

Basic and Clinical Concepts of Lung Cancer

edited by

HEINE H. HANSEN

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Preface

The last volume dealing with lung cancer in this series in Cancer Treatment and Research was published in 1986 and entitled *Lung Cancer: Basic and Clinical Aspects*. The present book continues the outline of the previous volume by presenting up-to-date information on lung cancer in critical reviews of new important basic and clinical concepts of lung cancer. The present volume has broadened the scope by also including chapters dealing with issues such as epidemiology, prophylaxis, and histopathology of lung cancer. The content of the book thus reflects the increasing awareness of a global disease that is more and more in focus, not only scientifically but also politically. The latter fact results increasingly in changes in health legislation, with prevention measures influencing everyday life. The great interest in the disease is natural, considering that more than one patient dies from lung cancer every minute globally.

The first chapter is from the Cancer Unit, WHO, Geneva, and describes in detail the epidemiologic features of lung cancer, which is the second most frequent cancer in the world with 660,500 new cases annually; it will soon surpass stomach cancer as the leader. Thirty-one percent of the cases occur in developing countries, where the increase is especially dramatic. It is alarming to see that the practically unlimited expansion of the tobacco industry in most developing countries is accompanied by a lack of legislative measures to control tobacco use and a lack of public education about the dangers of tobacco use. In the second chapter, the impact of prophylactic measures in the control of lung cancer is described by Cullen, from the National Cancer Institute, Bethesda, U.S.A. An impressive decline in smoking in American adults is now observed, thanks to broad-scale awareness campaigns. Ongoing intensive, multifaceted intervention research programs to identify effective smoking-control strategies are also described.

Histopathological features of lung cancer are presented in the next three chapters. McKay, from Houston, reports on the application of new technical procedures such as the use of electron microscopy and immunochemistry to the various types of bronchogenic carcinomas. Kung et al., from Hong Kong, describe the intra- and interobserver variability among experienced histopathologists using both histological and cytologic material for the vari-

ous cell types; both the WHO 1967 and WHO 1981 classifications have been tested. The application of immunohistochemistry is dealt with specifically by Shimamoto et al. of the National Cancer Institute, Tokyo, who describes the usefulness of this procedure both for routine diagnostic pathology and for the study of lung cancer biology, especially with respect to cell differentiation and growth properties.

In the sixth chapter, Rodenhuis, from the National Cancer Institute, Amsterdam, brings us up to date on oncogenes, which are critical for the understanding of the biology of lung cancer. Their contribution to diagnosis, staging, and treatment is still modest, but is under rapid development.

Another area of biology with incipient clinical implications is covered by Mulshine et al., from the National Cancer Institute, Bethesda, U.S.A., in a chapter entitled *Autocrine Growth Factors and Lung Cancer*. The first phase-I clinical trials with monoclonal antibodies against growth factors have just been initiated. Additional biologic information is given in chapter 8 by Campbell et al., from Melbourne, who focuses on cytogenetic analysis of lung cancer and more recently developed techniques for molecular probing. It is conceivable that these studies will result in a reclassification of lung cancers that will better predict their biologic behavior and allow improved treatment selection.

The remaining part of the book treats a broad spectrum of clinical issues. Teeling et al., from Dublin, discusses the application of biomarkers in the clinical management of patients with lung cancer, suggesting that the presence of neuroendocrine markers in patients with non-small-cell lung cancer is a predictive marker for chemosensitivity. The issue of chemosensitivity is also addressed by Roed and Vindelev, from the Finsen Institute, Copenhagen, who have established a large panel of cell lines. The authors describe the ongoing investigations with the aim of evaluating the potential of in vitro sensitivity testing to guide the selection of new drugs in order to improve therapy of small-cell lung cancer. Preclinical models of lung cancer are also a part of the chapter by Ferguson and Smyth, from Edinburgh. They have used human non-small-cell lung cancer xenografts and observed growth retardation testing α -interferon. The clinical activity of this compound either alone or in combination with cisplatin is also described.

Aisner and Whitney, from Baltimore, give an overview of recurrent and newer approaches in the pretreatment assessment of patients with lung cancer, including the first experience with magnetic resonance imaging (MRI). As to prognostic factors, important new information is presented by Sørensen, from Copenhagen, who has analyzed a series of 396 patients with adenocarcinoma, encompassing all stages, using advanced sophisticated statistical methods. In the next chapter, Holmes, from Los Angeles, presents the most recent data on the use of radiotherapy and chemotherapy in combination with surgery, including some of the first encouraging therapeutic results from multicenter studies performed in North America. Another area of front-line clinical research is the use of high-dose chemotherapy of

small-cell lung cancer with and without bone marrow transplantations, described in chapter 15 by Sculier and Klastersky of the Institute Jules Bordet, Brussels. Small-cell lung cancer is also the topic of the chapter by Kristjansen and Pedersen, from Copenhagen, who critically review the various forms of therapy of CNS metastases, including the controversial issue of prophylactic cranial irradiation. The last two chapters deal with consequences of treatment. Feld, from Toronto, covers all the complications associated with treatment of small-cell lung cancer, while Kaasa, from Oslo, sheds light in his chapter on the complex issue of the psychosocial aspects of lung cancer.

Altogether the book thus contains 18 chapters, with contributions from 12 countries covering four continents.

It has not been our aim to give a complete survey on lung cancer, but it has been our purpose to present information that will stimulate further research activities. The task is urgent, if we want to make an impact on this common malignant disease in this century.

Heine H. Hansen

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1. Lung Cancer in Developed and Developing Countries

KEN STANLEY and JAN STJERNSWÄRD

INTRODUCTION

After the first five years of life, cancer, cardiovascular diseases, and accidents are the three main causes of death in both developed and developing countries [1]. Developing countries account for approximately 2.3 million of the global 4.3 million cancer deaths and for 3.2 million of the 6.3 million new cancer cases worldwide each year [2,3]. Thus, in absolute figures, the majority of the world's cancer patients are in the developing countries.

In 1985, WHO reported its study of cancer mortality trends covering the period 1960–1980 in 28 industrialized countries, representing 75% of the population of the developed world. The age-adjusted cancer mortality rate for males increased by 19% over this decade. The most dramatic rise in mortality was registered for lung cancer (76% for men and 135% for women), confirming the urgent need for action against the use of tobacco [4]. The WHO analyses pointed out the limited impact of treatment on overall mortality for common cancers and the need for considerable strengthening of preventive measures, especially with regard to tobacco control.

If existing trends continue into the future, cancer mortality is expected to rise in nearly all regions of the world. The major reasons for this are a general increase in the age of the world population, control of other major health problems, and an increasing use of tobacco.

Although considerable resources have been allocated globally to cancer research, efforts to implement these findings, especially in developing countries, are lagging behind. At present in most countries, cancer-control activities lack overall coordination. Usually, most of the resources are used for therapy, often at relatively high costs and with limited effect, because the great majority of patients are incurable at the time of diagnosis.

LUNG CANCER

The most frequent forms of cancer globally, in males and females combined, are stomach cancer (669,400 cases per year), lung cancer (660,500), breast

cancer (572,100), colorectal cancer (572,100), and cervical cancer (465,600) [3]. Incidence rates for specific cancers, such as mouth, cervix, esophagus, and liver cancer, are high in certain geographic regions in developing countries and exceed the corresponding rates for virtually all developed countries.

Lung cancer is the leading cancer in males globally and is the leading cause of cancer mortality in males in more than 35 countries. For females, lung cancer is the sixth leading cancer; it is expected to become more common as the percentage of women smokers continues to increase.

Table 1.1 gives estimates of the annual incidence of lung cancer by region for 1980, the year of the most recent global estimates. Of an estimated 660,500 new cases, 31% are from the developing regions. Lung cancer is not, as many believe, a problem solely of the industrialized countries.

The highest crude lung cancer incidence rates for males are found in Europe (76.4 per 100,000), North America (74.6 per 100,000), and Australia/New Zealand (61.6 per 100,000). While there is a large difference in the rates between the developed and the developing countries, it must be remembered that these are crude rates and have not taken into account the high proportion of younger age groups found in developing countries, and that in the aforementioned high-risk areas the rate of cigarette smoking has been high for many years.

Over the last 20 years, death rates from lung cancer in women more than doubled in Japan, Norway, Poland, Sweden, and the United Kingdom, increased by more than 200% in Australia, Denmark, and New Zealand, and increased by more than 300% in Canada and the United States [5]. During the 1960s, mortality from breast cancer was three to six times higher than from lung cancer in these countries. In recent years, this ratio has

Table 1.1. Estimated annual lung cancer incidence by region in 1980.*

	New cases per year (in thousands)			Crude incidence rates for males (per 100,000)
	Males	Females	Total	
North America	91.7	39.1	130.8	74.6
Latin America	32.0	9.1	41.1	17.7
Europe	180.3	34.1	214.4	76.4
USSR	63.5	14.6	78.1	51.2
Africa	7.4	1.9	9.3	3.1
China	43.6	22.7	66.3	8.5
Japan	17.8	6.6	24.4	31.0
Australia/New Zealand	5.5	1.4	6.9	61.6
Other Asia	71.8	17.4	89.2	9.5
Developed regions	358.8	95.8	454.6	65.3
Developing regions	154.8	51.1	205.9	9.2
World total	513.6	146.9	660.5	23.0

* Adapted from [3].

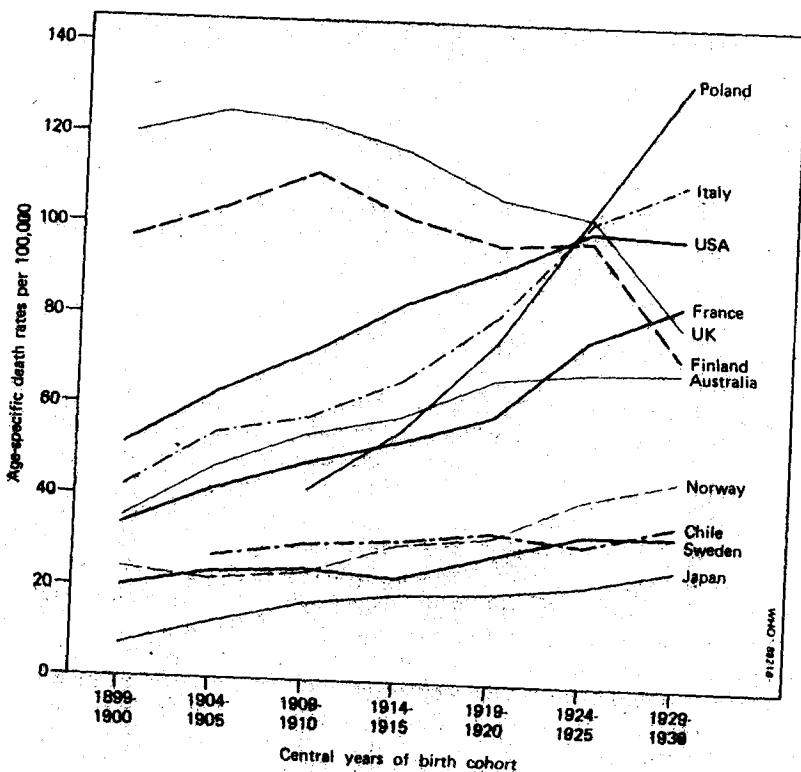


Figure 1.1. Lung cancer mortality rate trends for selected countries; age-specific rates for cohorts of males with mortality at ages 50 to 54. (Adapted from [6].)

declined to around 1.5, and indeed it is estimated that lung cancer deaths will exceed breast cancer deaths in 1988 in Scotland and the United States.

Because lung cancer is strongly associated with age and smoking history, it is necessary to look at age cohorts to obtain an accurate picture of the trends. Lung cancer mortality trends for some selected countries are presented in figure 1.1. The figures presented are the age-specific mortality rates for cohorts of males who died of lung cancer at ages 50 to 54 [6].

Marked declines are evident for Finland and the United Kingdom. For the other countries in this figure (and for all other countries worldwide), the pattern is either a steady increase or an increase and a leveling off. Between 1962 and 1975, the overall incidence of lung cancer doubled in Shanghai, China's largest city, where the rate in males is 50.2 per 100,000—higher than in many North American or European populations.

A rough estimate of the future number of lung cancer cases is possible if we assume that world tobacco-smoking rates will stabilize at their current

figures, lung cancer rates in developing countries will increase to half the magnitude of current lung cancer rates in developed countries in 15 years' time, and the rates will be equivalent in 40 years' time. Under these conditions, by the year 2000 there will be two million cases of lung cancer per year (60% in developing countries). By the year 2025, this will increase to more than 3.5 million cases per year. And in the worst-case scenario, where women in developing countries will increase their smoking to match that of the men, one can predict five million cases of lung cancer per year (more than 80% in developing countries) by the year 2025.

TOBACCO VERSUS HEALTH

The association between tobacco use and ill health has been reviewed by many national and international committees and organizations. Consistently, they conclude that tobacco use is associated with significant ill health [7-10]. In countries where smoking has been a widespread habit, it is responsible for 80-90% of lung cancer deaths, 75% of bronchitis deaths, 40% of bladder cancer deaths, and 25% of ischaemic heart disease deaths. Further, the risk of lung cancer in nonsmokers is increased by 25-35% due to passive smoking, the breathing of other people's tobacco smoke. Tobacco habits, including traditional forms of tobacco chewing such as of the betel quid, are also responsible for 90% of oral cancer deaths in Southeast Asia. Worldwide, tobacco use is now responsible for more than 2.5 million premature deaths each year. Table 1.2 gives the mortality attributable to smoking for the United States in 1984. Lung cancer is the single largest contributor, followed by ischaemic heart disease. Lung cancer accounts for 29% of the mortality attributable to smoking [11].

Perhaps the most important feature in the relationship between cigarette smoking and lung cancer is the strong correlation between the duration of regular cigarette smoking and subsequent lung cancer rates. A doubling of duration of regular tobacco use will result in an increase in lung cancer incidence of approximately 20-fold. This relationship holds particular relevance for evaluating the effect of prior smoking history on the current health of a population and then projecting the health problems of countries where substantial increases in tobacco smoking have occurred in the last decade but where the full health effects have not yet been felt.

The concept that atmospheric pollution might be an important cause of lung cancer dates back to the 1930s, when it was observed that lung cancer rates were higher in cities than in towns. However, subsequent investigations that have considered the effect of smoking habits, as well as national and international reviews, have led to the conclusion that no more than 10 cases per 100,000 males each year could be ascribed to atmospheric pollution in the high-risk populations and that the proportion of lung cancer attributable to smoking is of the order of 90%.

Table 1.2. Mortality attributable to smoking—United States, 1984.*

Disease category	Adults ≥ 20 years old			
	Males		Females	
	Percentage of deaths	No. of deaths	Percentage of deaths	No. of deaths
Neoplasms				
Lip, oral cavity, pharynx	69	3,958	41	1,110
Esophagus	59	3,717	54	1,257
Stomach	17	1,455	25	1,467
Pancreas	30	3,459	14	1,653
Larynx	81	2,385	41	274
Trachea, lung, bronchus	80	65,659	75	27,170
Cervix uteri	0	0	37	1,685
Urinary bladder	37	2,447	27	853
Kidney, other urinary	24	1,319	12	403
Circulatory diseases				
Hypertension	16	2,099	15	2,645
Ischemic heart disease				
< age 65	29	22,362	18	4,892
Ischemic heart disease				
≥ age 65	16	33,461	8	16,816
Cardiac arrest	40	7,745	34	5,950
Cerebrovascular disease	10	5,692	14	12,228
Arteriosclerosis	24	2,200	32	4,797
Aortic aneurysm	62	6,444	47	2,244
Respiratory diseases				
Pneumonia, influenza	21	5,986	9	2,679
Chronic bronchitis, emphysema	85	9,097	69	3,821
Chronic airways obstruction	85	26,541	69	11,545
Digestive diseases				
Ulcers	48	1,556	45	1,497
Pediatric diseases, < one year old				
Short gestation, low birthweight	18	314	18	279
Respiratory distress syndrome	18	396	18	251
Other respiratory conditions of newborn	18	360	18	275
Sudden infant death syndrome	13	405	13	264
TOTAL		209,057		106,063

* Adapted from CDC report [11].

In addition to the association between tobacco and cancer, cardiovascular disease, bronchitis, and emphysema, the evidence also indicates that the risk of perinatal mortality is increased among infants of women who smoke tobacco during pregnancy, that tobacco increases health risks in combination with occupational exposure to asbestos and other chemical carcinogens affecting the lungs, and that smoking contributes significantly to accidents

involving flammable and explosive material. The harmful effects of tobacco are no longer questioned except by the tobacco industry.

In the United Kingdom, a report of the Royal College of Physicians expressed the extent of the problem by stating that among 1000 young male adults in England and Wales who smoke cigarettes, on average about one will be murdered, six will be killed on the roads, and 250 will be killed before their time by tobacco [7].

The risks associated with tobacco are well known by the medical community worldwide. In a survey of the members of the International Association for the Study of Lung Cancer, 97% stated that at least 80% of all cases of lung cancer are caused by tobacco; 65% also indicated that the risk of lung cancer is increased among those highly exposed to cigarette smoke (passive smoking) [12].

TOBACCO USE PATTERNS

It is estimated that in the industrialized world, one third of all males above age 15 smoke cigarettes; in the developing countries, about one half. The rate for females in the industrialized world is slightly lower than the rate for males; in the Third World, about 10% of females smoke, but the proportion is rising rapidly.

Smoking rates are already high in many developing countries. Table 1.3 gives the smoking prevalence rates from recent surveys in 65 countries. Eight of the 10 countries with the highest smoking rates among males are developing countries; of the top 30 countries, only nine are industrialized countries. However, at present, the number of cigarettes smoked per capita in the Third World tends to be somewhat lower than in the developed countries.

Although the prevalence of smoking is very low among certain groups of women in developing countries, such as Moslem women, among other countries it approaches that of men. In rural areas of Andhra Pradesh in India, 67% of the women, as compared to 81% of the men, smoke. Smoking in pregnancy is a problem in Latin America; surveys show that more than 20% of pregnant women in urban areas smoke.

In the industrial world, smoking among men became widespread at the time of World War I, 1914-1918, peaking in the mid-1970s. Women in these countries have been smoking since World War II, 1939-1945; but, as a result of advertisements in the 1960s that, for instance, linked smoking to women's rights and proclaimed 'You've come a long way, baby,' today women are smoking nearly as much as men, if not more. In the Third World, cigarette smoking among men became predominant in the mid-1970s—later than in industrialized countries—and the increase among Third World women has only begun recently.

Some 120 countries produce tobacco, and the developing countries now