glutathione-S-transferase (GST), enzymes that metabolise these chemopreventive compounds. Similarly, a study from Singapore has shown that in a Chinese female population, the risk of lung cancer is inversely related to dietary isothiocyanates, mainly in non-smokers with homozygous deletion of GSTM1 and/or GSTTT1.

Infections

Tuberculosis

A case-control study in Shanghai showed a significant increase in the incidence of lung cancer among tuberculous patients independent of smoking. It is not known whether the relationship between tuberculosis and lung cancer is due to scarring from previous tuberculous infection. Scar cancer has long been recognised, and adenocarcinoma is reported to be the predominant cell type. Several African countries have a high burden of tuberculosis; however, there are no published studies of the association between tuberculous and risk of lung cancer.

Human papillomavirus infection

Human papillomavirus (HPV), 16/18 type, has been implicated in neoplasms of uterine cervix, anus, penis, vulva, skin, oesophagus, head and neck. HPV infection has also been associated with lung carcinoma in Japanese and Scandinavian studies. More recently, Cheng et al. in Taiwan found an OR for the presence of HPV 16/18 infection of 10.12 (95% CI 3.88–26.88) in non-smoking female lung cancer patients, much higher than the 1.98 (95% CI 0.84–4.76) in non-smoking male lung cancer patients. This result strongly suggests that HPV infection is associated with lung cancer development in non-smoking female lung cancer patients in Taiwan.

Microsporum canis infection

Lung cancer incidence among Northern Thai women is one of the highest in Asia. Two close areas with similar cultures were studied: the Sarapee area, and the Chom Tong area, with crude lung cancer rates of 40.9 and 8.5, respectively. Lifestyle factors and diet were investigated, and chemical examination of drinking water and mutagenicity testing of urine samples were performed. The most distinct finding was the high incidence of chronic benign respiratory diseases among women in Sarapee, who had a raised serum antigen concentration of a fungus M. canis commonly found in air inside houses in Sarapee.

Human immunodeficiency virus infection

It is well known that Kaposi’s sarcoma and non-Hodgkin’s lymphoma occur in excess in persons with human immunodeficiency virus (HIV) infection. An increased incidence of lung cancer has also been observed in HIV and acquired immune-deficiency syndrome (AIDS) infected patients in the US, with risk ratios of 4.5–6.5. HIV infection is prevalent in many Asian and African countries, but no data on its association with lung cancer are available.

Gender differences in susceptibility

Several studies have suggested that women are more susceptible than men to lung cancer induced by smoking. There is a significantly higher OR for lung cancer in women than in men with equivalent tobacco exposure, while others have found significantly lower mean pack-years of smoking for women diagnosed with lung cancer compared with men. The risk of lung cancer in lifetime non-smokers is about 2.5 times more common in women than in men. Thus, if women are more susceptible to the adverse effects of tobacco than men, the incidence of lung cancer among female non-smokers may reflect increased susceptibility to exposure to environmental tobacco smoke and possibly other low-level environmental carcinogens. Adenocarcinoma of the lung, which shows a weaker association with tobacco smoking than other types of lung cancer, is also found predominantly in women. The reasons for gender differences in susceptibility to lung cancer are not clear, but endogenous and exogenous oestrogens have been implicated: early age at menopause is associated with a reduced risk of adenocarcinoma of the lung (OR = 0.3), while the use of oestrogen replacement therapy is associated with a higher risk (OR = 1.7) and a positive interaction between oestrogen replacement therapy, smoking and the development of adenocarcinoma (OR = 32.4).
Genetic factors
Lung cancer, like other cancers, is now thought to be due to deregulation of normal gene expression. There has been a great deal of interest in genetic factors in lung cancer, and polymorphisms of many genes and the risk of lung cancer have been studied extensively in both industrialised and Asian countries.

Tobacco-derived carcinogens require oxidation and conjugation for excretion and detoxification. The ary1 hydrocarbon receptor binds incoming aromatic hydrocarbons, and members of the cytochrome P450 family activate polycyclic aromatics, while GSTs inactivate these carcinogens. Thus polymorphisms of genes of these enzymes may lead to increased risk for lung cancer. The N-acetyltransferase (NAT2) slow acetylator genotype was found to be associated with an increased risk of lung cancer, especially adenocarcinoma, among non-smoking Chinese women in Singapore.119 As NAT2 activity is known to modify the risk of arylamine-induced carcinogenesis, the results of this study suggest that exposure to arylamines in the environment may play a role in development of lung cancer among non-smokers. More recently, the same group showed that Chinese women with slow NAT2 and rapid CYP1A2 activity were at highest risk for lung adenocarcinoma (adjusted OR [aOR] 6.9) relative to those with rapid NAT2 and slow CYP1A2 activity.120 CYP2E1 Rsal polymorphism but not Dra1 polymorphism was found to be associated with the development of lung cancer in Taiwan.121 The homozygote variants of Rsal genotypes were more common in controls (6.9%) than in lung cancer patients (0.8%) (aOR 0.12).

The mu (GSTM1) and theta (GSTT1) members of the GST multigene family are known to be detoxifiers of carcinogens. Deletion of these genes results in null GSTM1 and GSTT1 genotypes associated with a lack of enzyme action. The prevalence of GSTM1 null genotype occurs in about 50% of the population, and the association between GSTM1 null genotype and the risk of lung cancer has been more extensively studied.122 The results so far are controversial, with some showing an increased risk and others a protective effect. Hong Kong Chinese had a higher prevalence of null GSTT1 genotype (over 50%) compared to other ethnic groups; its occurrence among non-smokers increased the risk for lung cancer.123 The presence of this null gene probably potentiates the effects of low levels of environmental carcinogens such as ETS and outdoor air pollutants such as diesel particles.124

The p53 tumour suppressor gene is the most commonly mutated gene in cancer; a mutation incidence (most commonly in exons 5 to 8) of over 50% in patients with lung cancer has been reported in the West. Mutations in the p53 gene commonly reflect exposures to environmental carcinogens such as cigarette smoke in lung cancer. The p53 gene is induced by DNA damaging agents and delays cell cycle progression or steers the damaged cell into programmed cell death. Studies in Chinese groups showed conflicting results. Gao et al. in Guangzhou reported an overall mutation rate of 67%, with comparable rates between smokers (70%) and non-smokers (65%).123 Wang et al., from Taiwan, found a p53 mutation rate of 18% in their lung cancer patients, irrespective of their smoking habits.126 A study of Hong Kong female lung cancer patients showed that a high proportion of the mutations observed were deletions,127 suggesting the possible involvement of a distinct mutagenic factor(s) in Chinese female lung cancer patients. Another study from Hong Kong found a 16% mutation rate in the region of exon 5 to exon 8, but abnormal protein expression was present in 46% of patients, possibly indicating other genetic aberrations outside the hot spot region of exons 5–8.128 p53 polymorphisms have also been studied.129,130 The Pro allele of the p53 codon 72 polymorphism was found to increase the risk of lung cancer (especially adenocarcinoma) among female Chinese patients in Taiwan.131 Similarly, Ge et al., from Hong Kong, found that the A1 allelic frequency (of the p53 intron 2 polymorphism) was increased in adenocarcinoma of the lung.129

K-ras oncogene activation by point mutation occurs in about 30% of adenocarcinoma of the lung in Caucasians. However, K-ras gene mutation was not found in female patients with bronchial adenocarcinoma in studies from Taiwan132 and Hong Kong.133 This is not surprising, as it is now known that point mutation in the K-ras oncogene occurs as a result of exposure to cigarette smoking, and the majority of Chinese female lung cancer patients are non-smokers. Genome-wide screening by microsatellite analysis134 and comparative genomic hybridisation135 has identified target foci of frequent genetic aberration in 16p, 16q, 17q and 19q in adenocarcinoma of lung in non-smoking Chinese patients which do not overlap with those of smokers.

CONCLUSION
The global age-standardised incidence rates for lung cancer in 2000 were 30.9 and 11.9/100 000 for males and females, respectively, with considerable regional variation. In industrialised countries, lung cancer is the most common form of cancer in males and is growing in frequency among females; for both sexes, lung cancer rates reflect smoking behaviour. Epidemiological data on lung cancer are lacking in many Asian and African countries and studies on risk factors, environmental or genetic, are patchy and scarce. However, existing data have shown that the pattern appears to be different in Asia, particularly in China, where men’s high lung cancer rates reflect high smoking rates but high rates among non-smoking women appear to be related to other factors. In addition to tobacco smoking, a number of etiological factors have been identified for lung cancer: exposure indoors to environmental
tobacco smoke, cooking oil vapour, coal burning or radon, outdoor air pollution and occupational exposure to asbestos and other carcinogens. As the effect of tobacco for lung cancer is overwhelming, most of the studies of other exposures were carried out on non-smokers or adjusted for personal smoking habits; however, the influence of exposure to ETS was often not taken into consideration in these studies. Dietary factors have also been found to be important in lung cancer, but the results of clinical trials of chemoprevention using large doses of beta carotene and vitamin A failed to confirm the epidemiological observation that a high consumption of vegetables and fruits was protective. Certain infections, such as Mycobacterium tuberculosis, human papilloma virus, HIV infection and Microsporum canis, have been found to be associated with a high risk of lung cancer. As the prevalence of tuberculosis and HIV infection in developing countries is high, their role in lung cancer in Asia and Africa should be evaluated further. Individuals with polymorphisms of genes that control enzyme-regulating activation or detoxification pathways may be at increased risk of lung cancer when exposed to even low levels of tobacco smoke or environmental carcinogens. The role of genetic susceptibility and its interaction with carcinogens is being explored actively at present.

The major challenge continues to be the battle against cigarette smoking. With the rapid growth of cigarette consumption in developing nations, a major epidemic of lung cancer and smoking-related diseases is predicted. All health care professionals, government health authorities and national and international health organisations must join in a concerted effort against tobacco use.

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tando. Además del tabaquismo, se ha identificado un cierto número de factores etiológicos del cáncer del pulmón: exposición ambiental en interiores al humo del tabaco, al vapor del aceite de cocina, a la combustión del carbón o al radón, exposición a la contaminación ambiental y exposición ocupacional al asbesto o a otros cancerígenos. Estudios recientes demostraron que algunos factores alimentarios pueden ser importantes; así, un alto consumo de hortalizas y frutas sería protector, mientras que los alimentos en conserva y la alimentación grasa serían nocivos. Algunas infecciones, como aquellas por *Mycobacterium tuberculosis*, el virus del papiloma humano y por *Microsporum canis*, se asocian con un alto riesgo de cáncer del pulmón. En la actualidad, se estudia activamente la función de la susceptibilidad genética individual a los cancerígenos ambientales entre los no fumadores. Puesto que la causa única más importante del cáncer del pulmón es el humo del tabaco y teniendo en cuenta que con el incremento de las ventas se predice una epidemia mayor en Asia y África, todos los profesionales de la salud, las autoridades sanitarias gubernamentales y las organizaciones de salud nacionales e internacionales deben reunirse en un esfuerzo conjunto en contra del tabaco.