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EPIDEMIOLOGY OF CANCER OF THE LUNG

Report of a Study Group

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STUDY GROUP
ON EPIDEMIOLOGY OF CANCER OF THE LUNG

Geneva, 16-20 November 1959

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EPIDEMIOLOGY OF CANCER OF THE LUNG

Report of a Study Group

1. INTRODUCTION

The Study Group on Epidemiology of Cancer of the Lung met in Geneva from 16 to 20 November 1959.

Dr P. Dorolle, Deputy Director-General of the World Health Organization, opened the meeting of the Study Group on behalf of the Director-General and mentioned that it had been convened in pursuance of recommendations made by several committees. Cancer of the lung has been the subject of epidemiological studies in a number of countries where a marked increase in death rates has been occurring, and some well-defined factors in habits and environment have been indicated as possible causes. As a consequence, the Sub-Committee on Cancer Registration of the WHO Expert Committee on Health Statistics recommended in its third report [1] that WHO should facilitate or advise on field studies of air pollution and tobacco smoking. In 1958, the Expert Committee on Environmental Sanitation, after considering the effects of air pollution on human health, recommended in its fifth report [2] that research in many selected places in the world should be directed to field epidemiological investigations of those diseases suspected as being causally related to air pollution, such diseases to include primary lung cancer. The Scientific Group on Cancer Research, reporting to the Director-General in March 1959 on the proposed cancer research activity of WHO, advised that problems of the epidemiology of cancer should have a central place in the programme and mentioned cancer of the lung specifically ; this recommendation was endorsed by the Advisory Council on Medical Research in October 1959.

The Study Group elected Dr Richard Doll Chairman, Professor L. M. Shabad Vice-Chairman, and Dr H. F. Dorn and Professor M. L. Levin to act jointly as Rapporteurs.

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[1] *Wld Hlth Org. techn. Rep. Ser.*, 1959, **164**, 39

[2] *Wld Hlth Org. techn. Rep. Ser.*, 1958, **157**, 11

2. GEOGRAPHICAL VARIATIONS IN MORTALITY FROM CANCER OF THE LUNG

Official statistics from a large number of countries in different parts of the world have for some years been showing a notable and steady increase in age-adjusted mortality from cancer of the lung. In some countries, e.g., England and Wales, the increase appears to have started at least 40 years ago; in others, such as Chile and Japan, it has been noted only during the last 10-15 years. Trends in morbidity data, where available, have been in close agreement with those shown by mortality statistics.

Although part of the increase must be ascribed to improved recognition of the disease, it is generally accepted that in many countries the greater part of the increase is real and reflects an increased risk of contracting the disease.

In none of the countries studied is there at present any indication that the increase in mortality from cancer of the lung will cease in the foreseeable future, although in some countries (e.g., Great Britain) where mortality from this disease has reached a particularly high level, there has been no increase among men under 50 years of age.

It is clear that lung cancer now represents a major health hazard in many countries. In others in which the mortality rates are still relatively low, there are indications that a pattern of increase is developing similar to that observed elsewhere.

3. REVIEW OF KNOWLEDGE REGARDING ETIOLOGICAL FACTORS

The Study Group then reviewed the present status of information and research regarding etiological factors concerned in the occurrence of lung cancer.

3.1 Cigarette smoking

The relation between cigarette smoking and lung cancer is the aspect of the problem that has probably received the greatest research attention during the past decade, and it has certainly excited the greatest interest and discussion. A number of official, voluntary and other scientific bodies [1] have reviewed the evidence bearing on this association. The Study Group

[1] These include: the Public Health Cancer Association (USA) (1954); the Ministry of Health of England and Wales (1954); the Study Group of the American Cancer Society, the American Heart Association, the National Cancer Institute and the National Heart Institute (USA) (1957); the Medical Research Council of Great Britain (1957); the Netherlands Ministry of Social Affairs and Public Health (1957); the State Medical Research Council of Sweden (1958); the American Public Health Association (1959).

unanimously agreed that there was no reason to modify the conclusions reached by these experts that the sum total of the evidence available today was most reasonably interpreted as indicating that cigarette smoking is a major causative factor in the increasing incidence of human carcinoma of the lung. Recognizing that this conclusion has not been accepted by all who have studied or written on the subject, the Study Group agreed that while some of the criticisms levelled did suggest avenues for further investigation, none could be considered as casting any serious doubt on the conclusions reached on the basis of the extensive studies already made.

3.2 Air pollution

In all countries where detailed studies of lung cancer have been undertaken, the incidence has been higher in urban than in rural areas. These data suggest that there is an important "urban" factor in the production of lung cancer. After allowing for any possible influence of smoking habits, there still remain some urban/rural differences not fully explained. Differing standards of diagnosis, different occupational exposures, and the effect of air pollution have been put forward as contributory factors. Much evidence has been presented to support the view that pollution of the atmosphere by smoke is one of the principal factors to be considered under this heading. Chemicals known to be carcinogenic in animals have been found in the air of towns in all parts of the world where samples have been analysed.

Among them, 3 : 4-benzpyrene and other polycyclic hydrocarbons have been thought by many to be particularly important. The incomplete combustion of coal appears to be the main source of these compounds in England, but smaller amounts come from the exhausts of internal combustion engines. There is evidence that pollution from coal combustion has diminished and is still diminishing in some countries and it is therefore suggested that variations in pollution between areas with differing lung cancer incidence should be examined before conditions have changed to an even greater extent.

Special attention was paid to the occurrence of lung cancer in non-smokers. Data from the Liverpool area of Great Britain showed an excess of cases in the urban as compared with rural districts within this group, but in studies carried out in other places there appeared to be very little difference between the two.

The mortality from lung cancer so far in non-smokers in a prospective study among doctors in Great Britain was in fact so low that it did not leave room for much effect of air pollution. This did not, however, exclude the possibility of some effect among smokers, and it was pointed out that atmospheric smoke might be retained more effectively in lungs already damaged by some inflammatory process.

A further observation was that animal experiments on atmospheric smokes had generally been carried out by eluting the carcinogenic materials first and applying them in solvents. The activity of a carcinogen such as benzpyrene may vary from one situation to another, and in this connexion it was pointed out that the benzpyrene in cigarette smoke would be contained in droplets which are somewhat hygroscopic and water miscible, whilst that in atmospheric pollution is lightly adsorbed on carbon particles of irregular shape.

The general conclusion was that air pollution could be a factor of some importance in the etiology of lung cancer, but that in many countries its role appeared to be smaller than that of cigarette smoking.

3.3 Specific industrial causes

A specific increased risk for lung cancer was first established in the late 19th century among miners of radioactive ores. Since then, it has also been established that there is an increased risk among workers in the refining of nickel, the manufacture of chromates and of asbestos, and the production of illuminating gas. Furthermore, there is evidence that an increased incidence of lung cancer may be associated with industrial exposure to inorganic arsenic, particularly in concentrations sufficient to produce arsenical dermatoses.

Observations have been made suggesting an industrial hazard from exposure to, or association with, iron dust or fumes, the manufacture of isopropyl oil, the manufacture of beryllium, the mining and smelting of copper ore, and exposure to printing ink. The evidence regarding these possible hazards can at present only be regarded as suggestive. However, it seems unlikely that all existing industrial risks have been discovered.

While the contribution of known or suspected specific occupational causes of lung cancer to the total incidence of lung cancer is quite small, more precise definition of the conditions under which such occupational factors cause cancer would seem likely to lead to important knowledge regarding the mechanism of carcinogenesis in man.

3.4 Other possible factors

Among other factors which have been suggested to account for the occurrence of lung cancer are :

(*a*) ionizing radiations from non-industrial sources ;

(*b*) previous chronic pulmonary disease, particularly if it results in metaplasia and scarring ;

(*c*) heredity.

Sources of ionizing radiations to which exposure may occur include the decay products of radium and thorium in the inhaled air, radioactive

isotopes dispersed in nuclear explosions, and radioactive potassium and carbon in the body. There is also a small background of radiation from cosmic rays, and possibly added exposure to diagnostic radiography and radiotherapy. At the moment there is insufficient evidence upon which to base any conclusions regarding the possible influence of any of these forms of radiation in producing lung cancer.

Certain observations appear to indicate an association between chronic bronchitis, mucosal changes in the bronchi, and carcinoma of the lung, but the interpretation of this evidence is uncertain. Retrospective studies have thus far failed to reveal a significant association between lung cancer and healed tuberculosis; follow-up studies have not been sufficiently extensive or prolonged to provide evidence on this point. What part, if any, previous respiratory infection plays in increasing the risk of lung cancer is therefore still in question.

There is at present no evidence to indicate what role heredity plays in determining individual susceptibility to lung cancer. Extensive studies of malignant tumours indicate that some genetic basis for susceptibility exists, but this does not invalidate the mass of evidence regarding the influence of environmental agents. Observations which are being collected on the incidence of lung cancer in identical and in fraternal twins will in time furnish valuable information on this point; if the incidence is found to be high among the twin partners of affected individuals, this might be due either to a similar heredity or to exposure to similar environments, but if the excess risk is small it will be clear that the role of heredity cannot be large. It may be noted in this connexion that the fact that identical twins show a greater similarity in their response to exposure to environmental agents (such as alcohol and tobacco) than do fraternal twins does not provide evidence that the apparent effects of such agents are also genetically determined.

Other possible factors which have as yet been given very little consideration are (*a*) air pollution in dwellings caused by domestic heating and home industry, and (*b*) substances which might affect the bronchi after absorption from the skin or digestive systems.

4. RECOMMENDATIONS

4.1 Geographical variations

In view of the wide geographical variations in mortality from lung cancer that exist in many parts of the world and of the fact that an increase in the mortality from lung cancer can now be observed in several countries where this disease has previously been infrequent, the Study Group believes that high priority should be given to epidemiological investigations designed to throw light on the reasons for these variations and more especially on

the reasons for the increase in incidence in countries where the mortality rate has previously been relatively low.[1] It will be particularly important to determine the extent to which already identified etiological factors may be responsible for an increase in lung cancer in the latter group of countries.

4.1.1 *Studies based on histological typing*

In some of the countries where a marked increase in the incidence of lung cancer has already taken place, it has been noted that the frequency of epidermoid and oat-cell carcinomas has increased much more rapidly than that of other histological types of lung tumour. Professor Kreyberg of Norway has proposed that the epidermoid and oat-cell carcinomas be grouped together under the heading of Group I tumours and that all other lung tumours be combined under the heading of Group II tumours. Studies already made indicate that the ratio of the number of Group I to Group II tumours may be a sensitive index of whether or not an increase in the incidence of lung cancer is occurring and of the existence of a difference in the incidence of environmentally caused lung cancer between two or more population groups.

Inasmuch as an International Centre for Lung Tumours has already been established by WHO in Oslo, Norway, under the direction of Professor Kreyberg,[2] the Study Group recommends that studies of the relative incidence of lung cancer based on the histological typing techniques developed by this Centre be undertaken in areas where the necessary diagnostic facilities are available. It is especially desirable that these studies be carried out in areas where health and vital statistics are not now available, as well as in areas where there is reason to believe that an increase in the incidence of lung cancer may be starting. The value of these studies will be greatly enhanced if data concerning known or suspected etiological factors are collected simultaneously with information on histological types.

The Study Group strongly emphasizes the importance of basing these histological studies upon as representative a sample as possible of lung cancer cases occurring in a defined population or area. One way of doing this is to attempt to obtain data on all new cases diagnosed during a specified period of time. The type of information to be collected concerning etiological factors should be clearly and precisely defined and should be obtained by trained persons who will be responsible for the collection of the data in each area.

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[1] For all the special studies recommended it is of great importance that information should be obtained, as far as possible, about the means of diagnosis used for the individual cases of cancer, so as to permit their classification according to the degree of diagnostic validity.

[2] WHO Expert Committee on Cancer—unpublished working document WHO/CANC/2 Rev. 1

4.1.2 *Special morbidity studies*

In some parts of the world where reliable vital statistics are not available, medical care and diagnostic facilities may be sufficiently developed to make possible the carrying out of special morbidity studies of lung cancer. The studies of the incidence of cancer among the Bantu in South Africa and among Negroes in Uganda and Mozambique are illustrative of this type of investigation. Such studies can be undertaken in areas where statistics concerning the size and distribution by age and sex of the population can be obtained from official statistics or by a special survey and where it is believed that most of the cases of cancer are diagnosed. Information concerning all newly diagnosed cases of cancer, as well as data concerning possible etiological factors, is obtained from physicians, pathologists, and hospitals serving the population studied. It is believed that this type of study can be carried out in other parts of Africa, in South America and in parts of Asia. This method of study has the advantage of providing incidence rates for cancer of each specific site as well as for all forms combined. Another important advantage is that information can be obtained concerning the incidence of cancer in populations as yet unaffected by modern industrial conditions. If the full benefit is to be derived from these studies, it is essential that they be carried out before the conditions of life of such populations change too greatly.

4.1.3 *Studies in countries with large differences in lung cancer incidence*

Even in countries where the increase in the incidence of lung cancer began many years ago, large differences in current incidence rates exist. This is true not only for countries with varying degrees of industrialization and differing habits of life but also for countries in which other factors appear to be similar. As an example, the situation in Finland and Norway may be cited. The death rate for cancer of the lung among males is about five times as great in Finland as in Norway, whereas among females the ratio between the two national rates is less than 2 : 1. Epidemiological studies of the factors that may account for the difference in mortality rates for lung cancer in these two countries would be very worth while. It is recommended that encouragement and support be given to the organization of such studies in Finland and Norway as well as in other countries where similar situations exist.

4.1.4 *Special mortality studies*

National vital statistics have proved of great value for the purpose of geographical comparison, but the Study Group was of the opinion that further useful information would be likely to be obtained if separate statistics could be provided for the larger cities and regions within individual countries. This might be of value for countries in which the standard of

death certification varies appreciably between the large towns and the rural areas.

4.2 Study of special factors

Except under very unusual circumstances, it is difficult, if not impossible, to conduct planned experiments on human beings to test hypotheses concerning the etiology of a disease, especially if this would endanger health or would be likely to require observations over many years. Hence it is desirable to identify and study intensively groups of people who for one reason or another are either excessively exposed or hardly exposed at all to a factor thought to influence the incidence of a specific disease.

4.2.1 *Populations with decreased exposure to a specific agent*

Ideally it would be desirable to study groups of persons not exposed to one etiological agent but definitely exposed to a second agent. The Seventh Day Adventists in the USA are an example of such a population. Their religion prohibits the use of alcohol and tobacco and also imposes certain dietary restrictions. A study of several thousand Seventh Day Adventists living in areas of California where air pollution is a major problem is now under way. Undoubtedly, similar groups exist in other parts of the world.

Two precautions should be kept in mind when planning studies of special population groups:

(*a*) for purposes of comparison, information concerning the incidence of lung cancer must be available for the general population of which the group is a part;

(*b*) the group should be large enough to yield a number of cases of lung cancer sufficient to determine whether the incidence in the group differs from that in the general population; a precise number for the minimum size of the group cannot be set, but even if the study is restricted to adult males over 35 or 40 years of age, the number required would be of the order of tens of thousands.

4.2.2 *Populations with increased exposure to a specific agent*

The study of such populations is especially useful when the individual members are heavily exposed to a widespread suspected etiological agent. Examples of these populations are workers exposed to the exhaust fumes of gasoline and diesel engines or to the distillation products of coal. A comparison of the incidence of lung cancer among such workers with that for the general population would assist in assessing the importance of the suspected agent as a cause of lung cancer.

In many countries the organization of studies would be facilitated if the primary site of cancer were noted in the records of social insurance and pension plans for industrial workers, since such records usually contain information concerning occupation.

4.3 Simultaneous study of multiple factors

Cancer of the lung is believed to be caused by multiple factors. Hence it is useful to study populations known or believed to be significantly exposed to several agents. In planning such studies and interpreting their results it is important to keep in mind that current cases of lung cancer are probably due to agents to which the affected persons were exposed as much as 20-40 years previously. Information must therefore be obtained concerning the time the individual members of the group were first exposed to the separate factors to be studied.

The principal factors so far identified that might be studied in this way are air pollution, use of tobacco (particularly cigarette smoking), and occupational hazards. The general outline of the study would include the collection of the following in many cities in different parts of the world :

(*a*) data on air pollution ;

(*b*) information concerning the history of the use of tobacco, of occupations, and of residence for persons with lung cancer and for a suitable control group ;

(*c*) mortality rates from lung cancer among residents in these cities ;

(*d*) histological data for the classification of the cases of lung cancer.

In choosing the cities to be included, the following points should be kept in mind :

(*a*) widely contrasting environments should be represented ;

(*b*) an agency with qualified personnel interested in co-operating in the study should exist ;

(*c*) reliable mortality statistics by age and sex for lung cancer must be available ;

(*d*) more than one city in each country or cultural area should be included ;

(*e*) consideration should be given to the past history of mobility of the population in each city.

It will be necessary to establish and reach agreement upon the methods of measuring the amount of air pollution, the substances to be identified, and the methods of detecting and measuring the amount of each pollutant. If agreement is reached on standard methods and techniques, the analysis of air pollution could be carried out in more than one laboratory.

The following points concerning the collection of histories of the cancer cases and of a control group should be kept in mind:

(*a*) the data to be collected should be clearly defined and collected by trained interviewers;

(*b*) histories should be collected from as large a proportion as possible of lung cancer patients. The ideal, but usually unattainable, goal is every newly diagnosed case among residents of the area;

(*c*) the validity of the interpretation of the results of the study will depend to a considerable extent upon the care with which the control group is selected. Unless a sample of the general population is used, it is desirable to have more than one control group.

Finally, a pilot project should be conducted in order to determine the feasibility of a large-scale study.

4.4 Genetic studies

Even though exogenous factors appear to be responsible for the increase in the incidence of lung cancer, genetic traits may determine, in part at least, the kind of person who will develop lung cancer when exposed to any given combination of exogenous factors. Some kinds of genetic study may also provide information concerning the role of environmental agents. An example of these is the study of twins, especially monozygotic twins.

Since monozygotic twins are genetically identical, they provide a source of data for the study of the effect of exogenous factors upon persons of a homogeneous heredity. Since the number of such twins in many countries is not large, international collaboration would be desirable.

One method of conducting a study would be to identify the first member of a pair of twins who develops cancer of the lung. Information concerning the exposure of this member and his co-twin to various suspected exogenous etiological factors would be collected and the co-twin would be kept under observation for some period of time. An analysis of the data for members of each pair would provide information on the effect of various exogenous factors on the development of lung cancer.

4.5 Experimental studies

As a rule, epidemiological studies of a disease such as lung cancer identify general factors that affect the incidence of the disease. The identification of the specific agent responsible for the effect of a general factor (for example, cigarette smoking or air pollution) must usually be made by laboratory and experimental studies. The Study Group recommends that such studies be encouraged. It wishes to emphasize the desirability of the

standardization of experimental and laboratory methods as well as the desirability of conducting experimental studies, whenever possible, under conditions that simulate the manner of exposure of a human population.

4.6 Prophylaxis

The Study Group recognized that its principal concern was to consider desirable avenues of research in the epidemiology of lung cancer, but it also wished to call attention to the fact that existing knowledge of the etiology of lung cancer is already sufficiently well established to justify prophylactic action aimed at reducing exposure to known etiological factors.