Lung Cancer

NATURAL HISTORY, PROGNOSIS, AND THERAPY

EDITED BY

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Preface

Lung cancer is one of the leading causes of death from malignant disease, and its incidence is increasing dangerously throughout the world. Cytotoxic agents and combined strategies, which have already enabled appreciable progress against some solid tumors such as breast cancer and ovarian cancer, have not, unfortunately, produced the same results against lung cancer. Far from being discouraging, this situation presents a challenge which should encourage greater effort in the analysis and refinement of existing concepts.

I have had occasion to meet fellow workers who are diligently engaged in achieving this goal. I asked them to contribute to this monograph which aims to provide an account of the knowledge acquired by several specialists through extensive personal experience; draw attention to methodologic progress, conceptual debates, and controversial points resulting from this experience; and encourage criticism, cooperation, and further investigation by other teams working in this field.

I have chosen to present papers from reknowned specialists in their fields in order to provide readers with recent, well-established data. My contributions are concerned with problems, speculations, and criticisms of current therapeutic strategies.

Due to the present frequency and widespread extension of this disease in all the advanced countries, this book should be of interest not only to specialists of respiratory diseases, but also to oncologists, surgeons, radiotherapists, immunologists, and internists. Only their combined efforts and interest can improve the prognosis of lung cancer.

I would like to extend my sincere thanks to all the authors who have contributed to this work with preciseness and independence of thought. I would like also to thank Dr. P. Chahinian whose help in editing this work was invaluable. We are indebted to Dr. R. Edelstein and Dr. M. L.

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LUCIEN ISRAEL

Contents

Chapter 1

Present Incidence of Lung Cancer: Epidemiologic Data and Etiologic Factors

A. Philippe Chahinian and Jacques Chrétien

The history of lung cancer merges with that of its etiology. In 1420, shortly after the opening of the Schneeberg mines in Saxony (renowned today not only for their richness in various metals but also for radon) Theophrastus Paracelsus described the *Bergkrankheit* (or mountain sickness) in miners. It was only in 1879 that Harting and Hesse recognized the malignant nature of this disease, which they erroneously termed pulmonary sarcoma [89]. The accurate diagnosis of lung cancer was established in 1913 [15]. It is true that at that time the disease was extremely rare, since Adler was able to collect no more than 374 cases in the world medical literature [89]! Nevertheless, the role of cigarette smoking was already suspected.*

* For more details, the reader can refer to "Lung Cancer" by Selawry and Hansen [81a].

Since then, the incidence of lung cancer has increased incessantly, until today it has reached an alarming level. This dramatic and exceptional progression is one of the most striking facts in cancerology. Lung cancer causes more deaths among the male populations of all industrialized countries, than any other form of cancer, with almost 70,000 deaths in the United States alone in 1972 [87].

I. PRESENT INCIDENCE

Tables I and II show the annual mortality rate for lung cancer for each sex in most industrialized countries. For Doll, the morbidity rate may be assessed by multiplying the mortality rate by 1.20; this coefficient clearly shows the disastrous prognosis associated with the disease. Even more striking than the present-day absolute levels is the increase in incidence: lung cancer is on the rise in all countries, Great Britain being the record holder [21]. However, it is difficult to make statistical comparisons between countries in view of the disparity in age groups, information contained in death certificates, and accuracy of epidemiologic surveys [21]. In fact, all these factors contribute to an underestimation of the true incidence of the disease. The absolute incidence has nearly doubled every 10 years over the past few decades. This rise is a real one and cannot be attributed to improved diagnostic procedures, population increase, longer life span, or more accurate death registers [21, 48].

However, the most recent statistics reveal that this increase is slowing down in some male populations, namely, in the United States (in Caucasians), Great Britain, Finland, Denmark, and Japan [81]. In view of this finding, it may be hoped that the incidence of lung cancer is becoming

TABLE I

Primary Bronchogenic Carcinoma[a, b]

	France		Great Britain		Germany		Italy	
Year	Male	Female	Male	Female	Male	Female	Male	Female
1955	20.6	5.5	69.3	10.6	34.4	6.0	15.6	4.1
1960	27.7	5.6	85.6	13.2	48.4	7.3	23.9	5.2
1965	35.0	6.4	95.7	17.0	56.9	9.0	34.0	6.2

[a] From Council of Europe [21].

[b] Mortality rate per 100,000 in four European countries.

TABLE II
Lung Cancer Death Rates per 100,000 Population in the United States[a]

Year	Male	Female
1958	31.9	5.5
1960	35.3	5.7
1965	43.0	7.7
1970	53.4	11.9

[a] SOURCE: "Vital Statistics of the United States," U.S. Department of Health, Education and Welfare. Data kindly provided by Edwin Silverberg, American Cancer Society, New York.

stable or even decreasing [81], and this change should be appreciable after 1980 [53].

II. EPIDEMIOLOGIC DATA

A. Age and Lung Cancer

Generally speaking, the incidence of lung cancer in the male population is highest around the age of 65 and around the age of 75 in the female population. Beyond these ages, the incidence decreases. In fact, these data, derived from conventional mortality tables, are inaccurate since they are based on deaths of persons of different age groups studied at the same time [21]. Correct analysis can be made only through the study of cohort mortality tables, that is by following groups of people born in the same period. This method reveals that the decrease in incidence is illusory and that, in fact, the mortality rate continues to increase with age [21]. Furthermore, the most marked increase in mortality rate occurs in the oldest section of the population. This factor alone can account for the more advanced age at which maximum death rate is observed in the female population, since increase in mortality rate due to lung cancer is a more recent phenomenon among females than among males [21]. These findings suggest the involvement of some carcinogenic processes with a cumulative effect and a long latent period.

In contrast, lung cancer is rare before the age of 40, accounting for approximately 2% of all cases [1]. The absolute number of cases for this age group has remained stable in all countries, and the epidemiologic profile of the disease seems unremarkable [1]. For example, male predomi-

nance is still observed, but to a lesser degree. It even appears that the incidence is decreasing in this age group in the United States and in Great Britain [81], possibly as a result of environmental changes.

B. Sex and Lung Cancer

Male predominance is a constant feature of lung cancer, but the sex ratio (ratio of the number of male cases to the number of female cases) is presently changing. In the United States, the sex ratio reached its peak in 1960 (6.8 : 1) and has fallen consistently since to less than 5 : 1 in the Caucasian population [81]. This phenomenon is not due to a decrease in the male mortality rate but to a more rapid rise in the female mortality rate. This rise in female mortality became appreciable only after 1960 [13, 94]. Since then, the mortality rates for women have risen and are increasing at more than an exponential pace, as determined in the United States (in Caucasians), in Great Britain (peak sex ratio = 6.2 in 1960 as against 4.9 in 1969), and in Denmark [81]. A continued decrease in the sex ratio is likely over the next few decades because of an increasing incidence in the female population [13].

C. Geographical Distribution

Lung cancer is encountered predominantly in highly industrialized regions. The first striking increase in the incidence of the disease was reported immediately following World War I in the large industrial cities of Germany [89]. All other factors being equal, the death rate is usually 2 to 5 times greater in cities than in rural areas. Moreover, there is a correlation with the density of population and with the degree of urban concentration. Thus, the mortality rate due to lung cancer in conurbations is 20% higher than in small towns [21].

D. Occupation and Social Class

The poorest classes are the most severely affected. Mainly unskilled laborers are affected, with skilled workers affected to a lesser extent [21]. Analysis of this data is complex and is connected with the study of etiologic factors, such as smoking, occupational hazards, and environment.

E. Ethnic Factors

In the United States, the mortality rate due to lung cancer in both men and women is increasing approximately twice as fast for nonwhites as for whites [62]. This phenomenon emphasizes the important role of environ-

mental factors in the causation of the disease [49]. The importance of the environment is even more obvious in studies of migratory populations. In the United States, the mortality rate due to lung cancer has decreased for British and German immigrants, whereas it has increased for Italian and Scandinavian immigrants [48]. In Italian and Scandinavian immigrants the incidence of lung cancer has tended to approach that recorded in the United States. It would thus appear that variations between different ethnic groups might, in fact, be related to environmental factors and personal habits.

III. ETIOLOGIC FACTORS

The 60 to 90 m^2 of respiratory epithelium are an ideal target for atmospheric carcinogens carried by the 12 m^3 of air daily inhaled by man. The large number of etiologic factors involved makes their study a complex one. Their analysis must take into account the interactions between numerous carcinogens, some of which have yet to be identified. These interactions may produce simple additive effects or synergistic effects. Furthermore, some factors are *initiators,* modifying the genetic apparatus and giving rise to a potential tumor cell. Others are *promoters*, inactive by themselves but able to stimulate the initiated cell, and thus contribute to tumor induction and proliferation [17, 18].

A. Tobacco

On this point, all epidemiologic investigations are in agreement [21]. In all countries, the increased incidence of lung cancer follows the increase in cigarette smoking. This strong relationship is based on the following evidence.

1. Statistical Evidence

The marked rise in the incidence of lung cancer coincided with a notable increase in cigarette consumption. In Finland, for example, annual cigarette production reached one million units a year as early as 1880, while in Norway production began only in 1886. In 1930 the incidence of lung cancer in Finland far exceeded that in Norway [51].

The following three statistical surveys were decisive.

a. The survey by Doll and Hill [25] involving 40,000 British doctors followed for 4 years. Of 36 cases of lung cancer, 25 involved smokers. The