Trends in incidence and prognosis of the histological subtypes of lung cancer in North America, Australia, New Zealand and Europe

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Abstract

Background: Since the incidence of the histological subtypes of lung cancer in industrialised countries has changed dramatically over the last two decades, we reviewed trends in the incidence and prognosis in North America, Australia, New Zealand and Europe, according to period of diagnosis and birth cohort and summarized explanations for changes in mortality. *Methods:* Review of the literature based on a computerised search (Medline database 1966–2000). *Results:* Although the incidence of lung cancer has been decreasing since the 1970s/1980s among men in North America, Australia, New Zealand and north-western Europe, the age-adjusted rate continues to increase among women in these countries, and among both men and women in southern and eastern Europe. These trends followed changes in smoking behaviour. The proportion of adenocarcinoma has 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 the diagnosis and treatment, the overall prognosis for patients with non-small-cell lung cancer hardly improved over time. In contrast, the introduction and improvement of chemotherapy since the 1970s gave rise to an improvement in — only short-term (< 2 years) — survival for patients with small-cell lung cancer. *Conclusions:* The epidemic of lung cancer is not over yet, especially in southern and eastern Europe. Except for short-term survival of small cell tumours, the prognosis for patients with lung cancer has not improved significantly. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Lung cancer; Trends; Incidence; Prognosis; Mortality; Histology

1. Introduction

At the beginning of this century lung cancer was a very rare disease, but rates in North America, Australia, New Zealand and Europe have increased so dramatically that lung cancer can be considered a major epidemic of the 20th century.

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Currently lung cancer is the first or second most frequent tumour type among men in industrialised countries and ranks second or third for women [1–5].

Trends in mortality are influenced by trends in incidence and survival. Since the incidence of the histological subtypes of lung cancer in industrialised countries has changed dramatically over the last two decades, we now review time and birth cohort trends in the incidence and prognosis of lung cancer in North America, Australia, New Zealand and Europe according to geography and histological subtype, and summarise explanations for the changes in mortality. Trends in incidence are described in the first part of this review, while the second part focuses on trends in prognosis, which so far have received little attention. We focused on industrialised countries, because the epidemic of smoking and the subsequent temporarily very high incidence of lung cancer in these countries are illustrative for other parts of the world where smoking is on the rise.

2. Methodological considerations

This review was based on a computerised search (Medline database 1966–2000). Included were English-written, peer-reviewed articles on trends in incidence, mortality, risk factors, prognostic factors and survival for the histological subtypes of lung cancer. We also used volumes IV to VII of 'Cancer Incidence in Five Continents', in which incidence of cancer in different geographical locations and distinct ethnic sub-populations between 1973 and 1992 are described.

2.1. Classification

Lung cancer is commonly classified as small-cell carcinoma and a heterogeneous group of non-small-cell carcinomas, which includes squamous cell carcinoma, adenocarcinoma, large-cell carcinoma, and some rare subtypes, such as adenosquamous cell carcinoma, mucoepidermoid carcinoma and adenoid cystic carcinoma. The first

histological classification of lung tumours by the World Health Organization (WHO) was published in 1967 and revised in 1981 [6]. The major difference between these two classifications was that a solid carcinoma with mucus formation was classified as 'large-cell carcinoma' in 1967, and as 'adenocarcinoma' in 1981. In some papers undifferentiated carcinomas were included in the group of 'large-cell undifferentiated carcinomas', in others they were not. Large-cell undifferentiated carcinoma has frequently been called a 'wastebasket' or nonentity, because the carcinomas are so poorly differentiated that squamous or glandular differentiation is no longer evident at the light microscopic level. Thus, the incidence of this histological subtype varies with the criteria used to classify the other forms of non-small-cell lung cancer. Primary adenocarcinoma of the lung may be difficult to distinguish from pulmonary metastases of adenocarcinoma of the breast, prostate, colon, rectum or stomach. However, in most population-based or hospital-based registries the diagnosis is corrected when the primary tumour is found. Although bronchioloalveolar carcinoma is a distinct pathological entity, it is similar to adenocarcinoma as far as gender, stage, race and age distribution are concerned, but prognosis of bronchioloalveolar is probably better [7–9].

2.2. Quality of the data

There are differences in completeness of data between the various countries. This depends not only on the completeness of cancer registries but also on the degree of ascertainment (access to specialised care and the availability and quality of death certificates). Access to specialised care depends on the number of chest physicians and/or internists per one million inhabitants, the distance to hospitals and the extent of health insurance coverage. The completeness of cancer registries also depends on the number of sources of data, such as the pathological laboratory, hospital record offices and radiotherapy institutes. Another indicator of the completeness of the data is the mortality/incidence ratio, which should be almost equal to one in the case of this lethal disease [2].

2.3. Stage migration

When reporting on trends in stage distribution one should take 'stage migration' into account: through improved diagnostic techniques lymph node involvement or distant metastases can be found more easily, thus some tumours that were identified as localised in the past will be considered as metastasised today [10]. Stage migration will result in a better prognosis for each stage group.

3. Trends in incidence

3.1. Geographical variations

Worldwide male lung cancer incidence rates between 1988 and 1992 were highest (> 50 per 100 000 person-years) in the USA, Canada, New Zealand (Maori) and most European countries, moderate (35–50 per 100 000) in China, Ireland, Malta, Spain, Australia and New Zealand (non-Maori), and low (< 35 per 100 000) in Utah (USA), Latin America, most Asian countries, Iceland, Norway and Sweden [2]. For women lung cancer incidence rates were exceptionally high (> 50 per 100 000) in New Zealand (Maori), high (20–50 per 100 000) in the USA, Canada, Denmark, Iceland and the UK, moderate (10–20 per 100 000) in Australia, New Zealand (non-Maori), Utah (USA), Austria, Germany, Ireland, The Netherlands, Norway, Poland, Sweden, Switzerland and Asia, and low (< 10 per 100 000) in Latin America, other European countries, India and Africa [2].

Incidence rates for lung cancer in industrialised countries have changed markedly over the past two decades. Fig. 1 shows the trends in age-standardised incidence rates. In North America, Australia, New Zealand and most countries of northwestern Europe the age-standardised rate for men increased markedly up to the 1970s or 1980s and then started to decline first among middle-aged men and later in the older age groups [3,11–22]. In southern and eastern Europe the peak in incidence was not reached at the beginning of the 1990s [2,20,23–25]. For women lung cancer incidence (being much lower than that for men) started to increase later and is still on the rise, except in southern Ireland and Switzerland (Geneva). In the USA, The Netherlands, Italy and Switzerland the highest rates were found for men born between 1910 and 1930 and women born after 1930 [16,17,19,20,26].

3.2. Variations between histological types

The trends in lung cancer incidence were not the same for every histological type. Among men in the USA and Western Europe the age-standardised incidence rate for squamous cell carcinoma rose to 25–60 per 100 000 person-years in the early 1980s and then declined to 20–40 in the 1990s. The same trend was found for small-cell carcinoma, the peak (12–18 per 100 000 person-years) also being reached at the beginning of the 1980s. The rates for adenocarcinoma rose from 5–15 per 100 000 person-years in the 1970s to 10–35 in the 1990s [14,16–19,21,27–30]; in the USA (black men) and the southeastern part of The Netherlands the peak was reached at the end of the 1980s; for white American men a plateau was reached in the early 1990s [17,18]. In other countries the peak in the incidence of adenocarcinoma had not been reached at the beginning of the 1990s.

Among European women the incidence rate for every histological type increased from 1–2 per 100 000 in the 1970s to 2–5 in the 1990s [14,16–19,21,27–30]. However, for American women the rise in the incidence of adenocarcinoma from 2–7 per 100 000 to 13–15 was marked [16,18,21]. In Australia and Europe squamous cell carcinoma is still the most common type of cancer among men, whereas in North America adenocarcinoma is now the leading lung cancer cell type among both men and women (Fig. 2). Adenocarcinoma is relatively more common in women (representing about one third of all lung carcinomas) than in men (15–25% of all lung carcinomas).

There was also a birth cohort trend apparent for the different histological subtypes of lung cancer: squamous cell carcinoma declined among men born after 1910–1925, whereas adenocarcinoma only declined among men born after

1930–1935, or even later [16,19–21]. Among women in Connecticut the incidence rates for squamous cell carcinoma and adenocarcinoma have decreased since birth cohort 1930–1939 [21], however, in Italy and Switzerland the rates for adenocarcinoma among women increased at least up to the 1950–1959 cohort [19,20]. Among Swiss women the rate for squamous cell carcinoma started to decrease with birth cohort 1940–1949 [19].

3.3. Discussion of trends in incidence

A lot of studies published since 1948 have indicated that smoking tobacco is the main cause of lung cancer with latency time between the start of smoking and lung cancer of 15 to 50 years [31–39]. Also the number of pack-years and the age at initiation of smoking are closely related to lung cancer risk [40,41]. A molecular link between a defined cigarette smoke carcinogen and human

a) **Men**
- ◆ North America white
- ■ North America black
- ▲ New Orleans white
- X New Orleans black
- ✳ Utah
- ● Australia and New Zealand (Non-Maori)
- + New Zealand (Maori)
- ○ Canada

- ■ Iceland, Norway, Sweden (South)
- ▲ Scotland, the Netherlands
- X Finland, Germany, Italy (North), Switzerland, England
- ✳ Denmark
- ● France
- + Ireland, Italy (South), Spain
- ○ Eastern Europe

b) **Women**
- ◆ North America (white and black), New Orleans (white and black)
- ✳ Utah
- ● Australia and New Zealand (Non-Maori)
- + New Zealand (Maori)
- ○ Canada

- ■ Denmark, England, Iceland, Scotland
- ▲ Ireland, Switzerland
- X Finland, Germany, Italy (North), the Netherlands, Norway, Sweden (South)
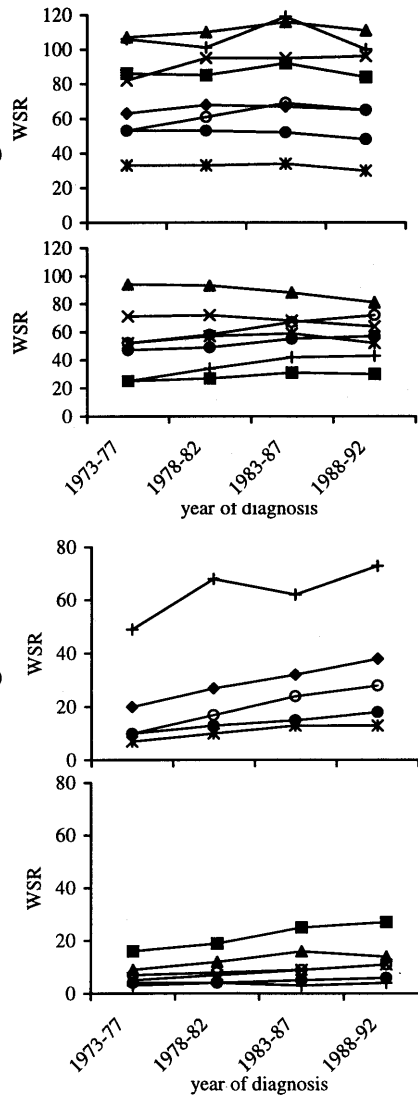- ● France
- + Italy (South), Spain
- ○ Eastern Europe

Fig. 1. Trends in age-standardized incidence rates (WSR) per 100 000 person-years. Source: Cancer Incidence in Five Continents, Vols. IV, V, VI, VII.
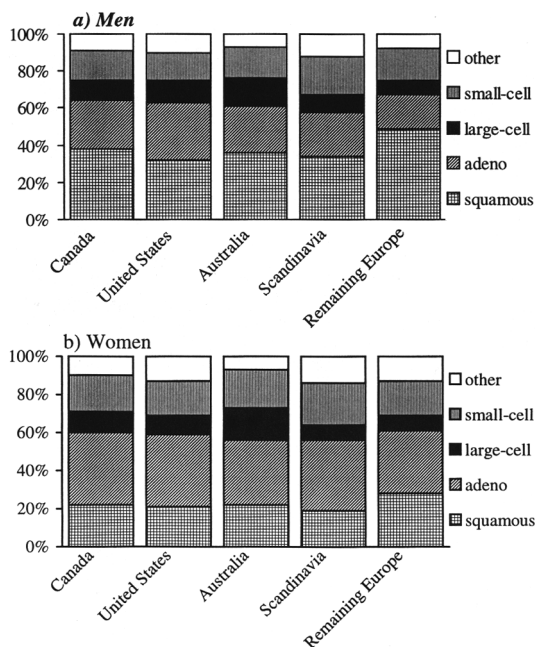
Fig. 2. Percentage distribution of microscopically verified cases by histological subtype (1988–1992). Source: Cancer Incidence in Five Continents, Vols. IV, V, VI, VII.

lung cancer mutations was not found until 1996 [42]. The relative risks of smoking are two to four times higher for squamous cell carcinoma and small-cell carcinoma (RR between 10 and 50) than for adenocarcinoma (RR between 2 and 15) [36,40,43–48]. The decline in risk after quitting smoking was also more consistent for squamous cell, small-cell and large-cell undifferentiated carcinoma than for adenocarcinoma [49]. However, the lower risk for adenocarcinoma could also be spurious, because the risk of adenocarcinoma in non-smokers (= reference group) is also higher [36,43,48,49]. The association between smoking and lung cancer cell types seems to be related to tumour location: adenocarcinoma is known to occur primarily in the peripheral lung zones, whereas squamous cell carcinoma and small-cell carcinoma occur mainly in central or hilar locations [36,40,50,51]. The association between smoking and lung cancer cell type is probably related to the inhalation pattern. A case-control study conducted in the USA between 1977 and

1984 revealed that lung cancer in cigar and pipe smokers was more likely to be a central (squamous cell or small-cell carcinoma) than a peripheral lesion (adenocarcinoma); the authors speculated that cigar and pipe smoke are not inhaled as deeply as cigarette smoke [52]. Other causes of lung cancer have been identified, such as air pollution [53], occupational exposure to asbestos or radon (however, only a small proportion of the population was exposed) [54–56], vitamin A deficiency [57–61], indoor radon [62], possibly bird keeping [63–68], and previous chronic lung diseases [69–72], but the effects of smoking are so predominant that trends in other exposures seem unlikely to be largely responsible for the changes in incidence.

The trends in lung cancer incidence for both sexes followed the temporal and geographical variations in smoking behaviour after 15–25 years. The percentage of smokers among men was much higher than among women but has dropped since the 1950s/1960s, first among younger men [49,73–76]. While the prevalence of smoking has decreased since the 1950s, the percentage low-tar filter cigarette smokers among smokers has increased markedly [74,77–79]. However, those who continued smoking were the heavily addicted ones [80]. In southwestern Europe the percentage of smokers did not start to decrease until the 1980s and in many eastern European countries the prevalence of smoking increased until the 1990s [76]. The very low incidence of lung cancer in Norway and Sweden can be explained by the strong anti-smoking campaigns in these countries [48,76]. The low incidence in Utah is probably due to the high proportion (about 70%) of Mormons, who are discouraged from smoking. The relatively high incidence among women in New Zealand (Maori) can be explained by the high percentage of smokers.

The decrease in incidence rates for squamous cell carcinoma and small cell carcinoma was probably due to a decrease in the percentage of smokers since the 1950s and to a change to low-tar filter cigarettes. This was not the same for men and women, nor for all age groups. The percent-

age of female smokers was much lower than the percentage of male smokers and started to decrease only at the end of the 1970s. This has resulted in an increase in incidence up to the 1990s. Among men both a period effect (decrease in the percentage of smokers since the 1950s and a change to more low-tar filter cigarettes) and a birth cohort effect (mainly the elderly — referring to the earlier birth cohorts — continued smoking non-filter, high-tar cigarettes) occurred.

The increase in adenocarcinoma is more difficult to explain. The extent to which changes in diagnostic techniques or classification were responsible for the increase in adenocarcinoma is likely to be small [21,30,81,82]: solid carcinoma with mucus production, only being classified as 'adenocarcinoma' after 1981 [6], is a very small group and is, therefore, probably not responsible for the major part of the increase. Furthermore, the inter-observer reproducibility for adenocarcinoma was good [83–85]. There are several hypotheses about changes in smoking behaviour, which could explain the increase in adenocarcinoma, which occurs primarily in the peripheral lung zones. First, the introduction of filter cigarettes since the mid-1950s may have led to an increase in the incidence of adenocarcinoma, because filters are less effective in eliminating smaller particles and filter use could also result in taking larger puffs and retaining smoke longer to compensate for the lower nicotine yield [21,36,49,78,86]. Since a study within the SEER database revealed that the increase in adenocarcinoma only occurred in smokers [21], the increased use of filter cigarettes seems to be a plausible explanation for the rise. Moreover, a multicentre hospital-based case-control study in the USA revealed that the risk of squamous cell carcinoma for smokers of filter cigarettes was lower than for smokers of non-filter cigarettes, but the risk of adenocarcinoma was not reduced [78]. A second, complementary hypothesis suggests that smoking low-tar filter cigarettes may increase the risk for adenocarcinoma because these cigarettes have a higher nitrate content. The increased yields of *N*-nitrosamines, especially NNK, induced adenocarcinoma of the lung in laboratory animals [87]. The higher proportion of Americans with adenocarcinoma can also be explained by the higher proportion of smokers who smoke low-tar filter cigarettes in the USA (almost 100% in 1992) compared to European countries (about 70%) [48,77]. The higher proportion of women with adenocarcinoma can also be explained by past smoking behaviour. Prior to the 1950s cigarettes were predominantly unfiltered, high-tar products smoked largely by men. In the 1950s, when women were just beginning to smoke, filter cigarettes were introduced and thus represented less of a change for women than for men. This has resulted in a higher baseline proportion of women with adenocarcinoma. Most of the temporal and geographical variations in lung cancer rates are thus probably related to different patterns of past smoking behaviour.

3.4. Conclusions concerning trends in incidence

Although the peak of lung cancer incidence among men in North America, Australia, New Zealand and northwestern Europe was reached in the 1980s, the rate for men in southern and eastern Europe and for women continued to increase, at least until the 1990s. The decrease in incidence first occurred in younger men, thus the proportion of elderly patients has been increasing.

The trends in incidence were closely associated with past smoking behaviour. Despite a decrease since the 1950s the percentage of smokers reached a plateau of 30–50% in the mid-1980s and teenagers have even been smoking more since 1990 [76]. Furthermore, the average number of cigarettes smoked per day has increased, because the smokers who continued smoking were the heavily addicted ones. Thus, the decrease in lung cancer incidence will probably reach a plateau in the beginning of the next century, but for those born after 1970 there will probably be an increase of lung cancer incidence after 2010.

The trend toward smoking more low-tar filter cigarettes probably caused the increase in the incidence of adenocarcinoma. This tumour type is already the major histological subtype in North America and may also become the major type in Australia, New Zealand and Europe in the near future. It is very likely that adenocarcinoma will

give rise to a new epidemic, although it probably will not reach the same magnitude as that of squamous cell carcinoma.

4. Trends in prognosis

4.1. Geographical variations

Worldwide, the prognosis for patients with lung cancer is very poor, because metastases are often present at the time of diagnosis. Survival is associated with age and tumour stage: 1-year relative survival rates decreased from 40% for patients younger than 45 years old to 20% for patients of 75 and older [88,89], and was better for patients with localised disease (40–65%) than for those with metastasised disease (15–30%) [80,90–92].

In North America the 1- and 5-year survival rates in the 1980s were about 30 and 12%, respectively, [93–96]. Between European countries fairly large variations in lung cancer survival rates existed between 1978 and 1989: 1-year rates varied between 21 and 42%, and 5-year rates between 5 and 15%, being highest in Finland, France, The Netherlands and Switzerland, and lowest in Denmark, England, Poland and Scotland [88–90,97,98].

Between 1975 and 1990 the prognosis for lung cancer patients, regardless of histological type, improved slightly although not significantly over time [88,89,93,95,96,98–100].

4.2. Variations between histological subtypes

Besides being dependent on age and tumour stage, survival for lung cancer patients is closely related to the histology of the tumour. Survival was best for patients with non-small-cell carcinoma and poorest for patients with small-cell carcinoma [90,92,93,97,101–106]. Despite recent advances in treatment the 5-year survival rate for patients with non-small-cell lung cancer is still less than 15% and that for small-cell carcinoma only 5% [92,94,97,107,108].

Although non-small-cell lung cancer is often considered to be one clinically uniform category, several studies indicate that survival differs according to histological subtype, being better for squamous cell carcinoma and adenocarcinoma (1-year survival rates of 40–50%) than for large-cell undifferentiated carcinoma (1-year survival rates of 25–30%) [90,92,94,97,101,103,109]. In Yorkshire, England, UK, the population-based survival for each histological subtype of non-small-cell lung cancer remained largely unchanged between 1976 and 1983 [110]; however, the percentage of patients with an unknown histology was very high [111]. In contrast, in the southeastern part of The Netherlands the population-based relative 1-year survival rates for adenocarcinoma decreased markedly from 59% in 1975 to 45% in 1992, while that for squamous cell carcinoma remained about 50% and that for large-cell undifferentiated carcinoma remained about 30% [92].

Small-cell lung cancer can be distinguished from other forms of lung cancer. Its features are: rapid progression, short doubling time, high growth fraction, and sensitivity to multiple chemotherapeutic agents and radiation therapy. Short-term survival seems to have improved since the introduction of chemotherapy in the 1970s [107,108,112]. In Mersey and Yorkshire, England, UK, the population-based 2-year survival rate improved from 2% in the 1970s to 8% in the 1980s and in the southeastern part of The Netherlands the population-based relative 1-year survival rate improved from 15% in the 1970s to 35% in the 1980s, but there was no further improvement in the 1990s and 2-year survival did not exceed 8% [106,113].

4.3. Discussion of trends in prognosis

Despite the improvement in survival for small-cell lung cancer, the overall prognosis for lung cancer remained poor and 5-year survival rates still do not exceed 15%. Until now, the only real chance of cure is surgery for patients with limited disease [97,104,114,115]. About 30% of the patients with non-small-cell carcinoma have undergone surgical treatment since the 1980s compared to only 5% of those with small-cell carcinomas [103,116]. Postoperative mortality, which is higher for the elderly, is related to the type of resection,

the risk being highest (6%) after pneumonectomy [117].

The proportion of patients undergoing surgery decreased slightly between 1974 and 1986; for smaller lesions a trend was apparent toward more lung-sparing resections; the use of radiotherapy has increased since the 1980s [93,118]. Selection for surgery has probably improved as a result of the introduction of flexible bronchoscopy, isotope scanning and computerised tomography as well as mediastinoscopy. These diagnostic techniques have probably increased the detection of metastases (stage migration). With the exception of small-cell carcinoma there was almost no change in the proportion of patients receiving chemotherapy in the USA and the UK [93,118].

The prognosis for lung cancer varied markedly between countries, probably due to differences in (1) detection of disease, (2) inclusion of patients in studies (selected or unselected cases, patients dead around diagnosis), (3) methods of data collection and completeness (depending on access to medical care and the quality and availability of death certificates), (4) methods of calculating survival (crude, disease-specific or relative survival) and (5) access to specialised care. Furthermore, the availability of medical expertise and facilities is dependent on the number of chest physicians and internists per 100 000 inhabitants. It is also influenced by geographical and socio-economic factors, including distance from specialised centres and the extent of health insurance coverage.

4.4. Non-small-cell lung cancer

Survival of non-small-cell carcinoma is closely associated with tumour stage and treatment. The treatment-of-first-choice for patients with stage I or II non-small-cell lung cancer is surgical resection [119]. Even for elderly lung cancer patients pulmonary resection is justified, however, a careful preoperative assessment ought to be performed and standard resections should be preferred [120,121]. Some patients with stage IIIa disease will qualify for surgical resection, others should be offered combined radiotherapy and chemotherapy. For most patients with stage IIIb disease, the preferred therapeutic modality is thoracic radiotherapy in combination with chemotherapy [119]. For patients with stage IV lung cancer, no curative treatment or 'standard therapy' is available [119,122]. Although radiotherapy was applied sparingly either alone or in combination with chemotherapy for non-small-cell lung cancer, its use has doubled in the last few decades [100]. Adjuvant chemotherapy produces a significant but clinically small advantage for non-small-cell lung cancer patients and should still be considered experimental [119,123]. Typing of oncogenes or tumour suppressor genes may provide a more accurate diagnosis and, therefore, facilitate the planning of suitable therapeutic approaches, e.g. adjuvant chemotherapy shortly after undergoing surgery for patients with cytokeratin 18 positive stage I non-small-cell lung cancer [124–129].

Despite an excellent description of the tumour's size and the extent of anatomic spread, the tumour node metastasis (TNM) system does not include important prognostic factors that are manifest in the clinical condition of the patient [130–133]. Since the proportion of elderly patients in most Western countries is growing, co-morbidity or the coexistence of various chronic illnesses in addition to the index disease is of growing importance for the clinical management (especially surgical management) of lung cancer patients. Co-morbidity increases the risk of peroperative and postoperative complications [134–137], especially those of the cardiorespiratory system [117,120,121,138,139]. Co-morbidity is also an independent prognostic factor [140–145]. Indeed co-morbidity in elderly patients was found to be associated with less surgery and poor survival [100,146].

In the southeastern part of The Netherlands a marked decrease in survival for patients with adenocarcinoma was found, despite increased application of better diagnostic techniques by more chest physicians [92]. The decrease in survival might partly be explained by the lift of screening for tuberculosis since the early 1980s and is possibly partly due to the higher concentration of carcinogens in the peripheral lung zones — due to the increased use of filter cigarettes — which may have caused a more rapidly metastasising

tumour. This needs to be confirmed in other countries.

4.5. Small-cell lung cancer

Prior to 1970 irradiation and sometimes surgery were the major modes of treatment of small-cell lung cancer. The overall 5-year survival rate with surgery was < 1–3%, even for patients with clinically resectable disease. Neither preoperative nor postoperative radiotherapy improved the poor results of surgery [147]. Currently, small-cell lung cancer patients with limited disease generally receive combination chemotherapy and radiotherapy, and approximately 50% experience complete clinical remission. Patients with extensive disease also exhibit an initial response to chemotherapy, but only 20–40% go into complete remission. Although the introduction of intensive combination chemotherapy in the 1970s has resulted in an increase in survival [110,118], death from recurrent disease occurs within 2 years of diagnosis in 80–98% of the cases [113,148–151]. Furthermore, results of chemotherapy have reached a plateau and further improvement seems impossible with the currently available tools [106–108,152]. The response rates and survival rates after combination chemotherapy with irradiation were moderately higher than after combination chemotherapy alone [112,153–156].

For elderly patients, whose proportion has been increasing, the survival rate was lower [113,157–159]. This could also be related to the presence of co-morbidity, which may complicate treatment and deteriorate the prognosis [135–137,160–162].

4.6. Conclusions concerning trends in prognosis

Despite earlier detection through the increased use of flexible bronchoscopy and fine needle aspiration cytology, lymphatic and hematogenous metastases are often present at the time that lung cancer is diagnosed, and prognosis is still very poor. Survival of lung cancer differs markedly, according to histological subtype. The prognosis for non-small-cell lung cancer has remained approximately constant, while the prognosis for adenocarcinoma — one of the subtypes of non-small-cell lung tumours — may even be decreasing over time. In contrast, progress has been made in the short-term survival of small-cell lung cancer — due to the introduction of chemotherapy since the 1970s — but it has stabilised since the mid-1980s and 2-year survival remains very poor. The growing proportion of elderly patients who often present with serious co-morbidity at diagnosis complicates treatment and indicates the need for adapted guidelines for these patients, who usually are not entered in clinical trials.

5. Summary and conclusions

Since the beginning of this century the incidence of lung cancer has been increasing dramatically in most Western countries; it is now the most frequent or second most frequent tumour in men and the second or third in women. The peak of the epidemic among men was reached in the 1970s or 1980s in North America, Australia, New Zealand and north-western Europe, first in the younger age groups. The peak among men in southern and Eastern Europe and for women has not yet been reached. The trends were not the same for every histological subtype of lung cancer. Among men the incidence of squamous cell carcinoma and small-cell carcinoma started to decrease earlier than that of adenocarcinoma.

These trends followed changes in smoking behaviour. Among men the proportion of smokers has increased markedly since the beginning of this century but has decreased since the 1950s or 1960s, except in southern and eastern Europe. Younger men were more inclined to quit smoking or to switch to low-tar filter cigarettes than the elderly. Women only started smoking in the 1950s and the percentage of female smokers did not decrease before the 1970s.

The incidence of and proportion of patients with adenocarcinoma have been increasing. Many studies have made it plausible that this increase is related to a shift from high-tar non-filter cigarettes toward low-tar filter cigarettes during the 1960s and 1970s, especially since the increase in adenocarcinoma was found to occur only in smokers.

Despite improvement in both the diagnosis — as a result of flexible bronchoscopy — and treatment, the overall prognosis for patients with non-small-cell lung cancer did not improve significantly over time. Recognition of specific patterns of mutational activation of oncogenes or disruption of tumour suppressor gene function, such as K-ras or cytokeratin 18, may facilitate tailor-made treatment and improve the prognosis for certain subgroups. In contrast, the introduction and improvement of chemotherapy since the 1970s gave rise to an improvement in — only short-term (<2 years) — survival for patients with small-cell lung cancer. New (combinations of) chemotherapeutic agents intend to improve long-term survival for patients with small-cell lung cancer. Studies on therapy should also focus on improvement of the treatment of adenocarcinoma, because more lung cancer patients will present with this histological subtype.

In this review we have shown that the trends in the incidence of lung cancer in industrialised countries were closely associated with past smoking behaviour by birth cohort. Furthermore, except for the improvement in short-term survival of small-cell lung cancer, the prognosis has not changed significantly over the last two decades. Since mortality is influenced by both incidence and survival the following trends in mortality can be expected in the near future.

First, the decrease in mortality among men in North America, Australia, New Zealand and northwestern Europe will reach a plateau at the beginning of the next century because of the steady percentage of smokers since the 1980s and a more or less steady survival. However, the incidence of lung cancer among those born since 1970 will probably increase after 2010, because teenagers have been smoking more since 1990. Among women in these regions mortality will start decreasing soon and will also stabilise at the beginning of the next century; the same trend is expected for men and women in southern Europe. In eastern Europe the percentage of smokers increased until the 1990s, thus a decrease in mortality is not expected before the year 2010. In other parts of the world, where smoking is still increasing, mortality due to lung cancer will increase dramatically in the next decades. Smoking can only be countered by a combined strategy of decreasing the availability of cigarettes, e.g. by increasing the price, and developing better strategies for handling nicotine addiction by offering less harmful nicotine delivery systems.

Second, the mortality of adenocarcinoma will probably increase worldwide, due to the increased use of low-tar filter cigarettes. In contrast, mortality due to squamous cell carcinoma and small-cell carcinoma will probably decrease because of a decrease in incidence and steady or slightly increasing survival rates.

In short, the epidemic of lung cancer in industrialized countries is not over yet, especially in southern and eastern Europe. Except for short-term survival of small cell tumours, the prognosis for patients with lung cancer has not improved significantly.

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