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# International lung cancer trends by histologic type: male:female differences diminishing and adenocarcinoma rates rising

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**Lung cancer rates have peaked among men in many areas of the world, but rates among women continue to rise. Most lung cancers are squamous cell carcinoma, small cell carcinoma, or adenocarcinoma; trends vary according to type. We compiled population-based morphology-specific incidence data from registries contributing to the International Agency for Research on Cancer (IARC) databases. Unspecified cancers and carcinomas were reallocated based on a registry, time period, sex and age group-specific basis. Where available, data from several registries within a country were pooled for analysis. Rates per 100,000 person-years for 1980–1982 to 1995–1997 were age-adjusted by the direct method using the world standard. Squamous cell carcinoma rates among males declined 30% or more in North America and some European countries while changing less dramatically in other areas; small cell carcinoma rates decreased less rapidly. Squamous and small cell carcinoma rates among females generally rose, with the increases especially pronounced in the Netherlands and Norway. In contrast, adenocarcinoma rates rose among males and females in virtually all areas, with the increases among males exceeding 50% in many areas of Europe; among females, rates also rose rapidly and more than doubled in Norway, Italy and France. Rates of all lung cancer types among women and adenocarcinoma among men continue to rise despite declining cigarette use in many Western countries and shifts to filtered/low-tar cigarettes. Renewed efforts toward cessation and prevention are mandatory to curb the prevalence of cigarette smoking and to reduce lung cancer rates eventually.**


**Key words:** lung cancer incidence; histology; trends

There have been epidemics of lung cancer as incidence and mortality rates rose rapidly during the 20th century, especially among men and in the industrialized countries.[1,2] Among men, rates in the United States, Canada, England, Denmark and Australia have peaked, but they continue to rise in Spain, China and Japan.[1] Among women, rates have been considerably lower, increases started later and rates in most areas have not yet peaked. During 2000, an estimated 1.2 million cases were diagnosed, and 1.1 million deaths were attributed to lung cancer. Lung cancer may appear as squamous cell carcinoma, small cell carcinoma, adenocarcinoma, large cell carcinoma and a variety of other less frequent types.[3] The patterns and trends in incidence have varied by type,[4,5] related to differences in smoking patterns and exposures to other lung carcinogens.[1,6] The availability of population-based histologic-specific incidence data from a number of registries contributing to the International Agency for Research on Cancer (IARC) databases[7] allows us to investigate the patterns in a number of geographic areas in a comprehensive fashion.

## Material and methods

Population-based cancer incidence data have been collected by many registries around the world for a number of years, and the IARC has compiled and published the data in the series of Cancer Incidence in Five Continents[7] and in EUROCIM, a large compilation of submitted European registry data.[8] In earlier years in a number of registries, the form of cancer was coded according to the International Classification of Diseases (ICD), which has undergone several revisions, with the most recent being ICD-10.[9] The ICD generally classifies malignancies according to the primary site of origin. Many of the registries, especially those in the Nordic countries, Europe, North America and Oceania, have collected and coded the tumor morphology, in addition to the anatomic site or topography. Many registries used the International Classification of Diseases for Oncology (ICDO),[10,11] which was based on the ICD and the earlier Manual of Tumor Nomenclature and Coding (MOTNAC),[12] while others have based classification on the earlier WHO Statistical Code for Tumors.[13] The ICDO, first published in 1976,[10] greatly expanded the morphology categories and codes from 4 to 5 digits (including the behavior code).

Some registries started to use ICDO for cases diagnosed during the late 1970s, while others did not change until later. From all registries providing continuous incidence data since 1980,[7,14–16] we selected those registries that reported morphology and where the histologic confirmation rate was at least 80%, the percentage of cases registered by death certificate only was 5% or less and the percentage of cases with poorly specified histology (morphology unspecified or specified only as carcinoma) was 25% or less. Registries in the Nordic countries (Denmark, Iceland, Norway and Sweden) and Slovenia were national. Other registries have not had national coverage and may have had regional coverage for a more limited number of years. We combined the data for 3 western provinces of Canada (Alberta, British Columbia and Manitoba); for the 9 Surveillance, Epidemiology, and End Results (SEER) areas of the United States (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco, Seattle and Utah); for 6 registries in France (1983 on; Bas-Rhin, Calvados, Doubs, Isere, Somme and Tarn); for Spain from Navarra and Tarragona; and for Switzerland (1983 on) from Basel, Geneva and Zurich. We used the data from Varese for Italy, from Eindhoven for the Netherlands and from New South Wales for Australia. Data of sufficient morphologic detail were not available from any registries in Central or South America, Asia, or Africa.

We selected cases diagnosed with lung or bronchus cancer diagnosed during 1980–1997. The morphology codes were grouped into 8 major categories according to the WHO scheme[17]: (1) squamous cell carcinoma (ICDO-2 codes 8050–8076); (2) adenocarcinoma (8140, 8211, 8230–8231, 8250–8260, 8323, 8480–8490, 8550–8560, 8570–8572); (3) small cell carcinoma (8040–8045); (4) large/undifferentiated cell carcinoma (8012–8031, 8310); (5) other specified carcinoma (8082, 8120–8123, 8141–8143, 8190, 8200–8201, 8240–8241, 8244–8246, 8290, 8320, 8430, 8470–8471, 8500, 8510, 8562); (6) unspecified carcinoma (8010–8011, 8032–8034); (7) other specified morphology (8580, 8693, 8720, 8730, 8800–8811, 8830, 8840–8920, 8933, 8940, 8963, 8972, 8980–8981, 8990–8991, 9040–9044, 9050–9053, 9064, 9070, 9080, 9085, 9110, 9120–9134, 9140, 9150, 9220, 9240, 9251,

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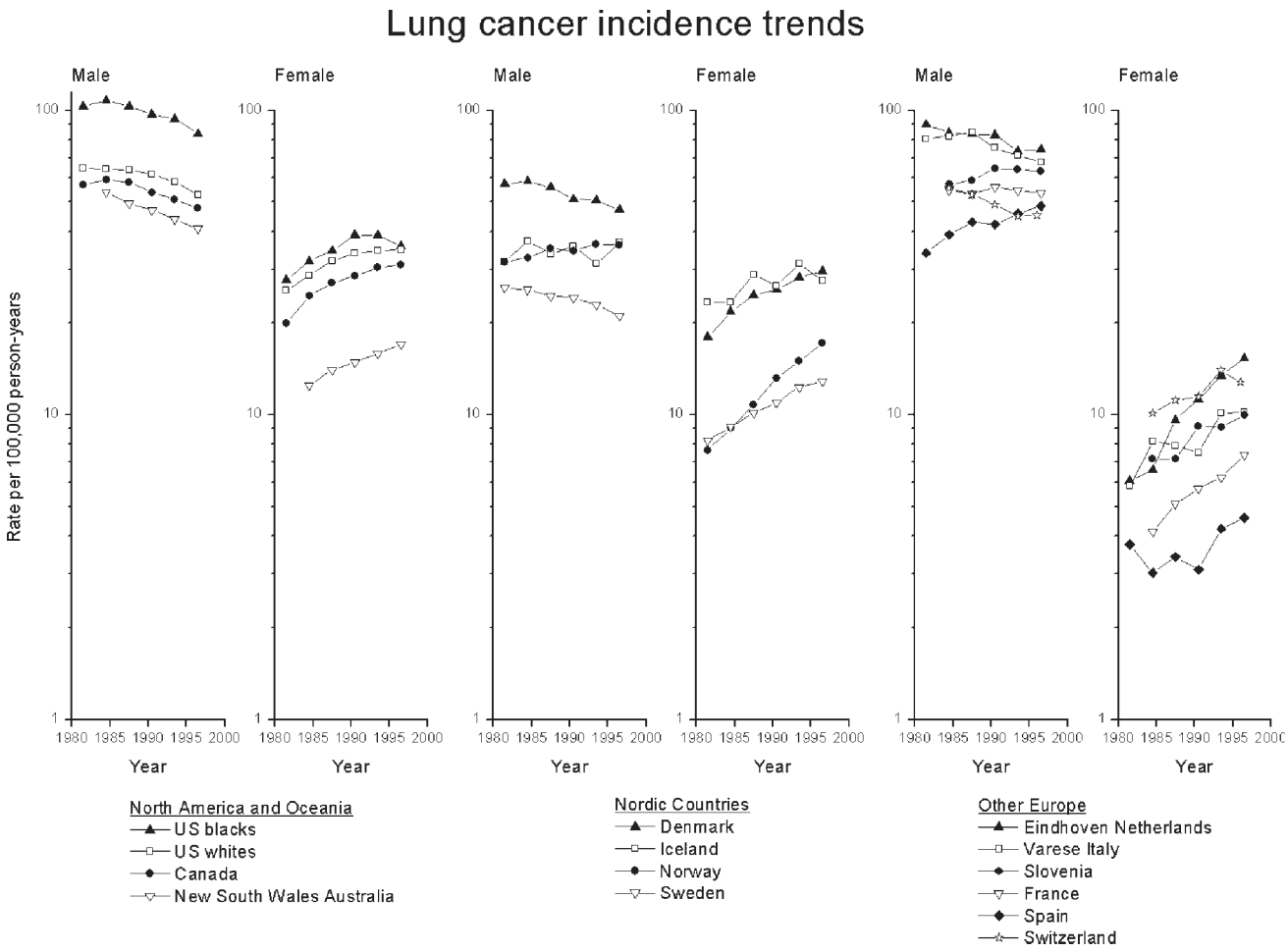


**FIGURE 1** – Trends in lung cancer incidence rates (age-adjusted, world standard) by geographic area, circa 1980–1982 to 1995–1997.

9260, 9364, 9473, 9503, 9540–9581); and (8) unspecified morphology (8000–8004). On a registry-, time period-, sex-, and age-specific basis, we proportionally reallocated the cases with unspecified morphology (8) among categories 1–7, then we proportionally reallocated the unspecified carcinoma (6) among categories 1–5.[18] This analysis focuses on the trends in total lung and bronchus cancer incidence and the 3 major forms: squamous cell carcinoma, small cell carcinoma and adenocarcinoma.

Incidence rates were calculated for 3-year time periods 1980–1982 through 1995–1997, age-adjusted by the direct method using the Segi world standard[19] and expressed per 100,000 person-years. Figures portraying the temporal trends were prepared using semi-log scales, with a y:x axis ratio of one log cycle = 40 years; a line with an angle of 10° thus portrays a change of 1% per year.[20]

## Results

Recent total lung cancer incidence rates among males varied by 4-fold, from 83.6 among U.S. blacks to 21.1 in Sweden (Fig. 1). Rates in the Nordic countries, which varied by 2-fold from a high in Denmark to a low in Sweden, still were generally lower than in other parts of Europe, where the rate was highest in the Netherlands. Rates in Italy, Slovenia and France were higher than in U.S. whites or Canada.

Among females, recent rates varied by almost 8-fold, with the highest among U.S. blacks (35.8) and the lowest in Spain (4.6). Rates were also high in U.S. whites and Canada. In contrast to males, rates were higher in the Nordic countries than in other European countries studied. The ranking of rates among females paralleled that in males, with the exception of Switzerland. Rates everywhere were higher among males than females. Male:female rate ratios varied from less than 2 in Iceland, U.S. whites, Canada, Denmark and Sweden to more than 6 in Slovenia, Italy, and France and more than 10 in Spain.

Among men, rates declined by 20–25% over virtually the entire time period in all areas except Iceland and France, where they were relatively stable, and in Norway, Slovenia and Spain, where they increased (Fig. 1). In contrast, rates among females rose rapidly in all areas over most of the time period; rates in the Netherlands and Norway more than doubled. Deceleration of the increases occurred in several areas, such as Canada, U.S. whites and Denmark, while declines in recent years were suggested for U.S. blacks, in Switzerland and possibly Iceland. In the earlier years, the male:female rate ratio was greater than 2 in every area except Iceland and ranged from 8 or more in Slovenia, Spain, France and Italy, to more than 14 in the Netherlands.

The proportion of lung and bronchus cancers that did not have a cell type specified ranged from less than 10% in France, Sweden, the Netherlands and Switzerland to more than 20% in Italy and Spain. The proportions generally varied little within registries, with a tendency to decline over time. Of those carcinomas with a histologic type specified, squamous cell, small cell and adenocarcinomas together accounted for 80–90% of the cases in virtually every registry, being somewhat smaller only in Australia and Sweden, and somewhat larger in Italy.

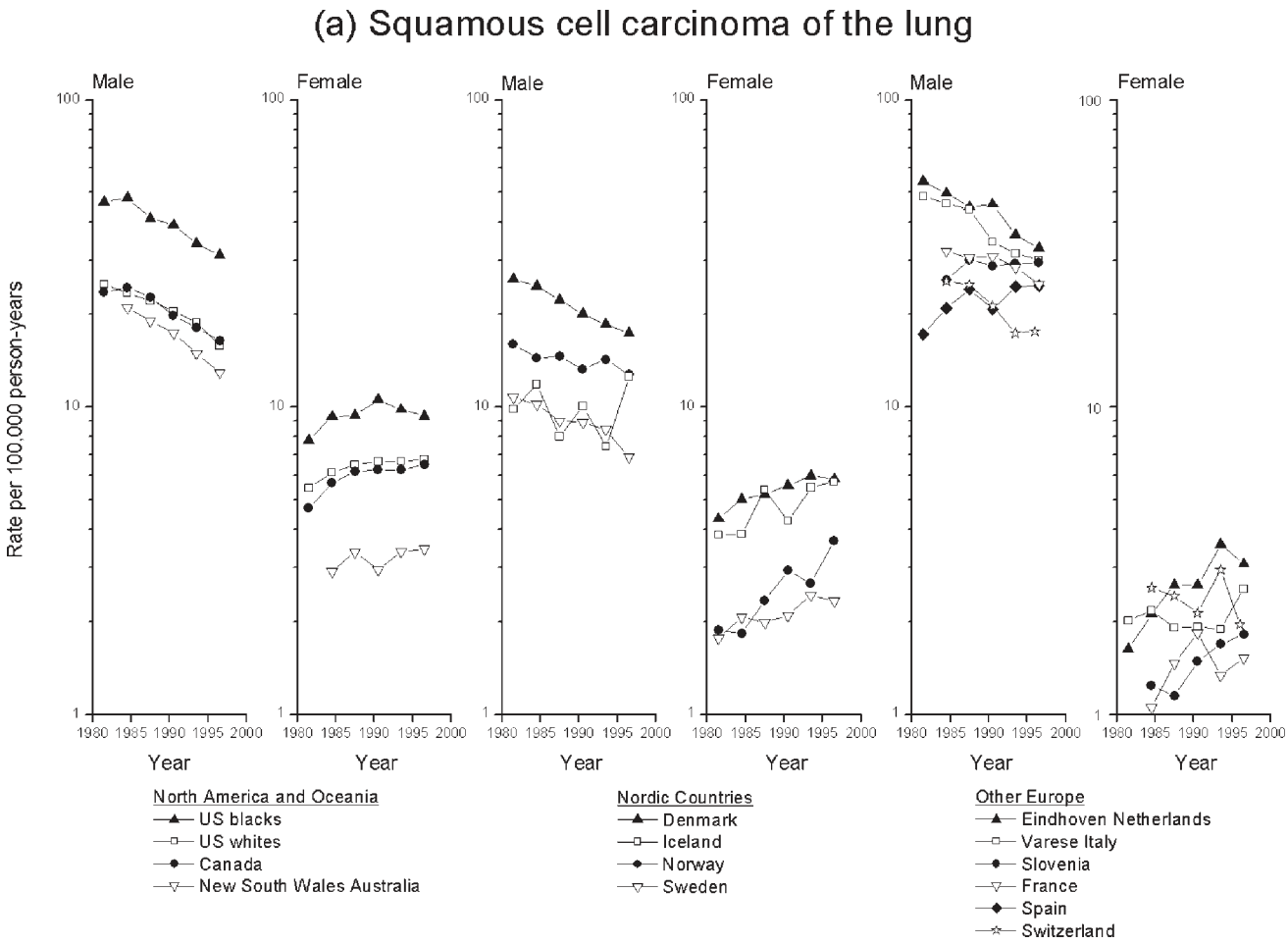


**FIGURE 2** – Trends in lung cancer incidence rates (age-adjusted, world standard) by geographic area, circa 1980–1982 to 1995–1997 by histologic type: (*a*) squamous cell carcinoma; (*b*) small cell carcinoma; (*c*) adenocarcinoma.

Figure 2 portrays the trends by histopathologic type for squamous cell carcinoma, small cell carcinoma and adenocarcinoma. Squamous cell carcinoma rates among males declined 30% or more in U.S. blacks and whites, Canada, Australia, Denmark, Sweden, Italy and the Netherlands (Fig. 2*a*). Rates changed less dramatically in many other areas and rose substantially only in Spain, where the increases occurred mostly during the early years. Rates among females rose in all areas except Switzerland; the increases were especially pronounced in the Netherlands and Norway. The rates appear to be plateauing in several areas, including the United States and Canada. Rates among Spanish women were all less than 1.0 and did not change greatly. Male:female rate ratios for squamous cell carcinoma ranged from less than 3 in U.S. whites, Canada, Iceland and Sweden in recent years, to more than 20 during the earlier years in France, Italy, the Netherlands, Slovenia and Spain, where it exceeded 50 around 1990.

Small cell carcinoma rates among males also decreased, although less rapidly than squamous cell carcinoma rates, in North America, Australia and the Nordic countries, except Norway (Fig. 2*b*). In Europe, male rates declined in the Netherlands, where they were the highest at each point in time, Switzerland and France, while increasing in Spain, especially during the earlier years. Rates among women rose virtually everywhere, more than doubling in Norway and tripling in the Netherlands. Among U.S. black women, rates peaked around 1990 and subsequently dropped by 24%. Rates among Spanish women again were all lower than 1.0, with no trends evident. Male:female rate ratios have been smaller for small cell carcinomas than squamous cell carcinomas, approaching 1 in recent years in U.S. whites, Canada and Iceland, after being around 3 in the early years in North America, Australia, Denmark and Norway, and exceeding 10 in the Netherlands, Italy, France and Spain.

In contrast to the generally declining squamous and small cell carcinoma rates among males, adenocarcinoma rates rose in virtually all areas, with the increases exceeding 50% in Norway, Iceland, the Netherlands, Italy, France and Spain (Fig. 2*c*). Rates among females also rose rapidly and more than doubled in Norway, Italy and France. Male:female rate ratios were largest in Europe, generally exceeding 3 in the early years and 2 in recent years. The ratios were consistently smaller in North America, Oceania and the Nordic countries and approached 1 in several areas in recent years.

Squamous cell carcinoma rates exceeded adenocarcinoma rates among males in all areas in the earlier years, but the varying trends have narrowed the differences. In recent years, adenocarcinoma has been the predominant form of lung cancer among males in Iceland and both U.S. blacks and whites. Among females, adenocarcinoma rates have always been higher than squamous cell carcinoma rates in every area, and the differences have widened over time.

## Discussion

Total lung cancer incidence rates have been declining among males in many but not all areas of North America, the Nordic countries, Europe and Oceania, while rates among females have

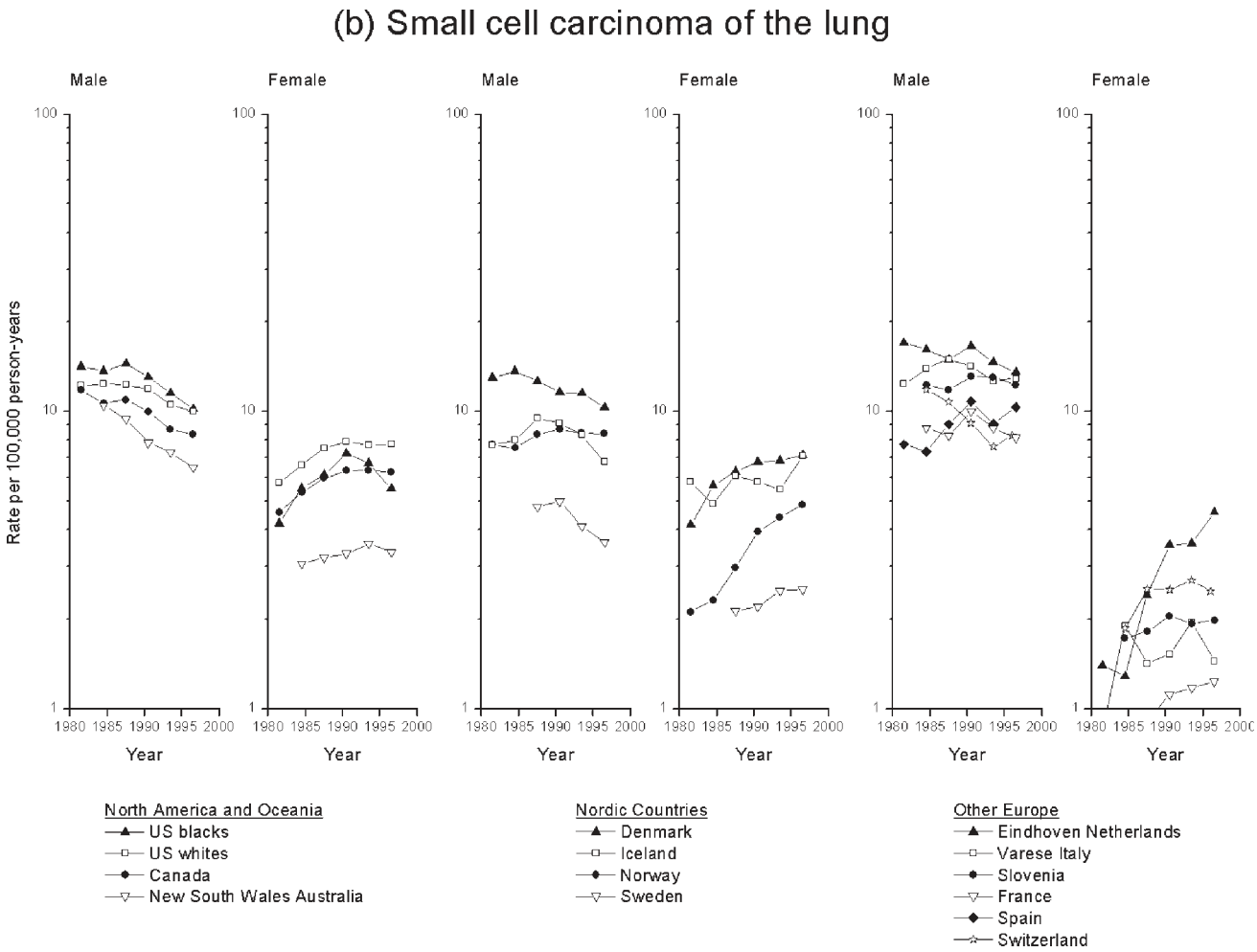


**FIGURE 2** – CONTINUED.

been rising rapidly virtually everywhere. The trends have varied by histologic type, however. Among males, rates of squamous and small cell carcinomas have decreased, in contrast to stable or increasing rates of adenocarcinoma. Among females, rates of all 3 types have been rising, at least until recently, and most rapidly for adenocarcinoma. The predominant form of lung cancer has been squamous cell carcinoma among males and adenocarcinoma among females, although adenocarcinoma surpassed squamous cell carcinoma in frequency among males in several populations in recent years.[18] Male:female squamous cell carcinoma rate ratios exceeded 20 in many European countries in the early 1980s and have declined everywhere, recently approaching 2.4 in U.S. whites. Adenocarcinoma sex ratios have been more modest, decreasing from 5 in several areas to 1.2 in other areas. Small cell carcinoma sex ratios have been intermediate. The convergence of rates has been especially pronounced at younger ages. In recent years, adenocarcinoma rates among U.S. whites aged less than 55 years have been higher among women than men and have been declining among both sexes,[21] suggesting that the age-adjusted rates should eventually peak and turn down. It is likely that the age-specific trends vary considerably in other geographic areas as well, which would be interesting to investigate, but an in-depth analysis of those patterns is beyond the scope of this article.

The overwhelming cause of lung cancer is cigarette smoking, with risk increasing with early age at initiation, intensity and duration.[6,22] Although the temporal trends in lung cancer rates lag behind the trends in smoking, the observed patterns in lung cancer rates reflect the historical prevalences of smoking among men and women, variations in cigarette composition and more recent cessation rates.[2,23] The prevalence of cigarette smoking among males has declined since the 1960s in virtually all the areas included in this analysis except Spain[23]; the peaks in lung cancer rates occurred about 20 years later, and rates in Spain are continuing to increase. Among females, the prevalence of smoking peaked in the mid-1960s in the United States and in the 1970s in most other countries included here except Spain, where the prevalence rose at least until 1990.[23] Total lung cancer rates among females have clearly peaked only among U.S. blacks. Historically, the prevalence of cigarette smoking has varied greatly by sex; the prevalence was about 70% among males compared to 15% or less among females during the early 1950s in France and Italy. The differences have been diminishing, however; in recent years, the prevalences in men and women were virtually identical in Denmark (31%) and in Sweden (23–24%). Cigarette smoking and subsequent lung cancer rates have varied considerably by birth cohort, with U.S. peaks in both occurring among males born in 1925–1930 and females born in 1935–1940[24]; recent rates among young U.S. adults have become very similar.[21] Among U.S. males, squamous cell carcinoma incidence has declined among cohorts born as early as 1920, whereas adenocarcinoma rates have shown clear decreases only among cohorts born since 1930.[21]

The strength of the association between cigarette smoking and lung cancer varies by cell type, with the odds ratios historically largest for squamous and small cell carcinomas and somewhat

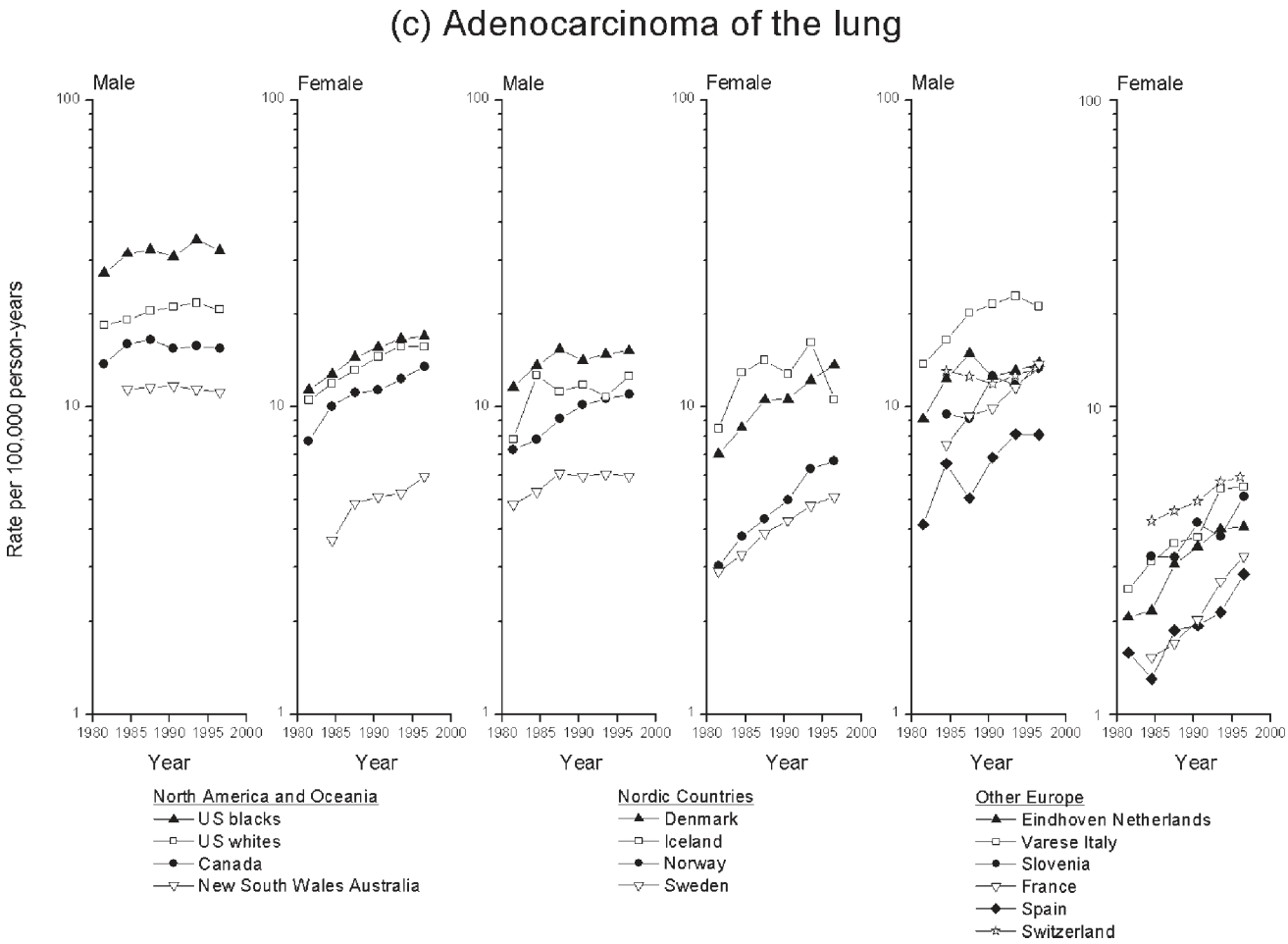


**FIGURE 2** – CONTINUED.

smaller for adenocarcinoma,[25] although recent data suggest there may be little difference.[26] The reduction in risk with smoking cessation is also more rapid for small cell and squamous cell carcinomas and less rapid for adenocarcinomas.[27] The type of tobacco in cigarettes (black *versus* blond *versus* mixed) and the chemical composition of cigarettes have varied geographically and over time.[28] With the switch from nonfiltered to filtered cigarettes, the depth of inhalation had been altered.[29] In particular, smoke from unfiltered strong cigarettes may be shallowly inhaled, resulting in chemical carcinogen deposition centrally in the bronchial area and giving rise to squamous cell carcinomas. Smoke from filtered milder cigarettes may be more deeply inhaled, resulting in carcinogen deposition more peripherally and giving rise to adenocarcinomas. Reducing the nicotine content may also promote deeper inhalation as smokers attempt to compensate.[30] The changes in cigarette composition reduced the yield of carcinogenic polycyclic aromatic hydrocarbons (PAHs), inducers of squamous cell carcinomas, while increasing the yields of carcinogenic tobacco-specific N-nitrosamines (TSNAs), inducers of adenocarcinomas.[28] These factors, along with the greater risk of adenocarcinoma than squamous cell carcinoma among former smokers, have contributed to the emerging predominance of adenocarcinoma in the lung cancer rates. Early case-control studies suggested that women were more susceptible than men to the adverse effects of cigarette smoking, but more recent cohort data have not supported pronounced sex differences in susceptibility.[31,32]

The proportion of cases with microscopic verification of the diagnosis varied across registries and over time. We reallocated the cases with poorly specified histopathologic type proportionally to the major cell types, specific for registry, time period, sex and age group. Reallocation generally raised the rates for the specified categories by less than 30%. The proportions poorly specified declined over time and were slightly lower among males than females. The temporal trends based on the original and the reallocated rates were remarkably similar, however. Notably, the estimates of the times that the rates peaked were identical in virtually all instances (data available at http://www.iacr.com.fr/devesa2004.htm). Diagnostic techniques may have varied among pathologists, by geographic area and over time, but the patterns and trends observed suggest real changes in rates.[33,34] Data were not available over the entire period for all registries. In the effort to include as many registries as possible, we used data for France, Switzerland and Slovenia for a somewhat shorter time period than the other countries, rather than using data from fewer registries for a longer period of time.

While the declines in squamous and small cell lung carcinoma rates among men are encouraging, the increases in all types of lung cancer among women and in adenocarcinoma among men are of concern. As the detrimental health effects of cigarette smoking were realized, industry strove to develop less harmful cigarettes; but the subsequent scientific evidence failed to show a benefit from changes in cigarette design and manufacturing.[35] The results presented here show that the shifts to filtered/low-tar cigarettes have merely altered the type of lung cancer, and rates have continued to rise despite declining cigarette use in many Western countries over the last half century. Tobacco control

programs have been associated with declines in smoking rates and subsequent lung cancer incidence rates.[36,37] Renewed cessation and prevention efforts are mandatory to curb the prevalence of cigarette smoking and to reduce lung cancer rates eventually.

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