Lung cancer trends. Part 2: Beyond North America

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1. INTRODUCTION

Estimation of the burden of cancer in terms of incidence, mortality, and prevalence is a first step toward instituting control measures in a global context. The present review (part 2) follows up an earlier review of lung cancer trends in North America [1] with a review of lung cancer trends in 23 world areas. Except where otherwise noted, all incidence and mortality rates mentioned in the text are age-standardised to the world standard population, thereby taking into account differences in the age structures of the various populations being compared. The high case fatality rate of lung cancer means that the incidence and mortality rates of the disease are nearly equivalent. Consequently, vital statistics provide a long record of the occurrence of the disease [2].

2. OVERVIEW OF LUNG CANCER TRENDS: THE 23 WORLD AREAS

The estimates of mortality from lung cancer with available long-term data are selected from a series of countries representative of the 23 "world areas" defined by the United Nations: Egypt (Africa); Cuba (Caribbean); Costa Rica and Mexico (Central America); Venezuela (South America); China and Japan (East Asia); Singapore (Southeast Asia); Israel (Western Asia); the Russian Federation, Slovenia, and Poland (Eastern Europe); Sweden, Norway, and Finland (Northern Europe); Italy (Southern Europe); the United Kingdom, Spain, France, Switzerland, and Germany (Western Europe); and Australia and New Zealand (Oceania). North America, East Asia (Japan), Eastern Europe, Northern Europe, Southern Europe, Western Europe, and Oceania (Australia and New Zealand) represent developed countries; the remaining areas represent developing countries. The sources of data for the estimates of mortality from the 23 countries are extracted from the World Health Organization Statistical Information System (WHOSIS) [3].

In 1990, lung cancer was the most common cancer in the world, in terms of both the number of cases (1.037 million) and the number of deaths (0.921 million) [4]. In 1990, global estimates of lung cancer incidence were 772,000 cases in men and 265,000 cases in women, and of mortality were 693,000 deaths in men and 228,000 deaths in women. Also in 1990, the lung cancer incidence rates and mortality rates per 100,000 were, respectively, 37.5 and 33.7 (male) and 10.8 and 9.2 (female).

Globally in 1990, lung cancer was the most common cancer in men, with the highest incidence rates being observed in North America and Europe (especially Eastern Europe). Moderately high rates were also seen in temperate South America, in Australia and New Zealand, and in parts of Eastern Asia. In women, the incidence rates were lower: overall, the rate was 10.8 per 100,000 women as compared with 37.5 per 100,000 men. The highest rates were seen in North America and Northern Europe. The incidence in China was also high (13.4 per 100,000), similar to that seen in Australia and New Zealand (16.1 per 100,000).

In 2000, the available international data [5] showed 10.1 million new cases of lung cancer, 6.2 million deaths, and 22.4 million people living with the disease. As the new millennium begins, lung cancer remains the main cancer in the world (12.3% of all new cancers), whether considered in terms of number of cases (1.2 million) or number of deaths (1.1 million). About 52% of all the new lung cancer cases occurred in developed countries. The disease is more common in men (75% of total cases worldwide), and the world areas with the highest incidence are Europe (especially Eastern Europe), North America, Australia and New Zealand, and South America. The rates in China, Japan, and Southeast Asia are moderately high. In developing countries, the highest rates are seen in places where tobacco smoking has been longest established: the Middle East, China, the Caribbean, South Africa, Zimbabwe, and countries of the Pacific Ocean. In women, the geographic pattern is a little different, reflecting a different historical pattern of tobacco smoking. The highest incidence rates are observed in North America and northwest Europe (the United Kingdom, Iceland, Denmark). Moderate incidence rates are seen in Australia and New Zealand, and in China [6].

The most important cause of lung cancer is tobacco smoking, and the incidence rates of the disease in a country closely reflect that country's history of tobacco smoking [7]. In countries or regions with a long history of smoking, 90% or more of cases in men are tobacco-related. The fraction is much lower in Africa and Southern Asia. In women, the proportion of cases that are tobacco-related are more variable—even in Europe, where it ranges from 80% in the United Kingdom to near zero in Spain and Portugal.

The estimated number of lung cancer cases worldwide has increased by 16% since 1985 (representing increases of 4% in men and 21% in women), with the increase in actual risk being about 2.5% in men and 9.5% in women. This overall upward trend disguises considerable difference among countries. In men, several populations have now passed the peak of the tobacco-related lung cancer epidemic, and incidence rates are declining: for example, in the populations of the United States and Northern and Western Europe. In contrast, incidence and mortality are increasing rapidly in Southern and Eastern European countries. In women, the epidemic is less advanced. Most developed countries are still showing a rising trend in female incidence and mortality, with Spain being an exception. For the United Kingdom, the peak of the trend may now have been reached.

The global variation in lung cancer incidence over the past fifty years is thought to be directly proportional to the smoking habits prevalent in the part of the world being considered [8]. During this time, lung cancer incidence showed a greater upward trend in the United States and in Central and Eastern Europe than it ever had before, especially in women. Japan has recorded a tenfold increase in incidence in both sexes since 1975. In India, the problem is further compounded by absence of authentic data on time trends. Recent available data suggest a more or less linear trend. Up to 1999, lung cancer was ranked among the top three killers in men in almost every metropolis in India. The highest incidence rate was recorded in Mumbai (14.6 per 100,000) and the lowest in Barshi (2.0 per 100,000). The exact number of lung cancer cases attributable to smoking cannot be known, because no case-control or cohort studies have ever been undertaken in India. The situation in other developing countries is even more alarming, because no authentic data are available on tobacco use or lung cancer incidence among women and passive smokers.

Lung cancer remains a highly lethal disease. Survival rate at 5 years as measured by the Surveillance, Epidemiology and End Results program in the United States is about 14%, the best result recorded at the population level. The average survival rate in Europe is about 8%, which is the same rate as that seen in developing countries.

Lung cancer has multiple histologic subtypes as classified by conventional light microscopy. The four major types are squamous-cell carcinoma, adenocarcinoma, large-cell carcinoma, and small-cell undifferentiated carcinoma. Smoking has been shown to cause each of the major histologic subtypes of lung cancer, although the dose–response relationship with the number of cigarettes smoked varies across the subtypes. Dose–response is steepest for small-cell undifferentiated carcinoma [9,10].

In the initial decades of the smoking-caused epidemic of lung cancer, squamous-cell carcinoma was the most frequent type of lung cancer observed in the population among smokers; small-cell carcinoma was the next most frequent. In the late 1970s, evidence showed a shift toward a predominance of adenocarcinoma, and adenocarcinoma of the lung is now the most common histologic subtype of lung cancer [11,12].

Given the dramatic change in the incidence of the histologic subtypes of lung cancer in industrialised countries over the last two decades, Janssen–Heijnen *et al.* [13] reviewed trends in the incidence and prognosis of the disease in North America, Australia, New Zealand, and Europe according to period of diagnosis and birth cohort, and summarised explanations for changes in mortality. Although the incidence of lung cancer has been declining since the 1970s and 1980s among men in North America, Australia, New Zealand, and northwestern Europe, the age-adjusted rate continues to increase among women in those countries, and among both men and women in Southern and Eastern Europe. The trends follow changes in smoking behaviour. The proportion of adenocarcinoma has also been increasing over time; the most likely explanation is the shift to low-tar filter cigarettes during the 1960s and 1970s.

Despite improvement in both diagnosis and treatment, the overall prognosis for patients with non-small-cell lung cancer has hardly improved over time. In contrast, for patients with small-cell lung cancer, the introduction of and improvements in chemotherapy since the 1970s have given rise to some improvement only in short-term (<2 years) survival. The epidemic of lung cancer is not over yet, especially in Southern and Eastern Europe.

Costa Rica, Egypt, Mexico, and Venezuela have relatively low mortality rates in both younger (age < 50) and older (age = 50+) men and women. Very similar patterns are seen in Australia, Finland, Germany, Italy, New Zealand, Norway, Poland, Singapore, Sweden, Switzerland, and the United Kingdom. In those places, mortality rates have reached a peak and have begun to decline for older and younger men. Mortality rates for older women are still rising, and for younger women, they are either flat or still rising moderately. All of those countries are developed countries. China, France, Japan, and Spain show mortality rates that are rising steadily or moderately for both older and younger men and women.

Cuba, Israel, the Russian Federation, and Slovenia have relative high, steady mortality rates for older men and women. The trends for younger and older members of both sexes are almost flat across all years (Figures 1 to 23) [3]. In general, mortality rates lag smoking rates by about 30 years.

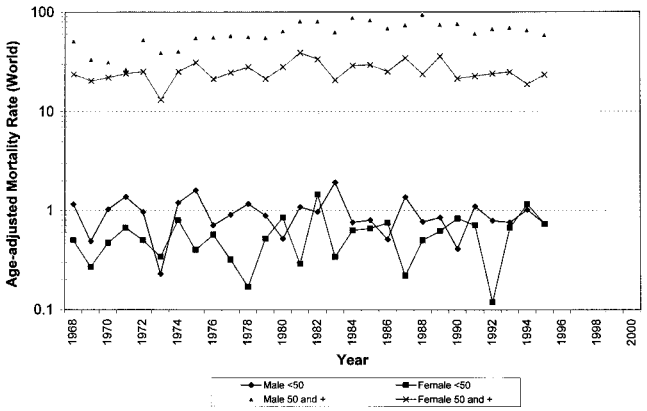

FIGURE 1 *Lung cancer mortality rates for Costa Rica, for men and women under the age of 50 years and aged 50 years and older* [3]

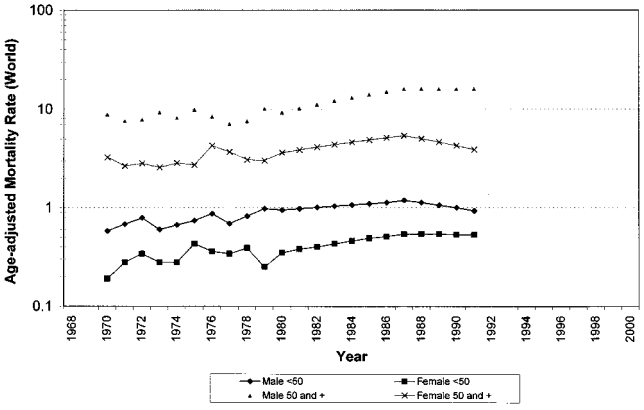

FIGURE 2 *Lung cancer mortality rates for Egypt, for men and women under the age of 50 years and aged 50 years and older* [3]

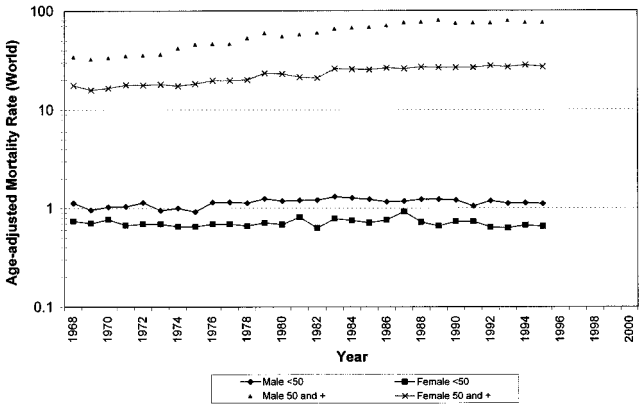

FIGURE 3 *Lung cancer mortality rates for Mexico, for men and women under the age of 50 years and aged 50 years and older* [3]

3. EUROPE

The highest incidence rates for lung cancer in men are seen in Europe, especially Eastern Europe. In women, high incidence rates are found particularly in Northern and Western Europe. Estimates suggest

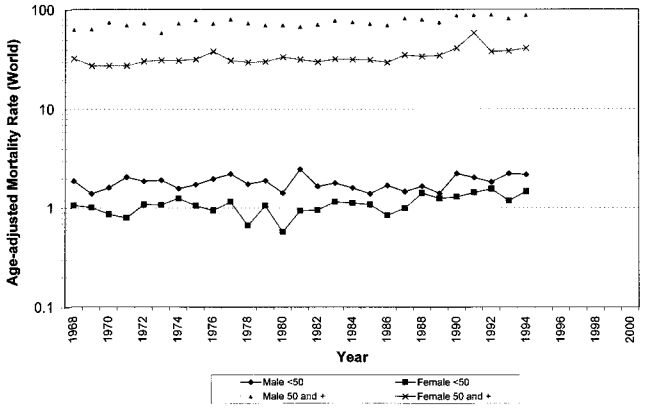

FIGURE 4 *Lung cancer mortality rates for Venezuela, for men and women under the age of 50 years and aged 50 years and older* [3]

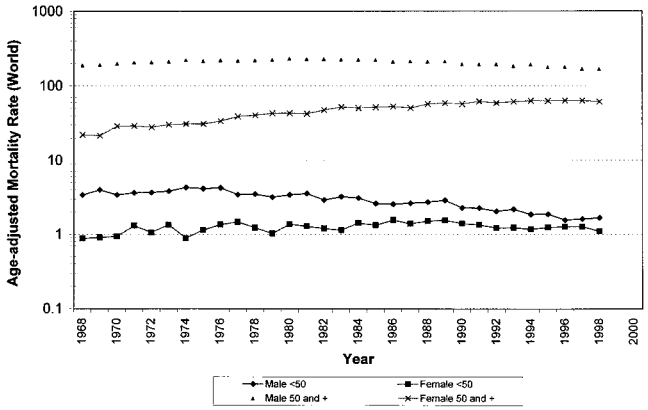

FIGURE 5 *Lung cancer mortality rates for Australia, for men and women under the age of 50 years and aged 50 years and older* [3]

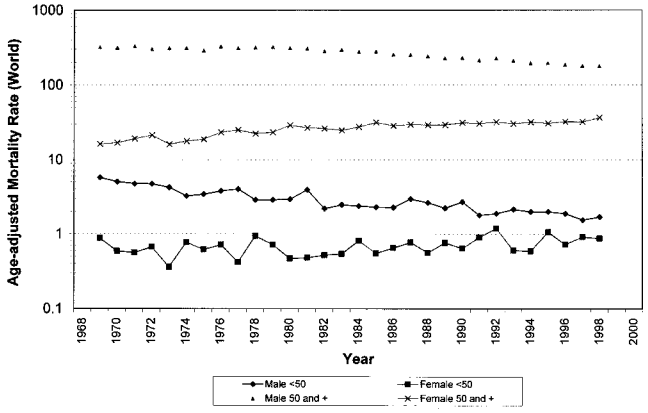

FIGURE 6 *Lung cancer mortality rates for Finland, for men and women under the age of 50 years and aged 50 years and older* [3]

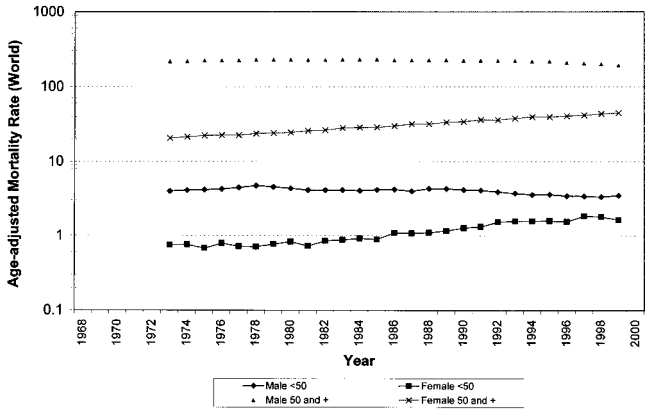

FIGURE 7 *Lung cancer mortality rates for Germany, for men and women under the age of 50 years and aged 50 years and older* [3]

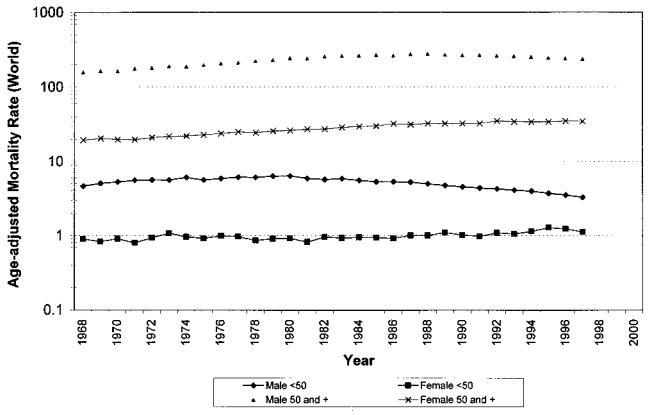

FIGURE 8 *Lung cancer mortality rates for Italy, for men and women under the age of 50 years and aged 50 years and older* [3]

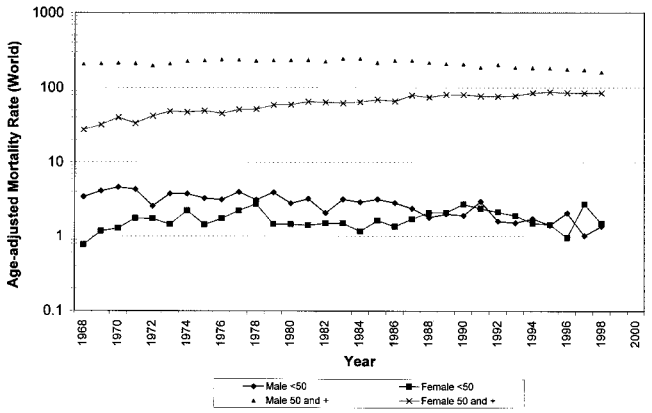

FIGURE 9 *Lung cancer mortality rates for New Zealand, for men and women under the age of 50 years and aged 50 years and older* [3]

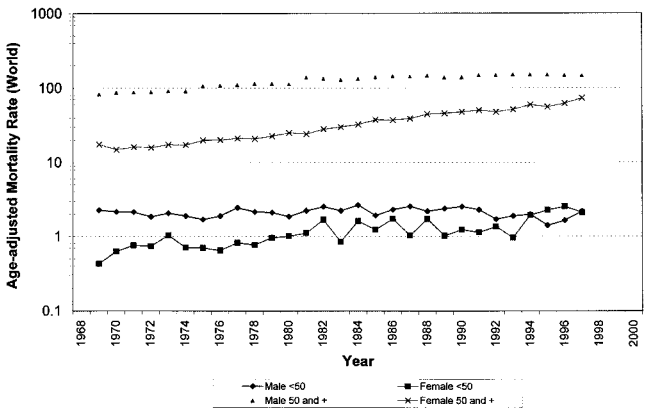

FIGURE 10 *Lung cancer mortality rates for Norway, for men and women under the age of 50 years and aged 50 years and older* [3]

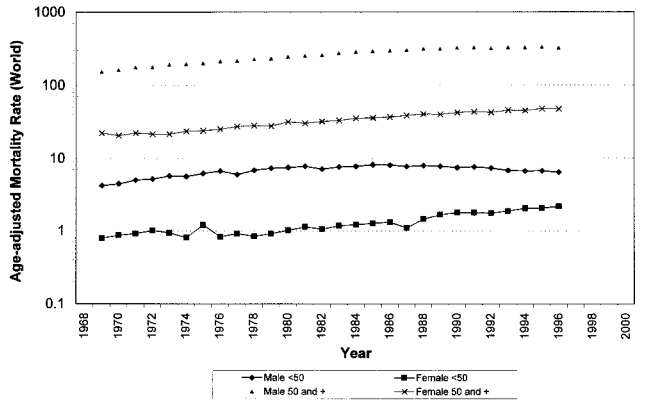

FIGURE 11 *Lung cancer mortality rates for Poland, for men and women under the age of 50 years and aged 50 years and older* [3]

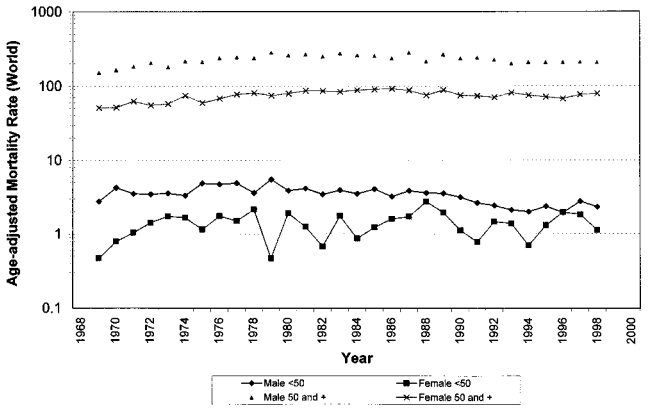

FIGURE 12 *Lung cancer mortality rates for Singapore, for men and women under the age of 50 years and aged 50 years and older* [3]

that, in 2000, about 375,000 cases of lung cancer occurred in Europe (303,000 in men and 72,000 in women). The number of resulting deaths was about 347,000 (280,000 in men and 67,000 in women). About 90% of cases are thought to be tobacco-related. Lung cancer risk has a clear dose–response relationship with number of cigarettes smoked daily, degree of inhalation, and age at initiation of smoking. A lifelong smoker has a risk for lung cancer 20 – 30 times that of a non-smoker. However, risk of lung cancer declines with duration of smoking cessation.

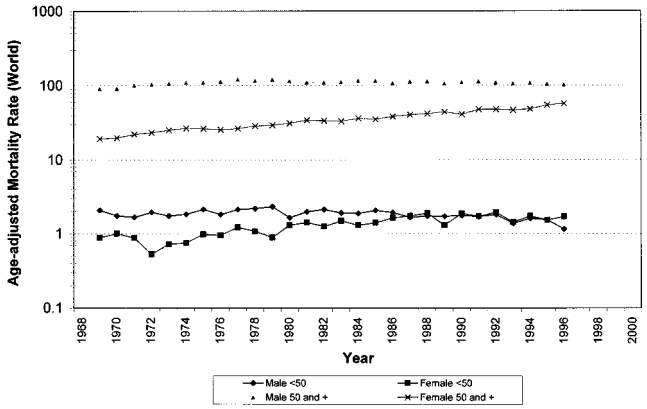

FIGURE 13 *Lung cancer mortality rates for Sweden, for men and women under the age of 50 years and aged 50 years and older* [3]

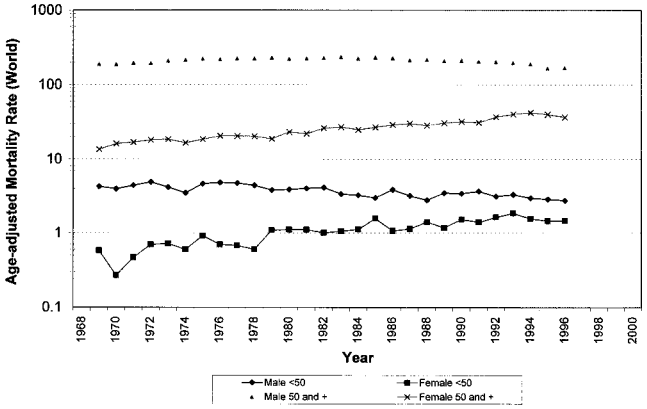

FIGURE 14 *Lung cancer mortality rates for Switzerland, for men and women under the age of 50 years and aged 50 years and older* [3]

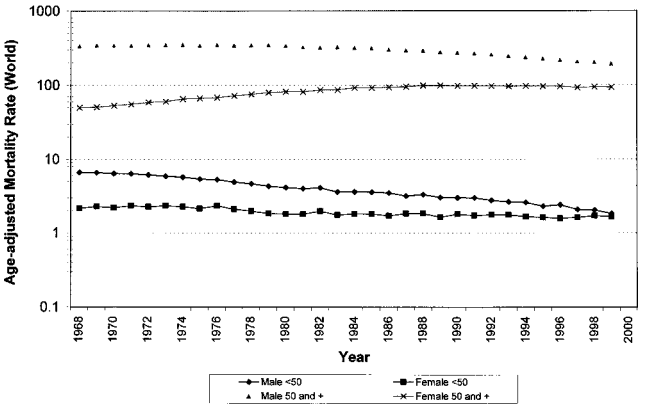

FIGURE 15 *Lung cancer mortality rates for United Kingdom, for men and women under the age of 50 years and aged 50 years and older* [3]

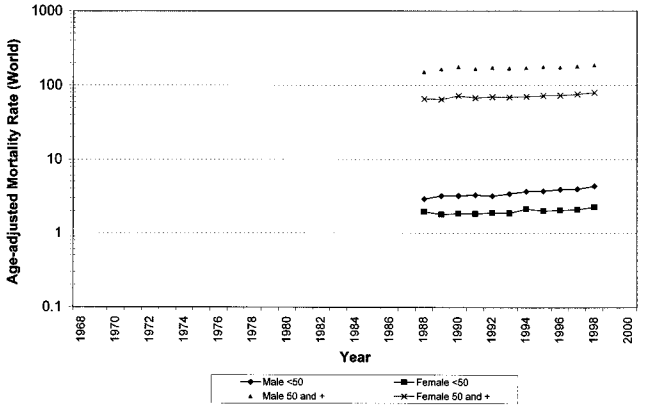

FIGURE 16 *Lung cancer mortality rates for China, for men and women under the age of 50 years and aged 50 years and older* [3]

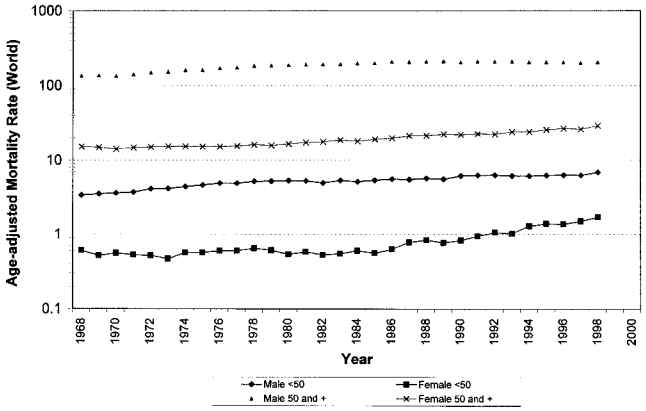

FIGURE 17 *Lung cancer mortality rates for France, for men and women under the age of 50 years and aged 50 years and older* [3]

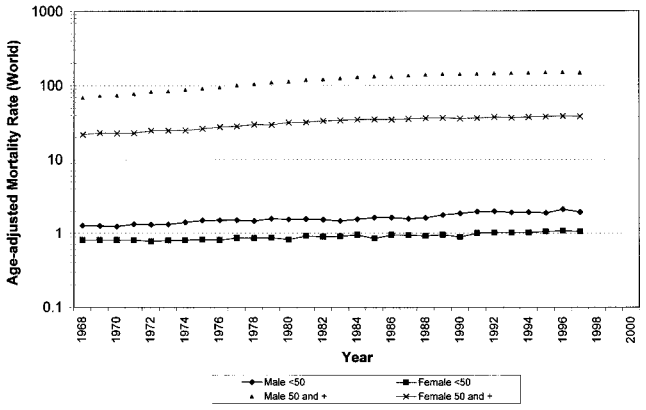

FIGURE 18 *Lung cancer mortality rates for Japan, for men and women under the age of 50 years and aged 50 years and older* [3]

In a study conducted by Tyczynski *et al.* [14], Europe was divided into four parts: Eastern Europe (Belarus, Bulgaria, Czech Republic, Hungary, Moldova, Poland, Romania, Russia, Slovakia, and Ukraine), Northern Europe (Denmark, Estonia, Finland, Iceland, Ireland, Latvia, Lithuania, Norway, Sweden, and the United Kingdom), Southern Europe (Albania, Bosnia–Herzegovina, Croatia, Greece, Italy, Macedonia, Malta, Portugal, Slovenia, Spain, and Yugoslavia), and Western Europe (Austria, Belgium, France, Germany, Luxembourg, Netherlands, and Switzerland). Substantial differences in incidence

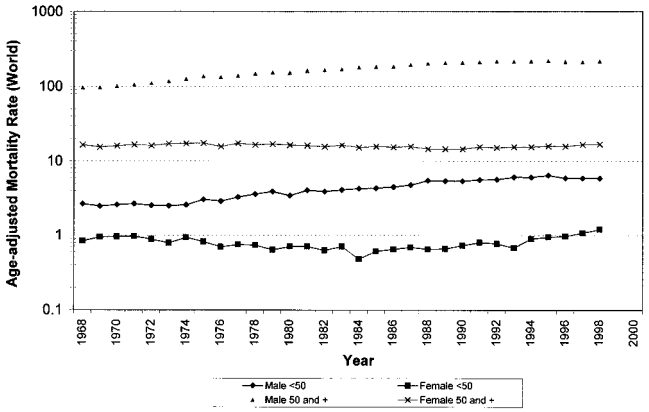

FIGURE 19 *Lung cancer mortality rates for Spain, for men and women under the age of 50 years and aged 50 years and older* [3]

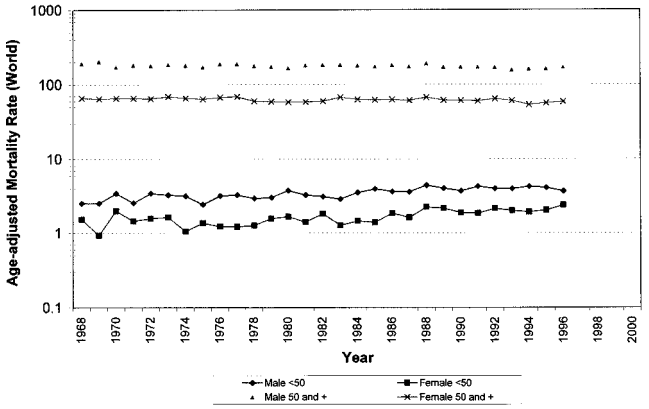

FIGURE 20 *Lung cancer mortality rates for Cuba, for men and women under the age of 50 years and aged 50 years and older* [3]

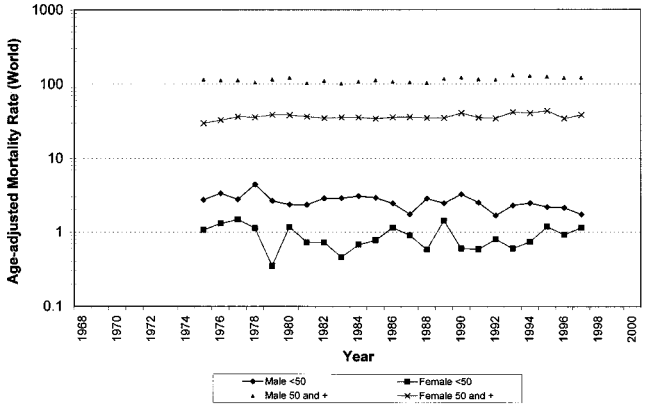

FIGURE 21 *Lung cancer mortality rates for Israel, for men and women under the age of 50 years and aged 50 years and older* [3]

and mortality are seen in the various regions and populations within Europe. In men, incidence and cumulative risk is highest in Eastern Europe—much higher than in other parts of the continent. In women, the highest incidence of lung cancer is in Northern Europe, where it is almost twice that seen in Western

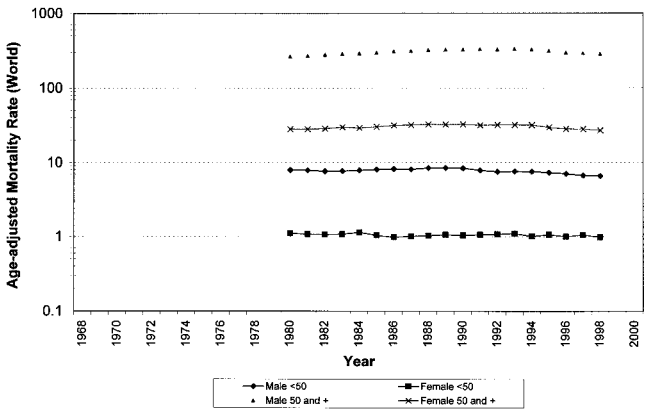

FIGURE 22 *Lung cancer mortality rates for Russian Federation, for men and women under the age of 50 years and aged 50 years and older* [3]

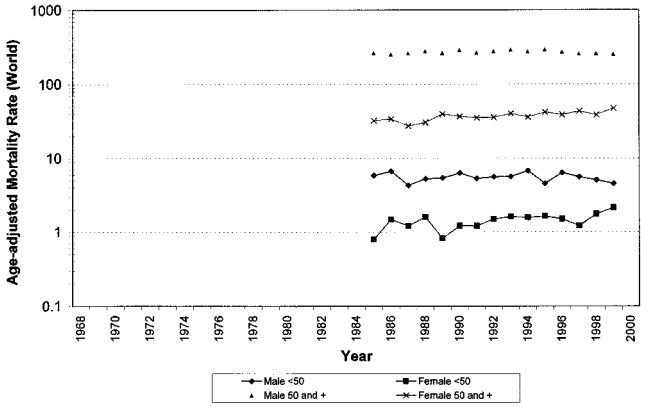

FIGURE 23 *Lung cancer mortality rates for Slovenia, for men and women under the age of 50 years and aged 50 years and older* [3]

Europe. The distribution of mortality shows a pattern similar to that of incidence (Figures 24 and 25) [14].

In men, lung cancer mortality is declining in Northern and Western Europe (in countries such as the United Kingdom and Finland), although it is already low and fairly stable in Sweden and Norway. In Central and Eastern Europe, however, lung cancer mortality is increasing, although it has been thought that, since the early 1990s, mortality rates in Poland are starting to level off. Until the end of the 1980s, mortality was high and increasing in women in the United Kingdom. Since then, however, a plateau has been reached, and rates have started to decline. In Sweden and Norway, mortality among older women has been increasing during the past 25 years, although the rate is still much lower than that in the United Kingdom. In Southern Europe, mortality from lung cancer for older women is either quite low or stable (in countries such as Greece) or increasing at a moderate rate (in countries such as Italy and Portugal).

Trends in lung cancer incidence by histologic subtype of the tumour vary according to the patient's

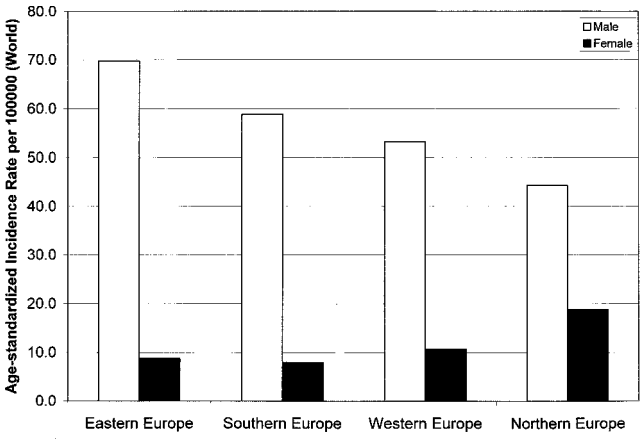

FIGURE 24 *Lung cancer incidence rates in Europe (age-standardised, world standard population)*

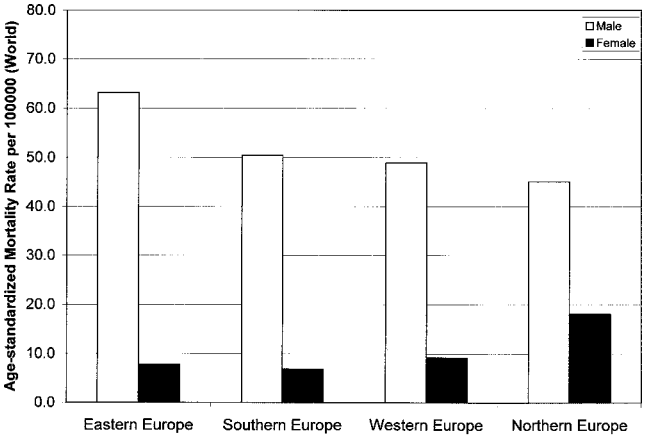

FIGURE 25 *Lung cancer mortality rates in Europe (age-standardised, world standard population)*

sex. Increasing rates of adenocarcinoma and decreasing rates of squamous-cell carcinoma have previously been reported in men in the United States [15] but lung cancers of all histologic subtypes have been increasing in U.S. women. A similar situation was observed in Europe (for example, in the Netherlands) in the second half of 1980s [12,16].

Changes in cigarette design and manufacturing technology in the latter half of the twentieth century may partly explain these changes, because the composition of tobacco smoke has been altered. The switch from high-yield to low-yield cigarettes and from unfiltered to filtered products in the 1960s and 1970s resulted in changes in the histologic structure of lung cancers: the frequency of adenocarcinoma increased relative to other histologic subtypes of lung cancer in Europe, the United States, and Australia [10,17–19]. Smokers who switch to low-yield cigarettes rather than quit increase their duration of exposure to carcinogens and are likely to compensate for the lower doses of nicotine by increasing the number of cigarettes smoked daily, by taking more puffs, and by inhaling more deeply [17,20,21]. Deeper inhalation and greater puff volume allows smoke particles to reach deeper into peripheral parts of the lung, increasing exposure to carcinogens.

In the past few decades, changes in tobacco consumption rates have occurred in several countries of Europe [22,23]. In most countries, these changes have resulted in lower incidences of lung cancer; however, in some areas (such as Norway, Spain, and Greece), smoking has been increasing among women [22]. In countries where the prevalence of smoking has been historically very low and has decreased over time (for example, in Sweden), lung cancer rates remain low. In other countries, particularly the United Kingdom and Finland, decreases in tobacco smoking among men were followed by a similar drop in lung cancer mortality about two decades later. An increase in smoking prevalence in women in some countries has later resulted in increased lung cancer mortality. In Norwegian females, smoking prevalence increased by nearly 50% between 1960 and 1980, and lung cancer mortality increased by 125% between 1980 and 1995.

In many countries of Europe—for example, the Netherlands [16], Denmark [24], and the youngest cohort in Strasbourg [25]—squamous-cell carcinoma has been the most frequent lung cancer in men, but adenocarcinoma has begun to increase. In Denmark during 1978 – 1994, squamous-cell carcinoma markedly decreased (43%) and adenocarcinoma increased (23%) in men. Adenocarcinoma in females also increased to become the most frequent lung cancer type, but the percentage was low (39%) [24].

Given the dramatic change in the incidence and mortality of the histologic subtypes of lung cancer in Europe during the twentieth century, Janssen–Heijnen *et al.* [26] studied the variation and change in incidence, treatment modalities, and survival of lung cancer in Europe. Although the incidence of the disease has been decreasing among men in Denmark, Finland, Germany (Saarland), Italy (Varese), the Netherlands, Switzerland, and the United Kingdom since the 1980s, the age-adjusted rate for men in other European countries increased at least until the 1990s. Among women, the peak in incidence had not been reached in the 1990s. The proportion of adenocarcinoma has been increasing over time, with the most likely explanation being the shift to low-tar filtered cigarettes.

Remarkable increases in lung cancer risk in the Central European area were observed by Kubik and Plesko [27], who in 1998 examined the patterns of lung cancer mortality rates and cigarette sales for the years 1965 – 1989 in four Central European countries. Their study encompassed a total population of 64.2 million, with 31,000 deaths from lung cancer in 1997. The patterns of increases in cigarette sales during the 1960s and 1970s varied by country, and, in the 1980s, the consumption in Hungary and Poland

exceeded 3,000 cigarettes per year per adult (15 years and older). Among men, the lung cancer death rates in 1989 for the Czech Republic (75.8 per 100,000), Hungary (74.0), Poland (69.4), and Slovakia (68.7) ranked among the highest in Europe, with the trends by country largely reflecting the prevalence and duration of smoking in that country in previous decades. The age-adjusted lung cancer death rates for females in the same countries (9.3, 14.4, 9.4, and 6.8 per 100,000 respectively) were much lower than those seen in the most developed countries and regions (for example, Scotland, the United States, Canada, England, and Denmark), but were rapidly increasing. In more recent birth cohorts, some decline has been seen in lung cancer mortality rates in men, but not in women. These trends in young adult life will spread to older age groups in future years. Hence, an increasing trend in lung cancer mortality can be predicted for the female population of the four countries studied by Kubik and Plesko, and that trend will probably continue well beyond the twentieth century. In most of the countries, the current, increasing trend in men can be expected to reach a plateau and to begin declining sooner than it will in women.

3.1 United Kingdom

Sharp and Brewster [28] studied the incident cases of lung cancer diagnosed from 1959 to 1993 and registered with the Scottish Cancer Registry; they then recorded deaths from lung cancer from 1919 to 1993. Scottish men and women were observed to experience rates of lung cancer that are among the highest in the world. In men, incidence rose from 1959 to a peak in the late 1970s; in the 1990s, it was decreasing steadily. Although women started from a lower baseline, incidence has risen steadily since 1959 (at a 5% annual rate of increase) and shows no evidence of a sustained decline. Between 1986 and 2000, the annual number of registrations in those younger than 85 years of age were estimated to fall by 20% in men and to rise by 8% in women. The incidence in the most deprived areas of Scotland was twice that in the least deprived areas. Survival prospects have changed little over the last 25 years. Although lung cancer incidence in men was falling, the peak of the lung cancer epidemic has likely not yet been reached in women.

Harkness *et al.* [29] examined trends in the incidence of lung cancer in Scotland from 1959 to 1997 and trends by histologic subtype from 1975 to 1997. Data were again extracted from the Scottish Cancer Registry. Incidence rates for adenocarcinoma increased steadily over time, but squamous-cell carcinoma remained the predominant type of lung cancer in Scotland.

Parsons and Somervaille [30] studied the U.K. data on 55,000 lung cancer patients in an age-cohort model of lung cancer incidence (1981 – 1995) and a parametric model of survival (1981 – 1991). Lung cancer trends were predicted to 2015, both at steady-state and with an incidence perturbation. The female lung cancer incidence rate was predicted to rise until, by 2015, the number will almost equal the male rate. Cohort coefficients revealed an increasing risk for lung cancer in women born after 1941. Survival of lung cancer was significantly associated with social deprivation.

3.2 Spain

Several changes in smoking patterns over past decades can be expected to result in a shift in lung cancer mortality rates in Spain. Franco *et al.* [31] examined the time trends in lung cancer mortality for 1973 – 1997. The standardised lung cancer mortality rate for men almost doubled to 58.6 per 100,000 in 1997 from 31.4 in 1973, with an average annual increase of 2.7%. As a consequence of increased cigarette smoking in successive birth cohorts, mortality increased for male generations born until 1952. However, if the slight downward trend observed for the two youngest generations continues, a more favourable outcome of the lung cancer epidemic among Spanish males is suggested for the coming years. For women, mortality rates were 5 – 9 times lower than for men: 6.3 per 100,000 in 1973, and 6.4 per 100,000 in 1997. However, the increasing mortality among the younger generations born since 1942 reflects the rise in the prevalence of smoking among women during recent decades. This mortality increase can be expected to spread to older age groups as a cohort effect, marking the early phase of the smoking-related lung cancer epidemic among Spanish females. The decreasing mortality trend observed in women until the late 1980s may be attributable to lower exposure to environmental tobacco smoke in the home as a result of a significant reduction in the prevalence of smoking in men.

Borras *et al.* [32] analysed the trends for 1980 – 1996 in the incidence of smoking-related cancers among men and women in Tarragona, Spain. The incidence of all smoking-related cancers combined increased significantly in both sexes. The annual increase was 3.0% in men and 4.5% in women. By cancer site, the annual increase among men was 4.3% (oral cavity), 5.1% (pancreas), 2.5% (lung), 3.2% (bladder), and 7.7% (kidney). Among women, the corresponding increments were 7.0%, 7.3%, 3.1%, 2.1%, and 6.9%. The increasing incidence of lung cancer in women consisted mostly of the adenocarcinoma histologic subtype. The effects of tobacco, alcohol, and occupational exposure to carcinogens could explain the high rates of larynx, bladder, and upper digestive tract cancers in men. The rising incidence rates of lung cancer observed in younger women was consistent with changes observed in smoking prevalence. Unless recent upward smoking trends in young women can be reversed, lung cancer in women will rise rapidly in subsequent years.

3.3 Denmark

The near doubling of lung cancer incidence in Copenhagen and rural areas of Denmark in the 1980s led to public concern. Engholm *et al.* [33] assessed the effects of air pollution and occupation on lung cancer in Denmark, with control for smoking habits, in a cohort study of the national population aged 30 – 64 years (927,470 men and 486,130 women), who were economically active in 1970. Differences in smoking habits explained about 60% of the excess lung cancer risk in Copenhagen for men and about 90% for women. Smoking is the main factor behind the regional differences in lung cancer incidence in Denmark, and occupational risk factors also seem to have an important role.

3.4 Sweden

Nordlund [34] studied data from three smoking habit surveys to construct age-specific smoking prevalence rates for nine 5-year birth cohorts between 1904 and 1948. Among men, smoking prevalence and lung cancer mortality were both relatively similar in all cohorts, although the 15- to 19-year-olds showed a successive increase in smoking prevalence with successive birth cohorts, resulting in a shift in peak lung cancer mortality from earlier- to later-born cohorts. Among women, it was apparent that smoking prevalence increased with successive birth cohorts and peaked in the late 1940s or early 1950s. Increases in cohort-specific lung cancer mortality were also seen, and the later-born cohorts with the highest smoking prevalence displayed the highest rates of lung cancer mortality. Because lung cancer is commonest at older ages, an increase in overall lung cancer mortality among women is expected over the next couple of decades.

3.5 Norway

Haldorsen and Grimsrud [35] analysed lung cancer incidence among cohorts from 1953 to 1992. In their analysis, they used a model that included an additive excess risk for smokers and that depended on daily dose and duration of smoking. The lung cancer incidence in later decades was adequately described by the model, which showed a simple relationship with smoking behaviour in the cohorts. For current smokers and former smokers alike, the excess risk was approximately proportional to the daily amount smoked and to the 4.5 power of duration of smoking. The age-specific rates for non-smokers were close to a 5th-power curve of age.

3.6 Netherlands

In the Netherlands, Siesling *et al.* [36] summarised the major population-based trends in cancer incidence and mortality for 1989 – 1998. Increases in incidence were found for cancer of the breast and lung for women. An increase in mortality was found for lung cancer in women. Trends in lung cancer incidence in women may be a result of changes in behaviour and smoking habits in the preceding decades.

3.7 France

In France, Menegoz *et al.* [37] studied all-cancer incidence in men, which increased throughout the period 1975 – 1995 to about 135,000 new cases in 1995 from about 92,000 in 1975. The increase was partly attributable to the aging of the French population, but the incidence rate had also increased, particularly between 1975 and 1985. The trend appeared to be levelling off in the 1990s, with an incidence rate in 1995 of about 482 per 100,000 population, standardised here (and elsewhere in this subsection) to the European standard population. Among women, the all-cancer incidence rate also increased during the 1970s and 1980s. Although the rate of increase was less pronounced than in men, the trend was continuing in the 1990s. The estimated age-standardised rate in 1995 was 309 per 100,000 population, representing 104,000 new cases. For women, the trend was dominated by a continuing increase in breast cancer, although increases in large-bowel and lung cancers were also seen.

For men, the most frequent cancers in 1995 were those of the prostate, large-bowel, and lung, incidences of which had all increased since 1975. Although estimates suggest that more new cases of prostate cancer than of lung cancer were diagnosed in 1995, the latter disease will cause many more deaths, particularly among young men.

Remontet *et al.* [38] studied the national cancer incidence and mortality trend over the longest period available in France. Data were collected for the period 1978 – 1997. The researchers selected 27 cancer sites and then estimated age-, sex-, and site-specific incidence and mortality rates for each year from 1978 to 2000. Cancer incidence increased by 63% during the study period to 278,000 new cases in 2000 from 170,000 in 1980. This change was chiefly the result of demographic change, but also of an increase in the risk of cancer, which was estimated to have risen by more than 35% during the same period. In men, the change was largely explained by an increase in prostate cancer incidence. Among women, it was dominated by a continuing increase in breast cancer incidence. Large increases were seen for lung cancer in women. Cancer mortality increased by 20% to 150,000 deaths in 2000 from 125,000 deaths in 1980. The trend of lung cancer mortality among women should be emphasised, because the situation will inevitably worsen in subsequent years. Lung cancer is already the third-leading cause of cancer death among women.

3.8 Italy

Decarli *et al.* [39] studied the trends in Italy in age-standardised rates for major cancer sites from 1955 to 1994. The age-standardised death certification rates in men from all neoplasms declined steadily to 186.3 per 100,000 in 1994 from a peak of 199.2 in 1988; in females, the decline was to 98.6 per 100,000 from 102.5. A major component of the favourable cancer mortality trends in men was a decline in lung cancer, which accounted for 31,000 deaths in both sexes combined in 1994. Overall age-standardised rates in men declined to 54.6 per 100,000 in 1994 from 60.3 in 1987 – 1989, and for ages 35 – 64, it declined to 72.7 in 1994 from the peak of 96.7 in 1983. In contrast, lung cancer rates in women have remained stable since 1992, but between 1985 – 1989 and 1990 – 1994, they increased to 7.7 from 7.2 at all ages and to 11.0 from 10.6 for ages 35 – 64. These different trends in the two sexes reflected the patterns and trends in smoking among Italian males and females. Cancer mortality trends in Italy over the period 1990 – 1994 were relatively favourable, reflecting mainly the decline in the lung cancer rate in males, but also the persistent declines in gastric cancer in both sexes and in cancer of the cervix uteri in women.

4. CENTRAL AND SOUTH AMERICA

Boffetta *et al.* [40] analysed mortality from cancers of the oral cavity and of the pharynx, oesophagus, larynx, and lung between 1955 and 1989 for the United States, Canada, and 14 countries in Latin America. Among men, the highest all-sites cancer rates were seen in Uruguay, Cuba, Argentina, and Puerto Rico; the lowest rates were seen in Peru, Ecuador, Dominican Republic, Mexico, and Colombia. Among women, the highest all-sites cancer rates were found in Cuba, Colombia, and Puerto Rico; Mexico, Paraguay, Ecuador, and Peru showed the lowest rates. An increasing trend in lung cancer mortality over time was seen in all countries except for Cuba (no change) and for Argentina, Paraguay, and Peru, which showed declining trends. In Latin America up to 1989, the tobacco-related lung cancer epidemic was in its early phase among men and its very early phase among women.

4.1 Mexico

In Mexico, the trend of lung cancer mortality from 1979 to 1993 showed an increase to 7.25 per 100,000 population from 5.01 [41]. In those fifteen years, 73,807 deaths from lung cancer were reported. This mortality rate is not decreasing, and 10,000 deaths from lung cancer are estimated for the year 2010.

Tovar–Guzman *et al.* [42] studied the mortality trends of cancer attributable to tobacco smoking, particularly lung cancer, for the years 1980 – 1997 in Mexico. The male:female ratio for lung cancer mortality was 2.10:1.00. The ratio for laryngeal cancer was striking: it was 4.21:1.00, which is probably attributable to the higher prevalence of tobacco smoking among men. Previous tobacco smoking was correlated with the mortality rate trends for lung cancer. Increased tobacco smoking, improved cancer diagnosis, and demographic transition were probably the main factors determining cancer mortality rates. However, other lifestyle-associated variables, such as urbanisation, physical activity, and intake of carotenoids and other dietary and toxic substances such as alcohol may also be influencing the morbidity and mortality rates.

4.2 Uruguay

In Uruguay, De Stefani *et al.* [43] estimated the risk of lung cancer associated with several food groups in the period 1988 – 2000. Total meat intake was directly associated with lung cancer risk; total vegetable and total fruit intake were inversely associated. When vegetable and fruit intakes were further adjusted for smoking status, years since quitting, cigarettes smoked daily, and age at smoking start, the protective effect for plant foods (total vegetables and fruits) was attenuated. Also, the effect of vegetables and fruits was closest to nil among smokers of black tobacco and hand-rolled cigarettes. Thus, the study was consistent in showing moderate associations with major food groups (meat, vegetables, and fruits) and strongly suggested that stringent control of tobacco smoking is mandatory in studies dealing with diet and lung cancer risk.

The same researchers then examined the relationship between alcohol consumption and risk of adenocarcinoma of the lung in Uruguay during the period 1998 – 2000 [44]. Total alcohol intake was not associated with risk of adenocarcinoma of the lung. Nor was beer drinking so associated. On the other hand, wine drinking showed a marginally significant reduction in risk of adenocarcinoma of the lung, and intake of hard liquor was associated with a 40% increase in risk.

The same group also examined the relationship between diet and adenocarcinoma of the lung in Uruguay [45]. Red meat, total meat, and fatty foods were associated with a significant increase in risk. Fruits, tubers, and all plant foods showed significant inverse associations with adenocarcinoma of the lung. Among nutrients, total fat, "other fats" (saturated fat), and cholesterol were associated with an increased risk of adenocarcinoma of the lung. The risk associated with cholesterol intake was even higher after controlling for total fat, suggesting that these two nutrients (fat and cholesterol) have independent effects. Carotenoids and vitamin E displayed significant protective effects, but those effects were markedly attenuated when the micronutrients were adjusted for total plant intake.

Furthermore, red meat, fat, and cholesterol showed attenuation of effect after adjustment for total plant foods.

It could be concluded that tobacco smoking is the strongest risk factor for adenocarcinoma of the lung. Low consumption of plant foods and, to a lesser degree, high consumption of red meat, total fat, and cholesterol contribute to a higher risk of adenocarcinoma of the lung.

4.3 Brazil

In 2001, Algranti *et al.* [46] reported that lung cancer is the second-leading cause of death in Brazil. Crude and adjusted incidence and mortality rates for lung cancer were rising, particularly among women. The main reason was an acceleration in tobacco consumption and the spread of smoking among women.

Approximately 40% of men and 25% of women 15 years of age or older in Brazil are current smokers. In the state of Rio Grande do Sul, incidence and mortality rates for men are similar to those seen in U.S. data, and the rates for women are rapidly approaching those for men. In the industrialised area of Sao Paulo, occupations associated with risk of exposure to respiratory carcinogens showed rises in lung cancer incidence. The main occupational risks in Brazil are exposure to mineral dusts, silica, and asbestos. Although about 15 million Brazilians were exposed to pesticides, a case-control study showed that agricultural workers were not a risk group for lung cancer because pesticides containing arsenic and dichlorodiphenyltrichloroethane had been banned. In recent years, a trend toward a decrease in smoking by men has been noted, but a high tobacco exposure burden still exists in both men and women, with a forecast of further increases in rates of lung cancer incidence and death.

Wunsch–Filho *et al.* [47] estimated the risk for lung cancer from occupational exposures in the metropolitan region of Sao Paulo, the largest urbanised and industrialised area in Brazil. For the men in the 56 industrial and 122 occupational categories examined, an excess risk of lung cancer was found in the machinery industry. In pottery manufacturing, the risk was increased for workers exposed for more than 10 years. Textile workers employed for more than 10 years, with a latency of more than 40 years, had an elevated risk. For women, no significantly elevated risk was observed.

Formerly considered rare, adenocarcinoma has become the commonest form of primary lung cancer in Brazil. Kaisermann *et al.* [48] reviewed all biopsies from patients with a diagnosis of primary lung cancer obtained during 1988 – 1997 in a tertiary care hospital in Rio de Janeiro. Medical records were analysed. Adenocarcinoma was the commonest form of lung cancer [168 of 409 cases (41%)].

4.4 Chile

Cities in northern Chile had arsenic concentrations of 860 μg/L in drinking water in the period 1958 – 1970. Concentrations have since been reduced to 40 μg/L. In a case-control study from 1994 to 1996, Ferreccio *et al.* [49] frequency-matched patients diagnosed with lung cancer with hospital control subjects to investigate the relationship between lung cancer and arsenic in drinking water in northern Chile. The analysis revealed a clear trend of greater lung cancer odds ratios (ORS) with increasing concentration of arsenic in drinking water. Evidence of synergy between cigarette smoking and ingestion of arsenic in drinking water was also noted. This study provided strong evidence that ingestion of inorganic arsenic was associated with human lung cancer.

Smith *et al.* [50] investigated cancer mortality in a population of about 400,000 people in a region of northern Chile exposed to high arsenic levels in drinking water in past years. Arsenic concentrations were obtained for the period 1950 – 1998. Population-weighted average arsenic levels reached 570 μg/L between 1955 and 1969, and then decreased to less than 100 μg/L by 1980. Standardised mortality ratios were calculated for the years 1989 – 1993. Increased mortality was found for bladder, lung, kidney, and skin cancer. These findings provided additional evidence that ingestion of inorganic arsenic in drinking water was indeed a cause of bladder and lung cancer. It was estimated that arsenic might account for 7% of all deaths among those aged 30 years and older.

4.5 Argentina

The age-adjusted lung cancer mortality rate for men was high in Rosario City (62.7 per 100,000). The histologic distribution detected was squamous-cell carcinoma, 39%; adenocarcinoma, 34%; small-cell carcinoma, 13%; and "other" or "no specified cell type," 14%. Pezzotto and Poletto [51] compared a group unlikely to be exposed to occupational carcinogens and observed a 60% increase in risk for drivers and for construction and agricultural workers. With regard to squamous-cell carcinoma, increased risks were observed in the metal industry, particularly in welders and mechanics. Smoking was not a substantial confounding effect. Occupational exposures therefore partly accounted for the high lung cancer mortality rate among the men of Rosario City.

Pezzotto *et al.* [52] investigated the reasons for the high mortality rate. The ORS for the heaviest tobacco consumption category (as compared with the lowest category) were 15.3 for squamous-cell carcinoma, 11.6 for adenocarcinoma, and 11.6 for all lung cancer ($p < 0.0001$). Risks associated with the use of unfiltered cigarettes were 3 – 5 times higher than those with use of filtered cigarettes, depending on

cell type. For ex-smokers, risks after 10 years of not smoking were about 12 times lower than the risks for current smokers ($p < 0.001$).

Matos *et al.* [53] examined the risks for lung cancer associated with the lifestyle characteristics of smokers in Buenos Aires, Argentina, where lung cancer was then the leading cause of cancer mortality in men, tobacco propaganda was freely allowed, and no restrictions were placed on smoking. The OR for current smokers was 8.5, and for former smokers, it was 5.3. The risk increased with duration of smoking and with the number of cigarettes smoked daily. The attributable risk for smoking was 85%. Smokers of black tobacco and of more than 24 cigarettes daily showed a risk of 12.9 versus non-smokers, and an OR of 15.5 for 40 or more years' duration of smoking. The proportion of cases diagnosed as adenocarcinoma was higher than the proportion of squamous-cell carcinoma cases.

Hopenhayn–Rich *et al.* [54] conducted a study in Cordoba, Argentina, a town with a well-documented history of arsenic exposure from drinking water during the period 1986 – 1991. They found an increasing trend of kidney and lung cancer mortality with arsenic exposure. Those results added to the evidence that arsenic ingestion increases the risk of lung and kidney cancers.

4.6 Colombia

In Medellin, Colombia, Restrepo *et al.* [55] examined the effects of smoking cigarettes made predominantly of dark tobacco, consuming alcohol, and drinking coffee on the risk of developing cancers of the bladder, larynx, lung, and oral cavity or hypopharynx. The analysis showed that the intensity and duration of cigarette smoking were both statistically significant predictors of cancer at all four sites. In addition, heavy alcohol consumption and coffee drinking in excess of 7 cups daily were associated with some elevation of cancer risk at most of the sites studied.

5. ASIA

5.1 Japan

In Japan in the 2000s, the lung cancer rate is still increasing [56], and the transition of lung cancer cases to the older generation is continuing.

Morita [57] analysed lung cancer cases (66,650 in men and 20,890 in women) registered in the *Annual of Pathological Autopsy Cases* in Japan between 1958 and 1997 with regard to sex, age, and histology. The years were subdivided into decades [period I (1958 – 1967), period II (1968 – 1977), period III (1978 – 1987), and period IV (1988 – 1997)], and the lung cancer cases were compared with Japanese overall mortality statistics.

Among autopsy cases, the incidence of lung cancer increased to 12% from 6% in men and to 6% from 3% in women. Starting in period III, lung cancer became the most frequent cancer in men and the second most frequent cancer (after gastric cancer) in women. As for histologic distribution, adenocarcinoma was the most frequent and squamous-cell carcinoma was the next most frequent in both sexes for all periods.

In the recent past, a significant increase in adenocarcinoma and a significant decrease in squamous-cell carcinoma were observed in both sexes. In men, adenocarcinoma increased from period II to period IV, and the increase from period III to period IV was significant. Squamous-cell carcinoma decreased from period II to period IV, and the decreases from period II to period III and from period III to period IV were significant. In periods III and IV, small-cell carcinoma accounted for 19% and 20% of cases respectively, and large-cell carcinoma accounted for 10% and 8%. In periods I and II, anaplastic carcinoma accounted for more than 10% of cases; in period III, that percentage was markedly decreased to 2%. In women, adenocarcinoma increased from period II to period IV, and the increases were significant from period II to period III and from period III to period IV. Squamous-cell carcinoma decreased from period II to period IV, and the decreases were significant from period II to period III and from period III to period IV. In periods III and IV, small-cell carcinoma accounted for 15% and 14% of cases respectively, and large-cell carcinoma for 7% and 6%. Anaplastic carcinoma accounted for about 10% of cases in periods I and II, but those percentages decreased to 2% and 0% in periods III and IV respectively. In periods III and IV and overall, adenocarcinoma was significantly more frequent in women, and squamous-cell carcinoma, small-cell carcinoma, and large-cell carcinoma were significantly more frequent in men.

Smoking prevalence remains high (around 60%) among Japanese men, but smoking initiation among men born in the 1930s decreased by approximately 10% because of the economic difficulties following World War II. Soda *et al.* [58] examined this temporary decline in smoking initiation and whether it influenced the subsequent incidence of lung cancer, especially adenocarcinoma. Trends of lung cancer incidence by histologic subtype in both sexes were investigated using data from the population-based cancer registry in Nagasaki, Japan, for 1986 – 1995. During that period, 5,668 men and 2,309 women were diagnosed with lung cancer, and the overall incidence of lung cancers in both sexes remained stable. However, males aged 55 – 59 years showed a decrease in the age-specific incidences of adenocarcinoma and squamous-cell carcinoma. In birth-cohort analyses, the incidences of adenocarcinoma and squamous-cell carcinoma were lower in the 1935 – 1939 male birth

cohort than in successive cohorts. The incidence of lung cancer among women with low smoking prevalence did not change with birth cohort. The low smoking initiation among the 1935 – 1939 male birth cohort appeared to have resulted in decreased incidences of adenocarcinoma and squamous-cell carcinoma among middle-aged Japanese men. This study suggested that smoking prevention has an effect in reducing the incidence of both lung adenocarcinoma and squamous-cell carcinoma among smokers.

5.2 China

The first analysis of time trends in cancer mortality at the national level in China was presented by Yang *et al.* [59] in 2003. Between 1987 and 1999, the age-standardised mortality rates for all cancers combined declined slightly in rural areas; however, since 1996, they have increased in urban areas. The mortality rates for leukaemia (except in urban men after 1996) and for cancers in oesophagus, stomach, cervix uteri, and nasopharynx declined, but lung cancer in both sexes and breast cancer in women showed significant increasing trends in both urban and rural areas.

Those observed trends reflect the dramatic changes in socioeconomic circumstances and lifestyle in China during the last two decades. Tobacco smoking remains a major problem. Improvements in socioeconomic status, diet, and nutrition may be responsible for the declining risks for some cancers (oesophagus, stomach, and nasopharynx), but the risks for others (breast and colon or rectum) are increasing.

In recent decades, a rapid and substantial increase in tobacco consumption has occurred in China, particularly in men. Chen *et al.* [60] assessed the current health effects of cigarette smoking in eleven factories in urban Shanghai, China. After adjustment for other major risk factors, the excess mortality was almost twice as great among men who had begun smoking before the age of 25 years, and this mortality was significantly associated with the number of cigarettes smoked. The chief sources of the excess mortality were lung cancer, oesophageal cancer, liver cancer, coronary disease, and chronic obstructive pulmonary disease. About 20% of all deaths among the men in this Chinese population during the study period could be attributed to cigarette smoking. Of those deaths, one third involved lung cancer, one third involved other cancers, and one third involved other diseases. A statistically significant excess of overall mortality was also seen among women.

Cigarette smoking is a major cause of death in China, and among middle-aged Shanghai men, about 20% of all deaths during the 1980s were attributable to smoking. The excess was greatest among men who began smoking before the age of 25 years: about 47% of them were expected to die between the ages of 35 and 69 years (as compared with only 29% among non-smokers). These estimates reflect the consequences of past smoking patterns. The future health effects of current smoking patterns are likely to be even greater because of the recent large increase in cigarette consumption in China—particularly in people at younger ages. During the last two decades, the annual consumption of cigarettes in China increased from 500 billion in 1980 to 1,800 billion in 1996; two thirds of men now become smokers before age 25, and few give the habit up. The average daily cigarette consumption by men was 1 in 1952, 4 in 1972, and 10 in 1992 [61]. Of all the cigarettes smoked in the world today, one in three is smoked in China. This increasing epidemic of cigarette smoking is the major factor that underlies the increasing trend in lung cancer mortality.

Liu *et al.* [61] assessed the hazards at an early phase of the growing epidemic in China of deaths from tobacco. Family members or other informants provided information about the smoking habits before 1980 of 0.7 million adults who had died of neoplastic, respiratory, or vascular causes; that information was compared with information from a reference group of 0.2 million individuals who had died of other causes. Among male smokers aged 35 – 69 years, excesses of 51% for neoplastic deaths, 31% for respiratory deaths, and 15% for vascular deaths were seen. Among male smokers aged 70 years or older, excesses of 39% for neoplastic deaths, 54% for respiratory deaths, and 6% for vascular deaths were noted. Fewer women smoked, but among those who did, tobacco-attributable risks of lung cancer and respiratory disease were about the same as those seen in men.

For both sexes, lung cancer rates in smokers at ages 35 – 69 were about triple those seen in non-smokers, but because the rates among non-smokers in various parts of China varied widely, the absolute excess of lung cancer in smokers also varied. Of all deaths attributable to tobacco, 45% were due to chronic obstructive pulmonary disease, and 15% to lung cancer. Oesophageal cancer, stomach cancer, liver cancer, tuberculosis, stroke, and ischaemic heart disease each caused from 5% to 8% of deaths. Tobacco caused a total of about 0.6 million deaths among Chinese in 1990 (0.5 million men). This number was expected to rise to 0.8 million in 2000 (0.4 million at ages 35 – 69 years)—or more if the tobacco-attributed fractions increased. If current smoking uptake rates persist in China (where about two thirds of men, but few women, become smokers), tobacco will kill about 100 million of the 0.3 billion males currently aged 0 – 29 years. That figure will reach 3 million annually by the time the young smokers of today reach middle and old age (by the year 2050) [62].

The smoking situation among Chinese women is quite different from that among men. Few Chinese women have smoked, and a high prevalence of smoking is seen only among older women in big cities.

Nevertheless, the mortality rates from lung cancer in Chinese women are relatively high. For example, the estimated age-standardised mortality in Chinese women in 2000 was 13.5 per 100,000 population as compared with 1.8 per 100,000 in India [6]. This observation has highlighted the effects of other factors—for example, environmental tobacco smoke, coal smoke, cooking fumes, air pollution, exposure to indoor radon, and occupational exposures [63–65].

Niu *et al.* [66] monitored the evolving epidemic of mortality from tobacco in China following the large increase in cigarette use by men in recent decades. The overall mortality was higher among smokers. Almost all the increased mortality involved neoplastic, respiratory, or vascular disease. The overall risk ratios currently associated with smoking are less extreme in rural areas (1.26, 1.12, and 1.02 respectively for smokers who started before the age of 20 years, at 20 – 24 years, or at older ages) than in urban areas (1.73, 1.40, and 1.16 respectively). By 1990, smoking was already causing about 12% of Chinese male mortality in middle age. This proportion is predicted to rise to about 33% by 2030.

Lung cancer rates in rural Xuanwei County, Yunnan Province, were among the highest in China. Residents traditionally burned "smoky" coal in unventilated indoor fire pits, generating very high levels of air pollution. Since the 1970s, most residents have changed from fire pits to stoves with chimneys. Lan *et al.* [67] assessed whether lung cancer incidence from 1976 – 1992 decreased after this stove improvement, and a long-term reduction in lung cancer incidence was noted. Incidence reduction became unequivocal about 10 years after stove improvement. Levels of indoor air pollution during burning with chimneys were less than 35% of the levels seen during unventilated burning.

Although few Chinese women smoke, they have a modestly raised incidence of lung cancer. Most of these lung cancers are adenocarcinomas, and the relative risk in relation to smoking is small, so that it can be calculated that the incidence of lung cancer in non-smoking Chinese women is about 3 times that seen in U.S. female non-smokers [68]. An increased risk of lung cancer because of exposure to environmental smoke, particularly cooking fumes [69,70] and indoor smoky coal emissions [71] have been found in studies in China.

Lung cancer has gradually increased in both sexes in China from 1980 to 1989 [72]. Among clinical cases in men, squamous-cell carcinoma was the most frequent, but during that decade it decreased to 53% from 68%, and adenocarcinoma increased to 27% from 14% [73]. In females, adenocarcinoma decreased to 39% from 64%, and squamous-cell carcinoma increased to 32% from 22%.

Chan–Yeung *et al.* [74] investigated the risk factors associated with lung cancer in Hong Kong. Smoking was the most important of these, but the attributable risk was estimated to be 45.8% in men and 6.2% in women, considerably lower than that estimated in the early 1980s. The results of this study suggested that, as the prevalence of smoking declined, the influence of smoking as a risk factor for lung cancer decreased even further. Moreover, the contribution of other environmental, occupational, and socioeconomic factors may be more apparent as causes for lung cancer in a population with relatively high lung cancer incidence but low attributable risk from active smoking.

Lung cancer is the leading cause of cancer death in Taiwan. Cigarette smoking is considered to be the most important risk factor. In Taiwan, only about 50% of lung cancer incidence could be associated with cigarette smoking, particularly because fewer than 10% of Taiwanese women smoke. The high DNA adduct levels in Taiwanese women may be associated with frequent exposure to indoor cooking-oil fumes and heavy outdoor air pollution. Wen Cheng and Lee [75] reported that human papillomavirus (HPV) infection was associated with non-smoking-related lung cancer in women.

5.3 Singapore

Tan *et al.* [76] studied survival rates and their determinants in Singapore Chinese women, a primarily non-smoking population. Most tumours (70.5%) were stage III or IV at diagnosis. Three-year survival ranged from 72% among patients with stage I tumours to 7% with stage IV tumours. Overall, in all stages combined, no survival difference was seen between the various histologic subtypes. When limited to stages I and II, adenocarcinomas were associated with a better outcome relative to other histologic subtypes combined. Smoking was an independent risk factor (adjusted relative risk: 1.3). Nevertheless, non-smokers comprised 57.4% of this series, highlighting the importance of increased awareness among health professionals and the public that lung cancer is not a disease of smokers alone.

5.4 Korea

In Korean clinical cases of lung cancer in men in the 1980s, squamous-cell carcinoma accounted for more than half (54%), and adenocarcinoma was low (18%) [77]. In women, adenocarcinoma was the most frequent, although still less than half of cases (45%), and squamous-cell carcinoma was rather high (28%).

Bae *et al.* [78] estimated the number and trends of cancer deaths in Korea for the years 1983 through 2000. The forecast number of deaths from all cancers was increasing, so that the cumulative number of expected cancer deaths between 2001 and 2005 was about 309,000. Cancers of the lung, stomach, liver, and colorectum continued to be the most common causes of cancer deaths. The numbers of expected deaths from stomach and liver cancer showed a decreasing trend, but the trends for cancers of the

lung, colorectum, pancreas, breast, and oral cavity were increasing. These observations indicated that cancer deaths in Korea will be increasing through the early 2000s.

5.5 Thailand

Lung cancer is a major public health problem in Thailand. Limsila *et al.* [79] studied the issue of whether tumour histology varied with smoking status among lung cancer patients in Bangkok between 1967 and 1991. Overall, 78% of the patients were smokers, 72% being heavy smokers. The male:female ratio was 13:1 for smokers and 0.4:1 for non-smokers. The carcinomas were 29% squamous-cell, 29% adenocarcinoma, 24% large-cell, and 13% small-cell. Squamous-cell carcinoma was significantly more frequent among patients with a history of smoking Thai cigarettes, which are known to be high in tar and nicotine, than among non-smoking patients. Among the 350 non-smokers, 252 of whom were female, adenocarcinoma was the most common tumour (58%). These results suggested that Thai smokers could reduce their risk for lung cancer by quitting smoking, or by substituting lower-tar brands.

5.6 India

In India, lung cancer is one of the most common and lethal cancers, and tobacco smoking remains the most important causative factor. Gajalakshmi *et al.* [80] examined the effects of various forms of tobacco consumption, including smoking and chewing, on lung cancer risk in men in southern India, especially to compare the effects of bidi smoking to cigarette smoking on lung carcinogenesis. The lung cancer risk for former cigarette smokers, as compared with former bidi smokers, dropped more quickly after smoking cessation. No evidence was found for an effect of chewing on lung cancer risk, nor was there clear evidence of an effect of overall alcohol drinking among never-smokers, although Indian alcohol drinking seemed to remain associated with lung cancer risk under limited power (OR = 2.67). Bidi smoking seemed to have a stronger carcinogenic effect than cigarette smoking did.

5.7 Israel

Lung cancer rates in Israel are lower than in other developed countries, a situation that is not explainable by smoking habits. Given the varying relationships of squamous-cell carcinoma and adenocarcinoma with smoking, Rennert *et al.* [81] studied the histologic distribution of lung cancer in Israel for the period 1962 – 1982. Squamous-cell carcinoma was the leading tumour type in Jewish men, and adenocarcinoma was the leading tumour type in Jewish women. European/American (EA)–born men in the final study period showed a decrease in the rate of squamous-cell carcinoma; Asian/African (AA)–born men showed a steep rate increase in squamous-cell carcinoma that was most prominent among younger age groups. Rates of adenocarcinoma increased in both EA and AA men, but more steeply in the latter in most age groups. Only for large-cell carcinoma were the overall rates higher in AA-born than in EA-born men. Squamous-cell carcinoma increased in EA-born women and also steeply increased in AA-born women in the 55 years and older age group. Adenocarcinoma increased in EA-born women both young and old, but only in young AA-born women (it decreased in the older group).

The magnitude and dynamics of lung cancer incidence in Jews and Arabs in Israel during the years 1962 – 1982 were also studied by Rennert and colleagues [82]. In general, age-standardised incidence rates increased consistently during 1962 – 1976 among Jewish (24%) and Arab (39%) men, and to a lesser degree among Jewish women (15%). Arab women had the highest increase (77%). From 1977 to 1982, a general decrease occurred in incidence rates, with the largest decrease being seen among Arab men (19%) and women (15%). Rates among Jewish men were then 26% higher than among Arab men and were 162% higher among Jewish women than among Arab women. Lung cancer rates in both men and women in Israel (Jews and Arabs) were lower than in most developed countries in the world. Among the possible reasons are differences in the risk factors profile of the population, in the availability of health care, and in the level of diagnosis and ascertainment of cases.

Lung cancer incidence rates among Jews in Israel were significantly lower than in most developed countries in the world. Rennert *et al.* [83] produced a more detailed analysis of the rates among various Jewish ethnic groups that also showed low rates. Although EA-born Jewish men experienced an 11% increase in incidence rate between 1962 – 1966 and 1977 – 1982, AA-born Jewish men had a 45% increase, which resulted at that time in higher rates among North African than among East European Jews (the two dominant ethnic groups in Israel). In Jewish women, incidence rates have been relatively stable since 1972 – 1982; they were almost twice as high for EA-born women than for AA-born women, with less prominent differences between the ethnic groups. Smoking patterns probably explain the increase in incidence rates among AA-born Jewish males, but other possible risk factors and the overall smoking prevalence cannot explain the low incidences in the major Jewish ethnic groups.

Between 1981 and 1995, the national cancer registry in Israel received reports on 13,600 new cases of lung cancer. Baron–Epel *et al.* [84] evaluated the trends in total lung cancer and in the histologic subtypes in Jewish and Arab Israelis during that time. They found that the age-adjusted incidence of lung

cancer increased in the male Arab population, decreased nonsignificantly for male Jews, and remained stable for women in both population groups. When the data were analysed by age group, a significant decrease in the incidence rate was seen in Jewish men aged 75 years and older.

An analysis by histologic subtype showed two different trends. In the Jewish population, the age-adjusted incidence rates for squamous-cell carcinoma decreased and those for adenocarcinoma increased; in the Arab population, the incidence rates for both subtypes increased, although the increase was statistically significant only for squamous-cell carcinoma. The changes found in the Jewish population were similar to those found in other Western countries, where the rates of adenocarcinoma were increasing and the rates of squamous-cell carcinoma were decreasing. The trends in the Arab population in Israel were different. That finding may be attributable to different trends in the prevalence of smoking in the two populations.

6. AUSTRALIA AND NEW ZEALAND

Skegg and McCredie [85] compared the cancer mortality and incidence data from New Zealand and Australia for 1996 – 1997. New Zealanders of both sexes experienced more deaths from cancer than expected in every age group. If Australian rates had applied, there would have been 215 fewer cancer deaths per year in New Zealand men, and 616 fewer in New Zealand women. The largest differences related to breast cancer and lung cancer in women, and colorectal cancer in both sexes. The overall incidence of cancer was higher in New Zealand, but mortality and incidence ratios were also higher for many cancer sites, suggesting that survival after treatment has been poorer in New Zealand than in Australia.

In Tasmania, Australia, the 1939 – 1964 birth cohort lung cancer incidence for 25- to 44-year-old women has reached that of 25- to 44-year-old men despite less smoking by the women. Blizzard and Dwyer [86] investigated whether this finding could be the result of greater female:male relative risk for smoking during 1994 – 1997. The male smokers had greater accumulated exposure to smoking and, in a reversal of the previously reported excess of female cases in this cohort, most of the 1994 – 1997 cases (99 of 160) were in men. Nevertheless, the proportions attributable to smoking were similar: 0.86 of cases in men and 0.87 of cases in women. Calculated relative to male never-smokers, the estimated relative risks were similar for male and female smokers, particularly with exposure measured by cumulative tar yield of all cigarettes smoked. No compelling evidence of greater susceptibility to lung cancer for female smokers was found.

McTiernan *et al.* [87] compared variations in cancer incidence among whites in eight geographic areas of the Pacific Basin for 1973 – 1977. Substantial differences were found for the occurrences of lung cancer, cancer of the corpus uteri, and malignant melanoma. White women living in New Zealand and Australia had the lowest risk of developing lung cancer; white men living in the western United States had the highest risk. In all areas, the incidence rates for cancers of the lung and corpus uteri and for malignant melanoma increased significantly between 1960 – 1966 and 1973 – 1977.

Hirohata and Fukuda [88] also studied the incidence of lung cancer in the Pacific Basin. The results showed great variation in the age-standardised annual incidence rates of lung cancer among 10 countries and 17 areas in the Pacific Basin where tumour registry statistics were available. For men, the incidence rates ranged from 10 to more than 70 per 100,000, and for women, from less than 5 to more than 30.

In 1977, the South Australian government established a Cancer Control and Surveillance Unit. By 1990, the unit's registry [89] had been notified of approximately 70,000 invasive cancer cases for a population that had increased to 1,400,000 from 1,287,550 in 1977. In 1990, 2940 cancers were recorded in men and 2640 in women. The leading sites in men were the prostate, lung, colon, and skin (melanoma); in women, the leading cancer sites were breast, colon, skin (melanoma), and lung. An increase in the age-standardised incidence rates for all cancer sites combined has been documented for the 1977 – 1990 period. The magnitude of the increase was 7% in men and 12% in women. Meanwhile, 1544 cancer deaths in men and 1203 cancer deaths in women were recorded in 1990. Among men, age-standardised mortality rates tended to decline in the 1980s, an effect that was largely attributable to a reduction in the age-standardised incidence of lung cancer. By comparison, an increased lung cancer incidence in women contributed to an overall increase of 6% in the age-standardised mortality rate for cancers in all sites combined.

7. AFRICA

In 1982, Taha and Ball [90] described the development of tobacco smoking in Africa, the increase in consumption, and the means by which tobacco use was promoted. They also presented evidence to show that smoking-related diseases similar to those seen in developed countries may be emerging in Africa.

Tobacco was first introduced into Africa in the sixteenth century by the Turks, who brought it into Egypt. The smoking habits of 1980s Africans were governed by local custom and economic status. Cigarette smoking was replacing the traditional pipe (the hookah), although the latter is still used today, particularly in rural areas. The prevalence of smoking was higher in urban than in rural areas. Traditionally, only men smoked, but the proportion of women

smokers was rising. Smoking was also increasing among African children and adolescents.

The researchers examined cigarette consumption in the six African countries for which statistics were available. In all of them, consumption rose steeply between 1967 and 1976; consumption actually doubled in Libya and Ethiopia. In Egypt, domestic cigarette sales increased by 23% between 1976 and 1978, but sales of imported cigarettes rose by 25% in one year alone. Consumption of imported cigarettes was rising in many African countries. Between 1965 and 1976, the volume of tobacco imports almost doubled. Cigarette smuggling was common in some African countries and may account for about one third of total cigarette consumption in Sudan.

Some African countries were expanding tobacco agriculture so that they could supply their own needs. Nigeria has increased tobacco cultivation by about 10% annually to meet local demand. Imports of tobacco in Zaire increased by about 30% between 1969 and 1973, but since then, the country has become self-sufficient in tobacco production. Tobacco output increased by a multiple of 7 in Tanzania between 1962 and 1974.

Cigarettes were heavily promoted in Africa. The advertisements presented smoking as socially desirable by showing young, happy people smoking and by relating the practice to manliness and success. Smoking-related diseases have already been seen in the continent. The two most common types in the Natal Bantu were lung and oesophageal cancers. During the 1970s, lung cancer in Natal men increased by a factor of 6 and in Natal women by about a factor of 5. The incidence of oesophageal cancer in blacks in Durban, South Africa, and in Zimbabwe was among the highest in the world. Other suggestive associations with cigarette smoking in Africans were bladder cancer, myocardial infarction, and chronic bronchitis. Many Western governments and health authorities now try to persuade people not to smoke, and in some developed countries, consumption has already begun to fall. As a result, tobacco companies have started to diversify and intensify promotion of cigarette use and the growth of tobacco in developing countries.

Pacella–Norman *et al.* [91] used data collected from an ongoing cancer case-control study in greater Johannesburg during 1995 – 1999 to estimate the importance of tobacco and alcohol consumption and other suspected risk factors in cancers of the oesophagus, lung, oral cavity, and larynx. Tobacco smoking was found to be the major risk factor for all of these cancers, with ORs ranging from 2.6 for oesophageal cancer in female ex-smokers to 50.9 for lung cancer in women, and 23.9 for lung cancer and 23.6 for laryngeal cancer in men who smoked 15 g or more tobacco daily. This was the first time that an association between smoking and oral and laryngeal cancers had been shown in sub-Saharan Africa. There was a slight increase in lung cancer (OR = 2.9) in men working in "potentially noxious" industries. The risks for oesophageal cancer in relation to alcohol consumption increased significantly in male and female smokers (OR = 4.7 in men and 4.8 in women).

Onadeko *et al.* [92] studied the clinico-pathologic pattern of carcinoma of the bronchus and lung at the University College Hospital, Ibadan, Nigeria, over a 20-year period, 1971 – 1990. An increased incidence of carcinoma of the bronchus and lung was observed as compared with a study that was carried out in the 1960s in the same environment. The researchers found that increasing industrialisation and increased acquisition of modern diagnostic facilities were responsible for the increased incidence.

Mzileni *et al.* [93] studied the incidence of cancer in African patients in Northern Province, South Africa, between 1993 and 1995. The risks of developing lung cancer as related to tobacco exposure, indoor pollution, a dusty work environment, and residential asbestos exposure were studied. A significant increase in the risk of developing lung cancer through smoking was seen. In men, the ORs were 2.2 in ex-smokers, 9.8 in light smokers (0 – 14 g daily), and 12.0 in heavy smokers (>14 g daily). In women, the ORs were 5.8 in ex-smokers and 5.5 in current smokers. Working in a dusty industry showed an elevated risk for lung cancer (OR = 3.2) only in men. Male residents of areas from which asbestos was shipped for distribution had a 2.5-fold increase in the OR for developing lung cancer, and residents of areas in which asbestos was mined had a 2.8-fold increase in risk. Female residents of heavily polluted asbestos areas showed a 5.4-times elevated risk of developing lung cancer. The data suggested that tobacco smoking was the most important risk factor for the development of lung cancer. However, environmental exposure to asbestos (in men), and perhaps to indoor air pollution, may contribute to the development of lung cancer in this province of South Africa.

Haldenwang [94] studied lung cancer in Cape Town, where the disease caused 1130 deaths during 1984 – 1986. It was the most prevalent cause of cancer death in men and was second only to breast cancer in women. It was responsible for 22.9% of all cancer deaths in Cape Town during the 3-year period studied. The representation of standardised mortality ratios showed that mortality from lung cancer in Cape Town was appreciably higher in men than in women and in "coloured" people than in white people. "Coloured" men were the group most at risk. Despite the important role that smoking habits played in causing lung cancer, the results of ecologic analyses showed that environmental factors were partly responsible for the incidence of the disease. In the case of white people, demographic and socioeconomic variables such as age, home language, religious affiliation, and level of education were identified as associated variables. In the case of

"coloured" people, the factors that played a role were chiefly socioeconomic ones such as unemployment, home ownership status, and type of housing. Positive relationships with low socioeconomic status pertained only to "coloured" people.

Between 1981 and 1985, Akhtar *et al.* [95] studied 1124 patients with histopathologically confirmed malignant disease registered at the sole oncology clinic of Libya. Of these 1124 patients, 664 (59%) were men, and 460 (41%) were women. Lung cancer was the most common tumour in men (22.4%), and the male:female ratio for the disease was among the highest in the world (18.6:1). Of the male patients, 85% were smokers, and more than 50% had been smoking heavily for 20 years or more.

8. CONCLUSION

Globally, lung cancer risk closely mirrors tobacco consumption, and the mortality rate for the disease continues to rise among other cancers. Although slight variations are seen among countries with different cultural backgrounds, lung cancer mortality in women is on a rising trend that will probably continue well into the twenty-first century. This outlook shows the urgent need for comprehensive global lung cancer prevention, with control of smoking as a priority, in particular for younger generations.

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