Advances in
CANCER RESEARCH

ADVANCES IN CANCER RESEARCH

EDITED BY

JESSE P. GREENSTEIN
National Cancer Institute, National Institutes of Health, U.S. Public Health Service, Bethesda, Maryland

ALEXANDER HADDOW
Chester Beatty Research Institute, Royal Cancer Hospital, London, England

Volume III

ACADEMIC PRESS INC., PUBLISHERS
NEW YORK, N.Y.
1955

Library of Congress Catalog Card Number: 52-13360

PRINTED IN THE UNITED STATES OF AMERICA

CONTRIBUTORS TO VOLUME III

RICHARD DOLL, *Statistical Research Unit, The Medical Research Council, London School of Hygiene and Tropical Medicine, London, England*

HAROLD P. MORRIS, *Laboratory of Biochemistry, National Cancer Institute, National Institutes of Health, Bethesda, Maryland*

A. PULLMAN, *Institut du Radium, Paris, France*

B. PULLMAN, *Institut du Radium, Paris, France*

P. RONDONI, *Cancer Institute, Milan, Italy*

MICHAEL B. SHIMKIN, *National Cancer Institute, National Institutes of Health, Bethesda, Maryland*

SIDNEY WEINHOUSE, *The Lankenau Hospital Research Institute and The Institute for Cancer Research, Philadelphia, Pennsylvania*

CONTENTS

Some Aspects of Carcinogenesis

Pulmonary Tumors in Experimental Animals

Oxidative Metabolism of Neoplastic Tissues

Etiology of Lung Cancer

RICHARD DOLL

Statistical Research Unit of the Medical Research Council, London School of Hygiene and Tropical Medicine, London, England

I. Introduction

1. Conclusions of Louvain Symposium

Knowledge of the causes of lung cancer was reviewed at an international symposium on the "Endemiology of Lung Cancer" held at Louvain in 1952 (Council for International Organizations of Medical Sciences, 1953). The members of the symposium were unable to decide what factors were responsible for the majority of cases, but important conclusions were reached on more limited problems. Firstly, it was agreed that "a significant part" of the increase in mortality which had been reported from many countries "is absolute and represents a real increase in the number of people suffering from primary cancer of the lung"; secondly, "that there is now evidence of an association between cigarette smoking and cancer of the lung, and that this association is in general proportional to the total consumption"; and thirdly, that "occupational hazards giving rise to lung carcinoma have been demonstrated in a number of industries, in particular, in the handling of asbestos and chromates, in gas-works, in a factory refining nickel and in certain mines bearing radio-active ores."

Other possible etiological factors were considered—in particular, atmospheric pollution by effluvia and smoke from factories and domestic chimneys and by exhaust fumes from petrol and diesel engines. The possibility that carcinogenic agents might be absorbed through ingestion or skin contact was reviewed, as was the possibility that individuals might vary in their susceptibility to the environmental influences to which they were exposed. No positive conclusions were reached with regard to these latter problems.

In the last two years, however, much new evidence has been obtained, and it is now possible to give a more complete picture of the etiology of the disease.

II. Increase in Incidence

1. Extent of Increase

The highest death rate from lung cancer is recorded in Britain, where, in 1953, it was 342 per million persons. For both sexes taken together, lung cancer was the commonest type of fatal cancer, accounting for 17% of all cancer deaths; it accounted for 5% of male deaths from all causes at all ages and, in the age group 45 to 64 years, for 10% of all male deaths. In other countries for which detailed statistics are available the rate varies from a seventh to approximately two-thirds the British rate (Table I).* The disparity between the rates is mainly due to a disparity between the rates for men; with the exception of England and Wales, Scotland, and Finland the female rates are similar, varying only between 34 and 47 per million women. Each of the countries listed has experienced an increase in the mortality attributed to lung cancer in the last half century, and the increase appears to be still continuing (Fig. 1).

* In Table I, the figures for England and Wales and for Scotland are shown separately. The Scottish rate for all persons has usually been lower than the English and Welsh rate, but in 1953 the rate was slightly higher—346 per million against 342 per million.

In England and Wales the rate of increase has slackened in the last five years, and the death rate among men under the age of 50 years is now steady. On the assumption that the rates at the younger ages remain steady and that the rates at the older ages continue to increase until the age distribution of deaths from lung cancer resembles that of other extragenital epithelial cancers, Mackenzie (personal communication) estimates that the male death rate may increase to approximately 1350 per million men, *i.e.*, to more than twice its present level of 602 per million, before it stabilizes. By a similar method, Clemmesen, Nielsen, and Jensen (1953)

TABLE I

Crude Death Rate from Lung Cancer in Various Countries

		Crude Death Rate per 1,000,000		
Country	Year	Men	Women	Persons
England and Wales	1951	530	91	303
Scotland	1951	470	104	279
Finland	1950	353	61	201
Holland	1951	271	45	158
Switzerland	1950	252	38	136
U.S.A.	1951	214	45	129
Denmark	1951	185	46	115
Australia	1951–52	173	37	106
Canada	1951	154	34	95
France	1950	161	47	87
Sweden	1951	111	43	77
Norway	1951	81	39	60
Iceland	1950	—	—	42

Rates have been shown for 1951, whenever possible, as data were available for the greatest number of countries around that year.

estimate that the death rate among men in Copenhagen may become even greater (*i.e.*, 2200 per million).

Much of the recorded increase is due to the advancing average age of the population. This factor can, however, be allowed for. In England and Wales, for example, the recorded death rate from lung cancer rose from 8 per million in 1900 to 342 per million in 1953; *i.e.*, 43 times. But if the sex and age-specific death rates of 1953 had occurred in a population with the sex and age distribution characteristic of the population at the beginning of the century, the total death rate would have been only 188 per million. The extent of the recorded increase after allowing for demographic changes is, therefore, 24 times, or little more than half the figure given by the comparison of the crude rates. Similar conclusions apply to the increases recorded in other countries.

How much of the increase "is absolute and represents a real increase in the number of people suffering from primary cancer of the lung" and how much is merely due to better diagnosis is uncertain. It is doubtful if the nature of the data concerned will ever permit a precise answer to be given. Rigdon and Kirchoff (1953) still maintain that the whole increase may be spurious, but in this opinion they are almost alone.

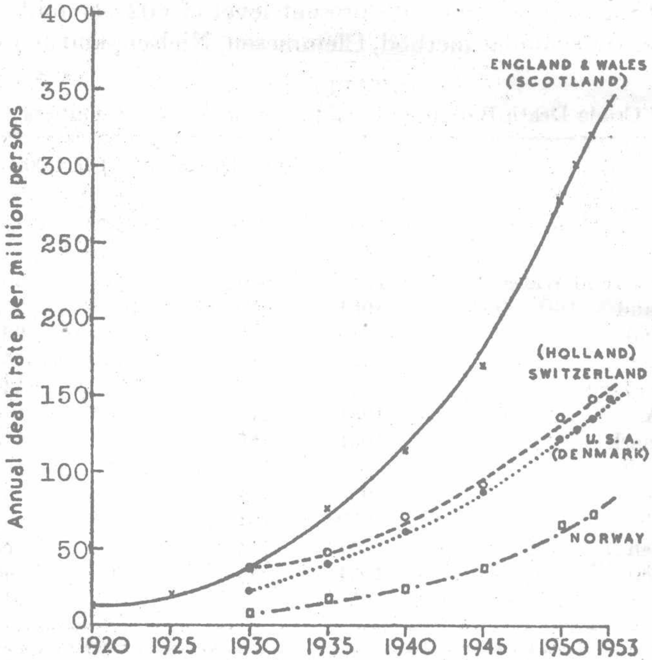

FIG. 1. Increase in crude death rate from lung cancer in various countries, 1920–1953. The trend of the death rate in those countries shown in parentheses has been similar to that in the countries against which they are placed.

Clemmesen, Nielsen, and Jensen (1953) in Denmark; Doll (1953a) and Stocks (1953a) in England; Kreyberg (1954b) in Norway; and Dorn (1954) in the United States have recently cited the reasons for believing that part of the increase is real. Three of the reasons are based on observations which are of special significance for the etiology of the disease. The observations are that the increase has fallen unevenly on:

1. The two sexes.
2. Different age groups.
3. Different histological types.

2. Changes in Sex Distribution

National mortality statistics and autopsy series both agree that the change in incidence of the disease has been accompanied by an increasing preponderance of male cases. Figure 2 shows how in different countries

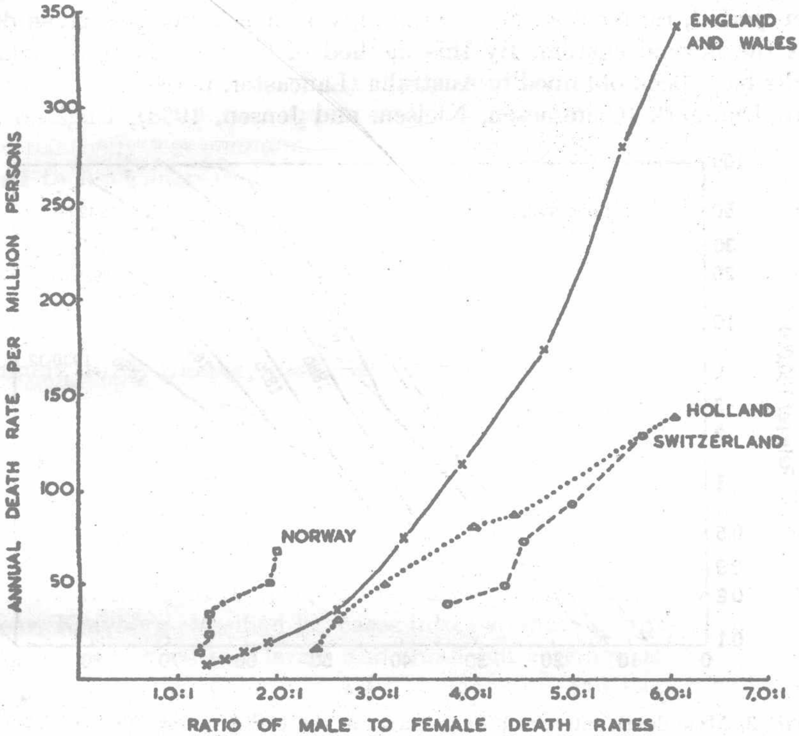

Fig. 2. Increase in ratio of male to female death rates with the increase in the crude lung cancer mortality in various countries.

the proportion of male to female deaths has become progressively greater as the total mortality has arisen. The reality and implication of this change are too well recognized to warrant further comment.

3. Changes in Age Distribution

It has long been noted that the age distribution of lung cancer in men differs from that in women and from that of other extragenital epithelial tumors, in that, in countries with a high incidence, the male mortality rises to a maximum comparatively early and falls off rapidly in the later age groups. The increase in mortality over the last 50 years did not affect all ages equally; at first the younger age groups were principally affected and the maximum mortality came to be between the ages of 60 and 64 years; recently the increase has been most marked in the older age groups and the age of maximum mortality has risen. Korteweg (1951) has pointed out that these trends can be understood if comparisons are made between the age-specific death rates of groups of men all of whom were born at a given period, rather than between groups of men living at a given date, as is the normal custom. By this method of "cohort analysis" similar results have been obtained in Australia (Lancaster, personal communication), Denmark (Clemmesen, Nielsen, and Jensen, 1953), England and

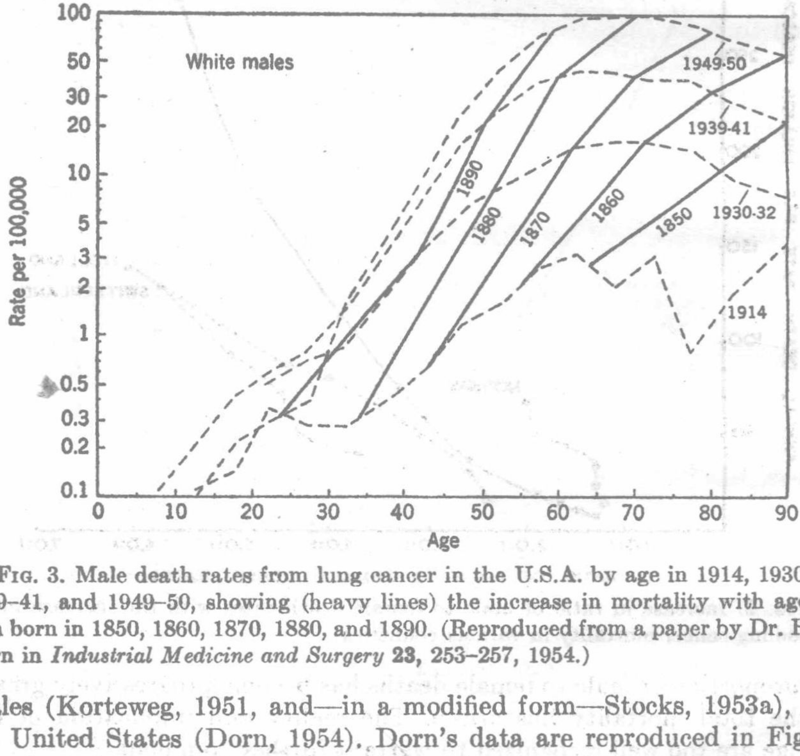

FIG. 3. Male death rates from lung cancer in the U.S.A. by age in 1914, 1930–32, 1939–41, and 1949–50, showing (heavy lines) the increase in mortality with age for men born in 1850, 1860, 1870, 1880, and 1890. (Reproduced from a paper by Dr. H. F. Dorn in *Industrial Medicine and Surgery* **23**, 253–257, 1954.)

Wales (Korteweg, 1951, and—in a modified form—Stocks, 1953a), and the United States (Dorn, 1954). Dorn's data are reproduced in Fig. 3. The dotted lines indicate the pattern of age-specific death rates when studied at different dates (1914, 1930–32, etc.); the solid lines indicate the pattern when men who were born at a given period (1850–59, 1860–69, etc.) are followed throughout their lifetime. It is seen that for each "cohort" the mortality increases continuously with age, but that the later "cohorts" have a progressively higher mortality at each age than the earlier ones. The changes in the shape of the customary age distribution curve for lung cancer can, therefore, be understood if it is postulated (1) that groups of men born at each period suffer a mortality which increases in a way similar to that observed for other forms of extragenital epithelial cancer and (2) that men born at successive periods were increasingly exposed to an environmental carcinogen. On the other hand, the observed changes cannot be explained, as Clemmesen (1954) has pointed out, if men of all age groups were equally exposed to a new agent at the same time.

4. Changes in Histological Distribution

With the increase in lung cancer the proportions recorded as belonging to the various histological types have altered; adenocarcinoma has become relatively less common, and its incidence must, therefore, be presumed to have increased less than that of other types. In conformity with this and with the comparatively small increase of lung cancer in women, the sex ratio for adenocarcinoma has remained close to equality, whereas that for other types has shown a marked male predominance. Moreover, adenocarcinoma was not observed among the industrial tumors from which the Schneeberg and Joachimstal miners suffered (Schmorl, 1928; Hueper, 1942; Šikl, 1950). For these and other reasons, Womack and Graham (1938, 1941), Lickint (1953), and Kreyberg (1954a,b,c,d) have concluded that lung cancer may be divided into two essentially different types—endogenous and exogenous in origin.

Kreyberg's papers are particularly important because the data have been collected in a country where the total lung cancer mortality is low and during a period when changes similar to those which took place in Britain and the United States 20 to 30 years ago are only beginning to appear. Kreyberg classified his cases into two main groups: group I consisting of squamous and large- and small-cell carcinomas, and group II of adenocarcinomas, bronchiolar cell carcinomas, and benign and malignant adenomas and salivary gland type tumors. The group I tumors were predominantly male (273 M to 31 F) and, when related to the size of the Norwegian population in 1950, showed an age distribution similar to that observed for all lung cancer in countries with a high incidence—save only that the characteristics of the distribution were more pronounced, *i.e.*, the "incidence" had an earlier peak (50 to 59 years) and fell off more sharply in the older age groups. The group II tumors were found almost equally often in each sex (81 M to 76 F) and showed an "incidence" which increased steadily with age in the case of adenocarcinoma and was approximately evenly distributed throughout the range of adult ages in the case of the adenomas and the salivary gland type tumors. When the cases were subdivided according to their date of occurrence, Kreyberg found that there had been no increase in the proportion of group I to group II cases among women over the whole period 1925 to 1953, despite the fact that the standardized mortality rate for women increased four and a half times. On the other hand, group I tumors became relatively much more frequent among men compared with group II tumors, while the standardized male mortality rate increased sevenfold. Despite the considerable difference in the total mortality experience of the two sexes, the sex ratio for the group II tumors remained close to equality.

It is easy to criticize Kreyberg's material on the grounds that it was heterogeneous in origin (part collected from clinical and part from autopsy series) and that the relative amounts collected in the different ways varied over the period studied. Moreover, it is likely that his cases provided a larger sample of those occurring in the younger age groups than in the older groups. Nevertheless, the characteristics of the histological types varied so markedly and the observations agree so well with the trend of the data obtained in other countries, that it would be unreasonable to dismiss the material because it falls short of perfection. Kreyberg interpreted his findings to mean that the group I tumors were largely the result of the introduction of some new carcinogenic agent into the environment, to which men were more exposed than women, whereas the adenocarcinomas "are probably caused by comparatively weak carcinogenic influences, evenly distributed over large areas, well established in the society and striking both sexes with equal force." The recorded increase in mortality in women in Norway may, he suggests, indicate the extent of the increase due to better diagnosis, and the total mortality in women (including a small proportion due to group I tumors) may, with present knowledge, be regarded as "unavoidable" cancer. In contrast, the increased mortality in men additional to that recorded in women and attributed solely to group I tumors can be regarded as "avoidable" cancer. It may well prove that these conclusions are of general significance and also apply to many countries other than the one in which the data were collected.

III. Etiological Factors

1. Tobacco

A. *Retrospective Inquiries.* When the Louvain symposium concluded "that there is now evidence of an association between cigarette smoking and cancer of the lung," it did so on the basis of evidence which was derived entirely from retrospective studies of patient's histories. In these studies the histories given by patients with lung cancer had been compared with the histories given by patients without lung cancer who, in one or other way, had been selected as "controls." Many studies of this general type have been reported, and the principal results obtained from them are summarized in Table II. All agree in showing that there are more heavy smokers and fewer nonsmokers among patients with lung cancer than among patients with other diseases. With one exception (the difference between the proportions of nonsmokers found by McConnell,

TABLE II

Principal Characteristics of Smoking Histories of Men with and without Lung Cancer, Reported by Various Authors

		Number of Men		Percentage of "Nonsmokers" among Men		Percentage of "Heavy Smokers" among Men	
Author	Date	With Lung Cancer	Without Lung Cancer	With Lung Cancer	Without Lung Cancer	With Lung Cancer	Without Lung Cancer
Müller	1939	86	86	3.5	16.3	65	36
Schairer and Schöniger	1943	93	270	3.2	15.9	52	27
Wassink	1948	134	100	4.5	19.0	55	19
Schrek *et al.*	1950	82	522	14.6	23.9	18	9
Mills and Porter	1950	444	430	7	31	—	—
Levin *et al.*	1950	236	481	15.3	21.7	—	—
Wynder and Graham	1950	605	780	1.3	14.6	51	19
McConnell *et al.*	1952	93	186	5.4	6.5	35	22
Doll and Hill	1952	1357	1357	0.5	4.5	25	13
Sadowsky *et al.*	1953	477	615	3.8	13.2	—	—
Wynder and Cornfield	1953	63	133	4.1	20.6	68	29
Koulumies	1953	812	300	0.6	18.0	66	31
Lickint	1953	224	1000	1.8	16.0	74	29
Breslow *et al.*	1954	518	518	3.7	10.8	74	42
Watson and Conte	1954	265	277	1.9	9.7	73	57
Gsell	1954	135	135	0.7	16.7	86	33
Randig	1954	415	381	1.2	5.8	34	18

Note. It has not been possible to make all the figures in this Table completely comparable. Some series include, for example, a few women; in others the proportions of heavy smokers are based on totals which are different from those used to calculate the proportion of nonsmokers. One series excludes adenocarcinoma. The individual papers should be referred to before any detailed use is made of the figures.

Gordon, and Jones), the differences are large enough to be important. More detailed results of two of the investigations are shown in Tables III and IV. From these it is seen (1) that there is a steady increase in the relative proportions of lung cancer to control patients as the amount smoked daily increases, and (2) that the difference in smoking habits between persons with and without the disease is more marked for men than for women.

TABLE III

Average Amount of Tobacco Smoked Daily: Lung Carcinoma Patients and Control Patients with Other Diseases*

Sex	Disease Group	No. of Patients	% Non-smokers†	% Smoking a Daily Average for 20 Years of: 1 g.–	10 g.–	16 g.–	21 g.–	35 g.+
M	Lung Carcinoma (squamous or undifferentiated)	605 (100.1%)	1.3	2.3	10.1	35.2	30.9	20.3
	Other Diseases‡	780 (99.8%)	14.6	11.5	19.0	35.6	11.5	7.6
F	Lung Carcinoma (squamous or undifferentiated)	25 (100.0%)	40.0	4.0	16.0	24.0	8.0	8.0
	Other Diseases‡	522 (100.1%)	79.6	9.2	6.9	3.2	0.6	0.6

* After Wynder and Graham, 1950.

† Nonsmokers defined as persons smoking an average of less than 1 cigarette a day (or its equivalent in pipe tobacco or cigars) over the previous 20 years.

‡ The age distributions of the control patients were different from those of the lung carcinoma patients; the percentages quoted were therefore obtained by weighting the age groups so as to make them have the same relative importance as they had in the group of 605 men with squamous cancer.

TABLE IV

Average Amount of Tobacco Smoked Daily: Lung Carcinoma Patients and Control Patients with Other Diseases*

Sex	Disease Group	No. of Patients	% Non-smokers†	% Smoking a Daily Average for 10 Years of: <5 g.	5 g.–	15 g.–	25 g.–	50 g.+
M	Lung Carcinoma	1357 (99.9%)	0.5	4.0	36.0	35.0	21.6	2.8
	Other Diseases‡	1357 (100.0%)	4.5	9.5	42.0	31.8	11.3	0.9
F	Lung Carcinoma	108 (100.0%)	37.0	14.8	22.2	13.0	13.0	0.0
	Other Diseases‡	108 (100.0%)	54.6	23.1	16.7	5.6	0.0	0.0

* After Doll and Hill, 1952.

† Nonsmokers defined as persons who had never consistently smoked as much as 1 g. of tobacco a day for as long as one year.

‡ Patients with other diseases matched to be within the same five-year age group and to be in hospitals of the same type and in the same region at approximately the same time as the lung carcinoma patients.

The conclusions to be drawn from these investigations depend on whether the comparisons between the smoking histories of the various groups of lung cancer and control patients are valid and on the extent to which the control patients were representative of the populations from which the lung cancer patients were drawn. In some of the earlier investigations there were reasons for doubting whether the comparisons were valid—for example, when the histories of the two groups of patients were recorded by different methods. Other investigations, in which the patients were interviewed by the same persons and by the same methods throughout and in which the control patients were chosen to "match" the lung cancer patients with regard to sex and age, the date of interview, and the hospital in which they were treated, were not open to objection on this score. Nevertheless, there was the possibility that bias of one or another sort could have entered into the selection of the patients or the recording of the results. The various types of bias which might have occurred were considered in detail by Doll and Hill (1950, 1952). They concluded that bias could not be responsible for their results and that the only logical explanation was that the observed association between the smoking of tobacco and the development of lung cancer was real.

Further important evidence has been obtained from the preliminary results of two "prospective" inquiries. These inquiries have been conducted on a different principle and are not subjected to the types of bias which might theoretically have occurred in the retrospective studies. Since they lead to the same conclusion, it is not now necessary to give further detailed consideration to the evidence from which it was deduced that the association shown by the retrospective studies was real.

B. *Prospective Inquiries.* In the prospective inquiries, the smoking habits of large numbers of "normal" persons have been recorded, and the subjects have subsequently been watched to see what diseases they developed. Preliminary results of studies of this type have been reported by Doll and Hill (1954a) and by Hammond and Horn (1954).

In Hammond and Horn's inquiry, a large number of people who volunteered to help the American Cancer Society were each asked to interview approximately 10 white men, aged between 50 and 69 years, to be chosen from among acquaintances with whom they expected to remain in contact for several years. The smoking histories obtained at the interview were recorded on a standard questionnaire. Subsequently, on the 1st of November each year, the interviewers filled in a follow-up form stating whether the men were alive or dead or had been lost sight of. The State Health Department was then asked to supply an abstract of the death certificate of each man reported to have died. When cancer was certified as the cause of death, an attempt was made to obtain further