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Cohort studies: history of the method I. prospective cohort studies

Summary

The term "cohort study" was introduced by Frost in 1935 to describe a study that compared the disease experience of people born at different periods, in particular the sex and age specific incidence of tuberculosis and the method was extended to the study of non-communicable disease by Korteweg who used it 20 years later to analyse the epidemic of lung cancer in the Netherlands. Such studies are now best described as generation studies or generation cohort studies to distinguish them from the common type of study that is now carried out that consists in defining groups of individuals distinguished by some variable (such as place of residence, occupation, behaviour, or environmental exposure) and following them up to see if the incidence or mortality rates vary with the selected variable. This type of study is now one of the most important tools for epidemiological investigation. Initially called prospective studies, because the information characterising the individuals in the cohorts was recorded before the onset of disease, they are now preferably called cohort studies and distinguished as prospective cohort studies, if the information obtained relates to the subjects at the time the study is started and they are then followed, or retrospective cohort studies, if the information characterising the individuals was recorded sometime in the past (for example, the receipt of radiotherapy, or entry to a specific occupation).

Studies of either type have the great advantage that they avoid all the most important sources of bias that may affect case-control studies, but the disadvantage that because incidence rates and more specifically mortality rates are commonly low, large numbers of subjects have to be followed for several (if not many) years to obtain statistically significant results.

Several early prospective studies are described: Namely, those of 34000 male British doctors, 190000 male and female American citizens with different smoking habits, some 5000 middle aged residents of Framingham with different blood pressures, blood cholesterol levels, etc, and 13000 children born in the UK in one week in 1946 with different family backgrounds.

Key-Words: Cohort studies – Prospective studies – Early examples.

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Nothing biological is constant, certainly not language, and the meaning of cohort studies has evolved over time. In this chapter, I examine first the type of study that was originally called a cohort study and then, with the development of epidemiology, the evolution of the term to include a large and important section of all epidemiological work. In doing so, I describe in some detail a selection of the early studies of each of the main types that we now recognise and I conclude by giving examples of the modifications that have been introduced to make cohort studies more flexible and more fruitful. I do not, however, include any discussion of refinements in purely statistical techniques as applied to cohort studies; these are described in detail by Breslow and Day[1] in their monograph on statistical methods in cancer research.

Generation cohort studies

Tuberculosis

The first type of investigation to be called a cohort study was one in which the trends with age in the sex-specific incidence of tuberculosis were compared in groups of men and women born at different dates. Such groups were called cohorts by Frost, the leading American epidemiologist of the day, who used this term in a personal letter to Dr Sydenstricker in 1935. The letter was published in 1939 after Frost's death as a footnote to a paper entitled "The age selection of mortality from tuberculosis in successive decades" in which he had used the technique. In this paper, Frost[2] discussed the meaning to be attached to the fact that the age distribution of the mortality rate attributed to tuberculosis varied between 1880 and 1930, as is shown for males in Figure 1, reproduced from Frost's article. He noted that after the childhood peak at 0–4 years of age the mortality declined to a minimum at 5–9 years and then rose to a second peak that occurred progressively later with the passage of time, at 20–29 years in the data for 1880, at 30–39 years in the data for 1910, and at 50–59 years in the data for 1930. These changes, Frost thought, did not correspond to reasonably probable changes of like extent in the rate of exposure to infection and he preferred to think that the predominant factor in the movement along the age scale was a change in human resistance. He pointed out, however, that, if looked at from a different point of view, the change in the pattern of the age distribution might be more apparent than real. For, if the pattern is examined for men and women who were born at different dates, it is seen to be the same throughout. This is shown in Figure 2, again reproduced from Frost's[2] article, which shows that the second peak occurs at the same age (20–29 years) for each cohort irrespective of date of

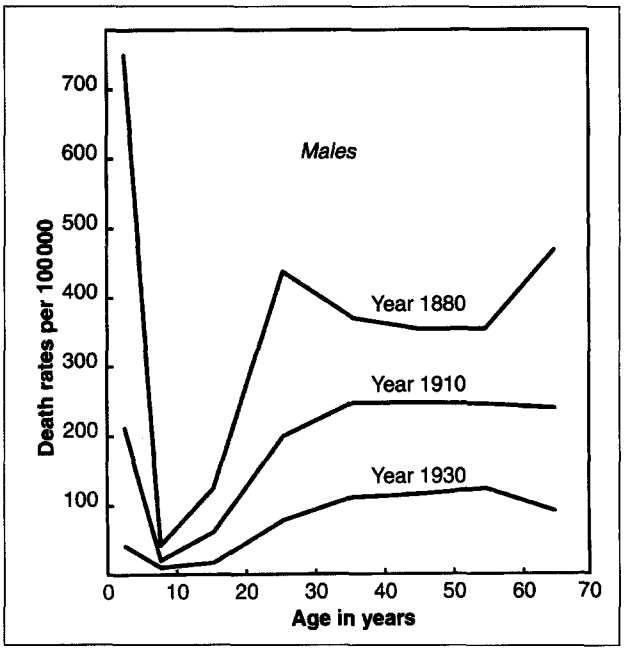

Figure 1 Age-specific mortality from tuberculosis among men in Massachusetts in 1880, 1910, and 1930[2]

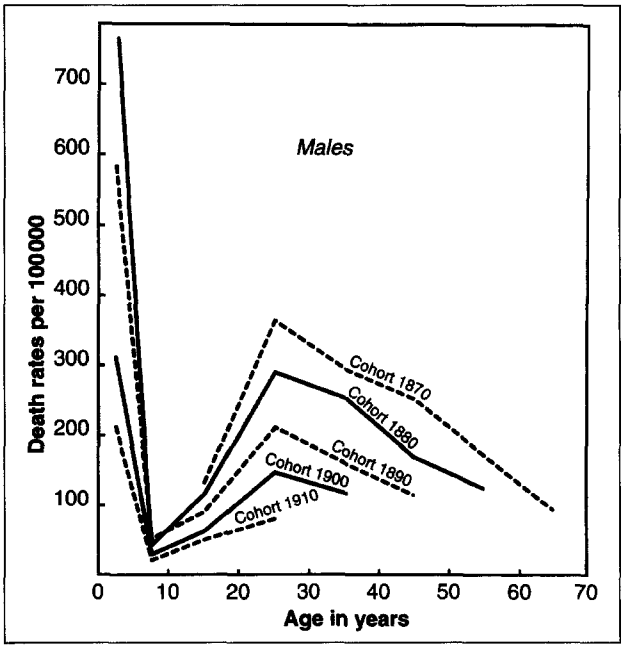

Figure 2 Age-specific mortality from tuberculosis among men in Massachusetts, plotted by year of birth[2]

birth. The progressive increase with the passage of time in the age at which the second peak occurs in cross-sectional data from different years can be interpreted as the result of the fact that the high rates in old age at the later dates are just the residuals of higher rates in earlier life.

This technique, described as a cohort analysis by Frost[2] and associated with his name, had, however, been used by

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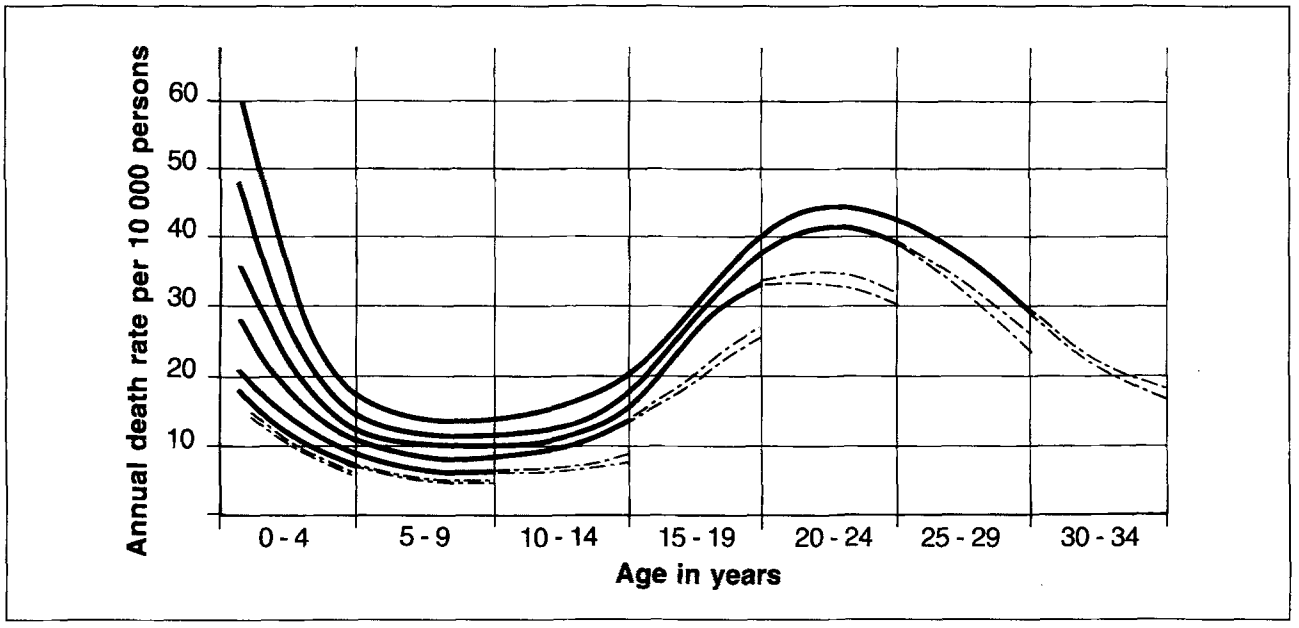


Figure 3 Age-specific mortality from tuberculosis among men in Norway between 1896–90 and 1926–27, plotted by year of birth[3]

Andvord[3] in Norway, nine years earlier and described as a study by "generations". Andvord had, in fact, analysed the mortality rates from tuberculosis in England and Wales, Denmark, Norway, and Sweden in exactly the same way as Frost had done with the rates for England and Wales and Massachusetts. His data for Norway from 1886–1900 to 1926–27 are shown in Figure 3. His conclusions, as expressed in the English summary to his article, bear repeating in full.

"By studying these tables and diagrams, we shall find it most conspicuous, that mortality of tuberculosis, shown within generations, has the distinct resemblance of undulatory motion, a wave, which during several decades of years has been upon its sinking phase nearly all over the civilized world. In England this fall in the tuberculosis death-rate in infancy commenced about the middle of the last century, while in Norway such a fall in the infancy death-rate is scarcely traceable till the eighties.

If we compare the diagrams of the countries in question, it is very conspicuous that they show a most prominent accordance in their main features. The fall is gradual and regular from one generation to the other, each new generation having evidently received greater powers of resistance than the preceding one to the tuberculosis virus. Each generation shows its own characteristic diagram, because the frequency of infection in infancy seems to indicate the mortality death-rate in later years of life, *a fall in mortality in infancy being invariably followed by a similar fall 20–25 years later among adults.*"

Consequently, as Frost[2] noted, Andvord was able to suggest that the analysis by generations formed a rational basis for extending estimates of future mortality at higher ages in the most recent cohorts.

Lung cancer

This technique of analysis by generation was not extended to the age specific incidence or mortality rates of non-infectious disease for some 20 years, until Korteweg[4] used it to examine the temporal changes in the mortality from lung cancer, without, however, realising that the method had been used previously in the study of tuberculosis. Korteweg had been struck by the difference between the pattern of the age-specific mortality rates for lung cancer in males and that for all other cancers in males considered as a group. The former had a maximum, in the data for England and Wales in 1945, at ages 55–64 years, while the latter showed a progressive increase up to 75 years and over. Was this decrease in the cancer death rate at a relatively early age something that was a characteristic of lung cancer, he asked, or was there some other explanation? Dormanns[5] he noted, had already suggested that the pattern might be an effect of the increase in lung cancer that had occurred over the previous 30 years, and Korteweg tested this hypothesis by comparing the mortality at each age with that at other ages in the group of persons born at about the same time; in other

words he examined the mortality in cohorts defined by date of birth. When he did this he found that the peculiar pattern of the age-specific mortality rates for lung cancer, shown for four different dates in Figure 4, disappeared and the pattern came to resemble that for the combined group of all other cancers. This is shown in Figure 5, in which, to facilitate comparison, he gave the age-specific rates as proportions of their sum. From this he concluded that the decline in the mortality from lung cancer in old age was a consequence of the extraordinary increase in the environmental factors that caused lung cancer, which showed their full effect first at young ages, and that the mortality in old age would go on increasing, even when it had stopped increasing in youth, until the pattern in any given year came to resemble that seen in Figure 5. This prediction was born out in the British data in the course of the next 30 years (Fig. 6) but Korteweg sadly did not live to see it.

In presenting this analysis, Korteweg attributed the increase in lung cancer to "irritating factors", and made no reference to cigarette smoke, which I know, from discussion with him, he believed to be the principal cause of the disease. The expression of his belief in the harmful effects of tobacco had, however, aroused so much antagonism in the Netherlands that he preferred not to mention tobacco in his article in the hope that his explanation of the pattern of the age-specific rates and its implication for the importance of an external "irritating factor" would be more readily accepted.

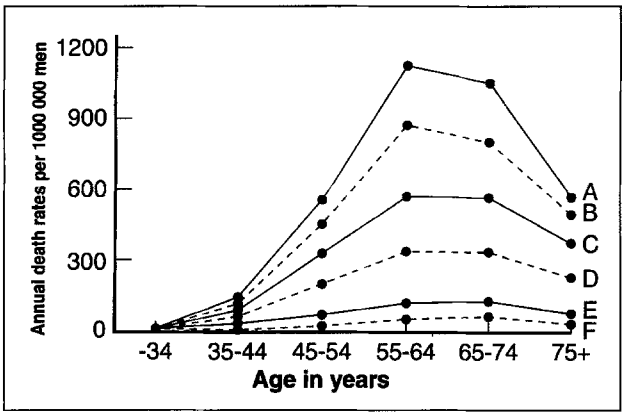


Figure 4 Age-specific mortality from lung cancer among men in England and Wales: A in 1945, B 1940–44, C 1936–39, D 1931–35, E 1921–30, F 1911–20[4]

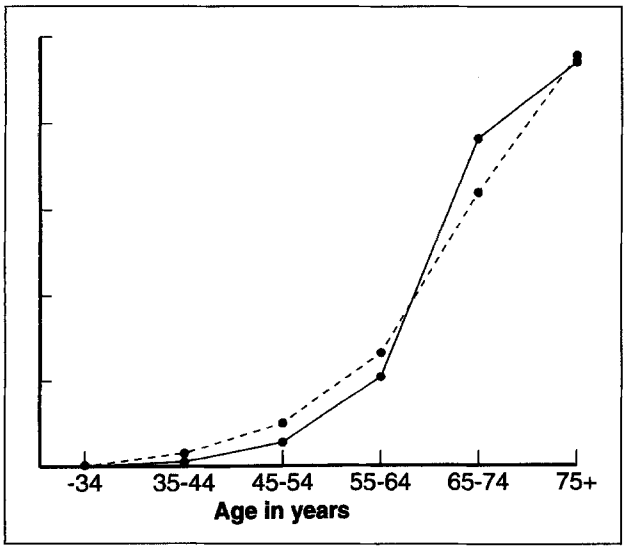


Figure 5 Age-specific mortality from lung cancer and from all other cancers among men in England and Wales in 1945, expressed as proportions of their sum: lung cancer —, all other cancers - - -[4]

Cohort studies: modern definition

Some 10 years after Korteweg's paper, the term cohort study began to be given the much wider meaning that it now has: namely, any study in which groups of people with defined characteristics are followed up to determine in incidence of, or mortality from, some specific disease, all causes of death, or some other outcome. The risk of these outcomes can then be compared either with some outside standard, such as the incidence or mortality recorded for all people of the same sex and same age distribution over the same period nationally or locally, or it can be compared internally between different sections of the cohort defined as having different characteristics. According to the Dictionary of Epidemiology, sponsored by the International Epidemiological Association and edited by Last[6] alternative terms for cohort study are follow-up, longitudinal, and prospective studies*. These according to Liddell[7] in his review of the development of cohort studies, embrace at least four classes, depending *inter alia*, on whether the members of the cohort are presumed healthy or diseased at the onset of the study, whether the difference between different sections of the cohort is determined by past events or by the investigator, the nature of the characteristic that determines membership of the cohort or of its sections, and the type of outcome in the follow-up period that is of interest. While this is logically defensible, it makes the definition of a cohort study undesirably wide and I shall exclude from consideration controlled trials and clinical studies of the progress of disease, both of which are included in Liddell's definition.

* The Dictionary says the term is synonymous with concurrent, incidence, follow-up, longitudinal, and prospective studies, but as I am not familiar with the term "concurrent study" and as the Dictionary goes on to say that alternative terms are the three cited, I have preferred to omit concurrent and incidence.

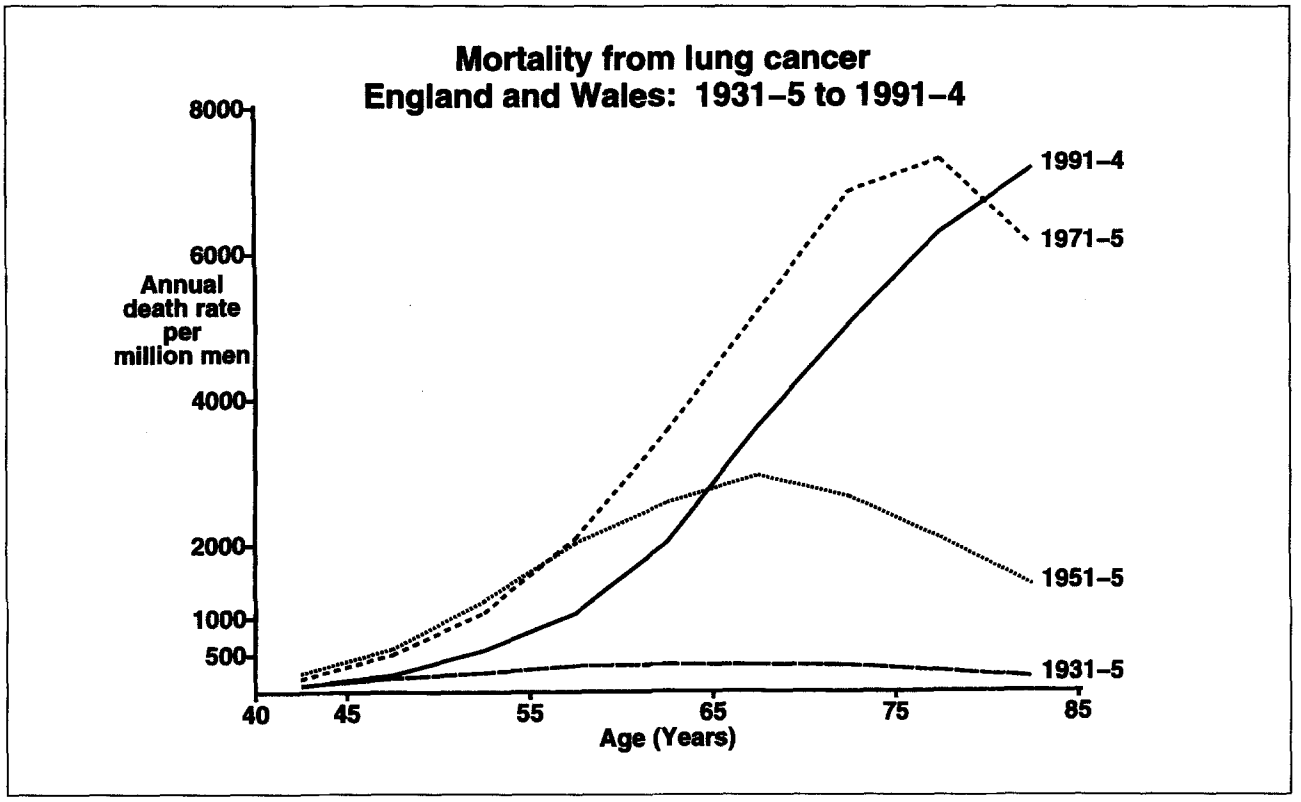


Figure 6 Age-specific mortality from lung cancer among men in England and Wales in 1931–5, 1951–5, 1971–5, and 1991–4

Cohort studies, even of the limited type that I shall consider, constitute one of the most important elements of modern epidemiology. The annual risk of death and the annual incidence of the most important diseases are both fortunately low and cohort studies consequently commonly require large numbers of people to be observed over long periods, so that they may be complex to organise and expensive to carry out. They have, however, one enormous advantage over case-control studies, in that they avoid several important sources of bias which may be introduced by the subjects when they know that a specific disease has occurred, by the investigator in questioning when he or she knows whether a subject is a case or a control, and unintentionally in the selection of the controls, because the subject's exposure to whatever is the factor of interest is recorded *before* the outcome is known and the controls are whole defined populations or contained within the cohort. There remains, of course, the possibility of diagnostic bias, if those responsible for diagnosing the outcome know the groups in which the affected individuals are placed; but this is seldom important, for diagnoses in cohort studies tend to the made in the ordinary course of medical practice independently of the investigators.

Prospective cohort studies

Studies which, in retrospect, may be called prospective cohort studies have probably been carried out since the beginning of the century, if not before. Liddell[7] cited as examples the studies of Farr[8] and Snow[9] that led to the discovery of the cause of cholera and those of Goldberger in the second and third decades of this century that led to the discovery of the cause of pellagra, but these seem to me to be more accurately described as case-control studies or surveys and included, in Goldberger's case, in preventative trials (see Terris[10]). This in no way detracts from their importance or the validity of the evidence that they obtained. Whatever they are called they remain outstanding examples of epidemiological research and have an established place in the history of preventive medicine. Weinberg's[11] study of the mortality of children born to tuberculous parents, which was cited by Frost[12] but which I have not been able to trace, may have been a prospective cohort study by the strictest modern definition. It was, however, almost certainly small and the large studies that we now usually envisage under this head

were not developed until after the Second World War, when they were initiated independently and more or less contemporaneously in the UK and the USA.

British doctors study

By a stroke of good fortune, I was associated with their development in the UK, through my association with Professor Bradford Hill, who had asked me, at the end of 1947, to assist in a case-control study aimed at finding out the cause of the great increase in the mortality attributed to lung cancer in England and Wales over the previous 30 years. This had led to the conduct of a case-control study which was published in 1950 in which we concluded that (*I quote*) "cigarette smoking is an important cause of carcinoma of the lung"[13]. This conclusion was accepted by Sir Harold Himsworth, Secretary of the Medical Research Council, but by very few other scientists at the time, who were unaccustomed to the idea that firm conclusions about causation could be drawn from case-control studies, and it was clear that if the conclusion was to be widely accepted the conclusions would have to be checked by some other method of enquiry. The obvious way, Bradford Hill suggested, was to obtain the smoking habits of a large number of individuals and to follow them forward to see if the prediction could be confirmed that the cigarette smokers among them would have a higher mortality from lung cancer than the non-smokers and that the heavy cigarette smokers would have a higher mortality than the light smokers. Bradford Hill suggested that doctors would make a suitable population to study as they might be more interested in responding to a questionnaire about smoking habits than most other people, that having had a scientific training they might be more accurate in the description of their smoking habits, and, most importantly, that they would be relatively easy to follow up, because of the need to keep their names on the Medical Register for legal reasons.

With the help of the British Medical Association we wrote to all the 60 000 doctors on the Medical Register at the end of October 1951 and resident in the UK and obtained replies to a single enquiry from 40000. We should certainly had have a higher response rate if we had written again to the non-responders (as we did to a sample 10 years later) but it took a year, with the little help that we had, to open all the letters and to get the responses coded on Hollerith punch cards. The questionnaire used was extremely simple and covered only one side of a piece of quarto paper. No more than seven questions were asked, the number depending on the subject's classification as a current smoker, ex-smoker, or lifelong non-smoker, something that has sometimes been attributed to Bradford Hill's teaching that questionnaires should not ask more than five questions. This was not, in fact, what Bradford Hill taught. What he did teach was that before including any question in a questionnaire the investigator should ask himself five questions about the necessity for including it.

Initially we relied for follow-up on the staff of the Office of the Registrar General of births and deaths (the national bureau of vital statistics) to provide copies of the death certificates of men and women whose occupations recorded on the certificate were given as medical practitioner or some equivalent term. For causes of death we accepted the underlying cause as described on the death certificate except when lung cancer was given as the underlying or contributory cause, when we sought detailed information about the basis on which the diagnosis was made from the doctor who signed the death certificate. We counted as lung cancer only those cases in which the diagnostic criteria were adequate and grouped all lung cancers together, irrespective of whether they were given as underlying or contributory causes. In the event, the great majority of cases were amply confirmed and we seldom found any reason to change the diagnosis*.

The data obtained in this way enabled us to publish a preliminary report of the results of the follow-up with less than three years' observations. In this paper[15] the numbers of deaths in the 34000 men with different smoking habits were simply related to the original numbers in each smoking category, standardised only for age. The rates so obtained for men aged 45–74 years were expressed as percentages of the rates for all men and compared with the comparable percentages estimated from the previous case-control study of patients with and without lung cancer in London. The results, which are summarised in Table 1 with the same terminology that we used in the 1954 paper, amply confirmed our prediction.

The study was described as "prospective" on the grounds that when the smoking habits were obtained we were looking forward for the occurrence of disease in the future[15], while the case-control study that we had previously carried out was called retrospective because the occurrence of disease was known and we sought information about smoking habits that had occurred in the past. Such studies continued to be called respectively prospective and retrospective until Brian MacMahon in the USA suggested characterising them as cohort and case-control studies[16], on the grounds that studies very similar to our prospective

* Of 222 cases described as lung cancer on death certificates in our 10 year follow-up data[14], the diagnosis of only 10 (4.5%) proved unacceptable, the change of diagnosis being made by a chest physician who served as a consultant and was kept in ignorance of the individual's smoking habits.

Study	Rate as per cent of that in all men			
	Nonsmokers	Smokers of:		
		1–14 g/day	15–24 g/day	25+ g/day
"Backward" study of patients' histories	6%	79%	112%	203%
"Forward" study of mortality of doctors	0%	68%	133%	199%

Table 1 Standardised death rates from lung cancer of men aged 45–74 years in relation to the most recent amount of tobacco smoked[13,15]

study could be carried out by determining the cohort from records of past exposure and following the subjects to the present day, thus allowing cohort studies to be either prospective (like the doctors smoking study) or retrospective like the occupational studies to be described shortly. Lilienfeld proposed the alternative of prospective and historical cohort studies, but this lost the simple contrast and did not catch on and MacMahon's terminology has come to be most used.

Two years after publishing the preliminary results of our prospective cohort study of British doctors, Bradford Hill and I published the results of following them for five years[17] by which time the prediction regarding the risks of lung cancer was confirmed beyond reasonable doubt and four other causes of death were also seen to be related to smoking: namely, coronary thrombosis (or as I should now prefer to say, myocardial infarction), chronic bronchitis (or chronic obstructive lung disease), peptic ulcer, and pulmonary tuberculosis. For this report we calculated what would now be called the man-years at risks in each smoking group by the relatively simple method of counting the numbers of men living in each five year age group at the beginning of each year of the study, taking the average for each year, and summing over the whole period for all ages. Standardised mortality rates were then calculated by the direct method for each category of smokers, using the total number of man-years at risk in each age group as the standard population. The discovery that, with increasing numbers, some other causes of death were also found to be related to smoking, suggested that it would be worth continuing the study for longer, until many more deaths had been observed and more causes could be studied separately. It has, consequently, been continued, by now for over 40 years, with information about changes in smoking habits being obtained on five intermediate occasions.

By 1956, however, it had become clear that reliance on reports of death from the Registrar General was inadequate, as not all doctors were so described on their death certificates and we had sought additional information about deaths from the General Medical Council, which kept a register of qualified doctors for legal purposes, and from the British Medical Association. We did not, however, at that time seek to check that all those not known to be dead were still alive and it was only later that we took to writing to individuals, partly to obtain information about changes in smoking habits and partly to discover unreported deaths. Doctors, as Bradford Hill thought would be the case, have been easy to trace and after 20 years only 101 out of the original 34440 men (0.3%) were unaccounted for. At that time 2459 were known to be living abroad, 102 asked not to be followed further – one saying he was fed up with being our guinea pig – and 15 had been struck off the medical register for unprofessional conduct. Continued follow-up for a further 20 years of the other 21688 known to be alive and resident in the UK resulted in a loss of only another 118 (0.5%). The results after 40 years were reported in 1994[18]. Thirty causes of death were by then found to be positively related to smoking, but the most interesting finding was perhaps the difference in survival of different categories of smokers, which could now be analysed from 35 years of age to over 100. 50% of heavy cigarette smokers (of 25 or more cigarettes a day) had died in middle age – which we may now optimistically define as from 35 to 70 years of age – against 20% of non-smokers and only 8% survived to 85 years of age against 33% of non-smokers (Fig. 7). Men who gave up under 35 years of age, who, in this population, had smoked for an average of only 10 years had an expectation

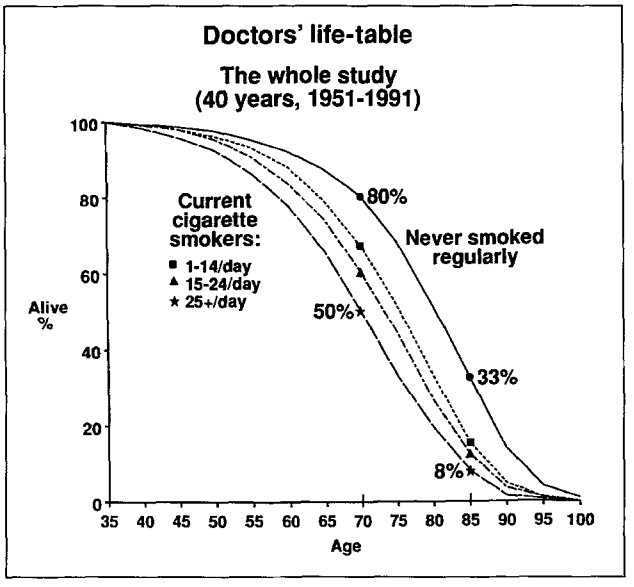


Figure 7 Survival of British doctors from age 35 years by smoking habits: lifelong nonsmokers —, cigarette smokers, smoking 1–14 cigarettes a day ·····, smoking 15–24 cigarettes a day – · –, 25 or more cigarettes a day – – –[18] (Reproduced with permission of the BMJ Publishing Group)

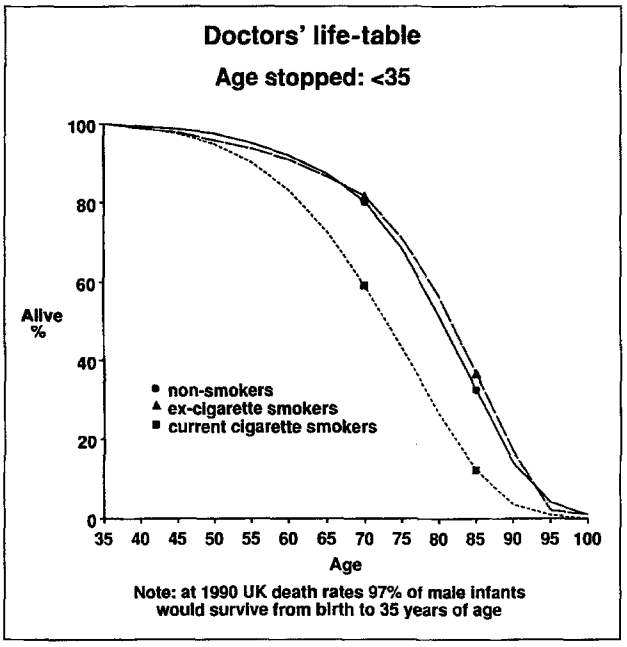


Figure 8 Suvival of British doctors from age 35 yrs by smoking habits: lifelong nonsmokers —, cigarette smokers stopped under 35 yrs of age –▲–, continuing cigarette smokers ··■··[18] (Reproduced with permission of the BMJ Publishing Group)

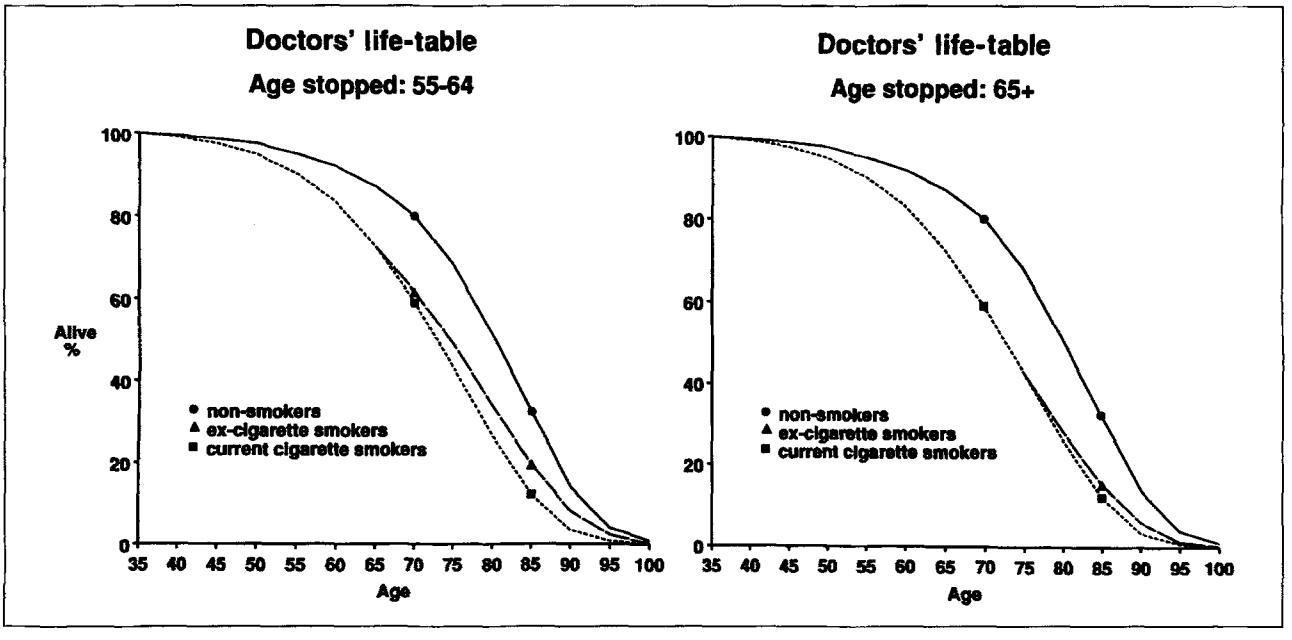
Figure 9 Survival of British doctors from age 35 yrs by smoking habit: lifelong cigarette smokers —, cigarette smokers stopped 65–74 yrs of age –▲–, continuing cigarette smokers ··■··[18] (Reproduced with permission of the BMJ Publishing Group)

of life that was indistinguishable from that of non-smokers (Fig. 8) but even those who stopped at 65–74 years of age (mean 71 years) had age-specific mortality rates beyond 75 years that were appreciably lower than those who continued (Fig. 9) and the rates would certainly have been lower still if it had been possible to exclude those who stopped specifically because of smoking-induced ill-health.

American Cancer Society study

In the USA a very similar study was begun independently a few months after the British doctors' study by Hammond and Horn[19] on behalf of the American Cancer Society. It was initiated, so Hammond told me, with the express purpose of disproving a causal relationship between cigarette smoking and lung cancer, which had been suggested not only by the case-control study in Britain to which I have referred, but also by the association recorded in several case-control studies in Germany and the USA, most notably in that reported by Wynder and Graham[20].

With the help of volunteer supporters of the American Cancer Society, Hammond and Horn obtained smoking habits for nearly 190000 men aged between 50 and 69 years who were friends of the volunteers and follow-up data were obtained approximately biennially by the same volunteers. Causes of death were obtained from death certificates and the diagnosis of cancer was checked by information obtained from personal doctors, hospitals, and tumor registries. A preliminary report in 1954 *confirmed* the predicted association with lung cancer and showed an association between smoking and coronary thrombosis, which was less



close but potentially more important because of the large numbers of cases[19]. Four years later, after a mean follow-up period of 44 months, a major report was published which gave death rates for each of the four five year age groups studied and the ratio between the number of deaths observed and the number expected from the rate in non-smokers for 32 diseases or groups of diseases[19]. Altogether nearly 12000 deaths were observed and it was possible to compare the ratios of the numbers of deaths observed from many different causes and the numbers expected from the experience of the non-smokers, for cigarette smokers smoking different amounts, for pipe smokers and cigar smokers, and for men who had stopped smoking for different periods. Excess mortality ratios for cigarette smokers were observed for 14 causes of death or groups of causes, with particularly high ratios for lung cancer (10.4 to one) and cancers of the upper respiratory and digestive tracts (5.1 to one). In total, the mortality among cigarette smokers was increased by 57% and over half of this was attributable to the excess of deaths from coronary heart disease, despite the mortality ratio being only 1.7, because the disease was relatively so much more common as a cause o death than any other.

This study was remarkable for two reasons. First, because it was so large; the cohort of nearly 190000 being by far the largest of its type until it was overshadowed by the American Cancer Society's study of a million men and women in the 1960s[20]. Secondly, because of the care that was taken to check the diagnoses of the 2350 neoplasms referred to on death certificates, information being obtained about 95% (2242). Only six of the diagnoses of a neoplasm were found to be incorrect and 79% of the cancers said to have caused death were microscopically proven.

Framingham study

Two studies had, however, antedated both these in their inception, although the results of one were not published until later and the other was envisaged only with immediate short-term aims. The cardiovascular risk disease study that was begun by Dawber and his colleagues in 1949[21] was different in character from the two smoking studies, as the cohort was much smaller, but instead of the individual members being asked just to complete a questionnaire they were also subjected to a detailed clinical examination, gave blood samples, and had an electrocardiogram. Moreover, it was planned that surviving members would be re-examined every two years. Originally the cohort was intended to be a random sample of all residents of the town aged 30–59 years, but the response rate of 69% was thought to be too low to provide a big enough cohort and 740 volunteers were added to it. On first examination, 81 subjects were found to have evidence of coronary heart disease and the cohort eventually consisted of 5128 subjects without evidence of coronary heart disease, of whom a little over half (55%) were women. Apart from the standard demographic details the information obtained from each respondent included serum cholesterol and several other blood lipid indices, blood pressure, weight expressed as a percentage of the norm for sex and height, electrocardiographic findings, respiratory efficiency, and smoking habits.

After eight years, 85% attended for the fifth round of examinations, 11% failed to attend but were known to be alive, 4% had died and only 19 (0.4%) were lost to follow-up[22]. During the previous eight years, 245 were found to have developed indications of coronary heart disease. The risk had been greater in men than in women, had increased in each sex with age, blood cholesterol, systolic (and diastolic) pressure, the presence of left ventricular hypertrophy, cigarette smoking, and decreasing respiratory capacity. Several of these factors, moreover, acted synergistically and the risk among men aged 30–59 years at entry was found to have increased progressively with the number of the leading predictive factors (namely, serum cholesterol 245 mg per 100 ml or more, blood pressure more than 165/95, and smoking 20 or more cigarettes a day). When all three were present the risk became 12 times greater than when none was present (Fig. 10). Adiposity, however, had little or no effect when the leading factors were taken into account, unless it was gross (that is, 30% or more above the median).

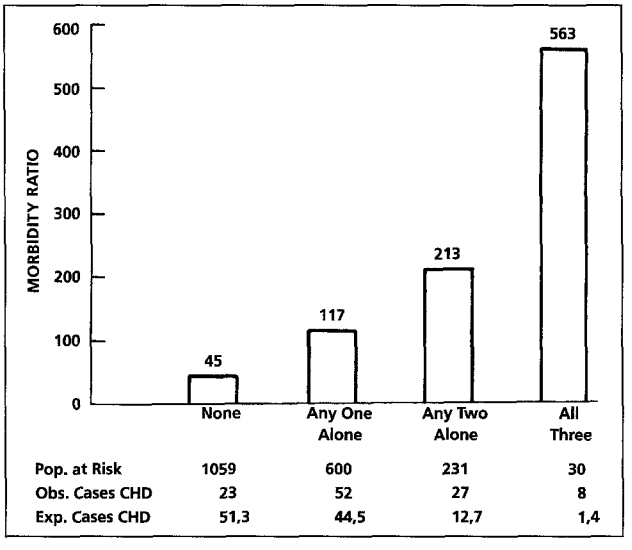


Figure 10 Incidence of coronary heart disease in men aged 35–59 yrs followed for eight yrs, standardized for age, by number of risk factors present (serum cholesterol 245 mg per 100 ml or more, blood pressure higher than 165 systolic 95 diastolic, smoking 20 or more cigarettes a day)[22]

This study, like the study of British doctors, was continued for many years and reached much the same conclusions about the effects of smoking. After 34 years' follow-up, the investigators emphasised, in particular, the great effect of smoking on the risk of cardiovascular disease. Major innovations, they wrote, have occurred over the past decade in the treatment and prevention of cardiovascular disease. "However", they added, "none of these advances offer as much benefit as avoiding or quitting smoking. Because of its powerful independent effect, its continued prevalence in over one fourth of the [US adult] population, and the ability to eliminate it as a risk factor, cigarette smoking deserves the highest priority among preventive compaigns against cardiovascular disease"[23].

The continuation of the study for so long and the repeated clinical examinations enabled it also to make some unique contributions to medical knowledge. Thirty years of follow-up enabled it to differentiate the association between cholesterol levels at different ages. Under 50 years of age on first examination, increasing levels were associated with increasing mortality without any evidence of a threshold. At older ages, however, the relationship was confounded by an association of decreasing levels with increased mortality due, at least in part, to an effect of the presence of disease predisposing to death[24]. More important, perhaps, are the observations on the extent to which physiological features of the individual, such as blood cholesterol and blood pressure, persist over time. These have recently been examined by Clarke et al.[25] and show much less stability than, I suspect, has previously been assumed.

The 1946 birth cohort

The other early post-war study was begun in 1946 as a simple cross-sectional survey to provide answers to questions about the availability, use, and effectiveness of the maternity services in Great Britain, specifically to find possible reasons for the apparent decline in fertility rates[26]. It was conceived by James Douglas, a physician with a special interest in social medicine and public health, who sought to find out what might be discouraging families from having children. It aimed to involve all the women who gave birth in one week in March 1946 and actually recruited 13687, 91% of the total. The post-war baby boom quickly made questions about fertility less urgent, but the information resulting from the maternity survey was of acute interest to the National Health Service, which was to begin in July 1948, and it was realised that the families could provide the basis for a cohort study to assess the impact of family and social conditions on subsequent personal development, behaviour, and children's health. A random sample of over 5000 children was consequently drawn, stratified so as to increase the proportions born to agricultural and non-manual workers, and the members have been followed ever since, with periodic personal visits, interviews, questionnaires, medical examinations, school reports, and psychological tests. From 1969, special enquiries have also been made about the cohort members' own children at four years of age and reading tests have been applied to them at eight years of age.

The early results mostly concerned the impact of family relationships and educational facilities on personal development and behaviour[27]. Parental level of interest, for example, was found to be even more important in determining children's reading ability than social background. Subsequently, interest began to focus on factors related to social background. Subsequently, interest began to focus on factors related to disease incidence, such as the relationship between early chest illnesses, local smoke pollution, and overcrowding in the home and the occurrence of chronic cough in young adult life[28]. Now, a fifty-one year follow-up is planned for 1997 when special attention will be paid to the links between low birth weight, poor early social environment, and the development of hypertension and other diseases of middle-age to test Barker's hypothesis that fetal nutrition affects the risk of cardiovascular and some other diseases in adult life[29,30].

The numbers of children in the study were too small to answer many questions that such a study could potentially answer. It demonstrated, however, that collaboration could be maintained effectively over many years and this encouraged the conduct of similar studies on a larger scale and all children born in one week in 1958[31] and in one week in 1970[32] are also now being followed.

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Zusammenfassung

Kohortenstudien, Geschichte der Methode

I. Prospektive Kohortenstudien

Der Begriff „Kohortenstudie" wurde 1935 von Frost eingeführt, um eine Studie zu beschreiben, die das Auftreten von Krankheiten – insbesondere die geschlechts- und altersspezifische Inzidenz von Tuberkulose – bei Personen verglich, die in verschiedenen Perioden geboren waren. Korteweg erweiterte die Methode zum Studium nicht-übertragbarer Krankheiten und setzte sie 20 Jahre später ein, um die Lungenkrebsepidemie in den Niederlanden zu untersuchen. Solche Studien werden am besten als Generationen oder Generationen-Kohorten-Studien bezeichnet, um sie von den heute üblicherweise durchgeführten Studien zu unterscheiden. Diese definieren Gruppen von Individuen, welche sich in einigen Merkmalen unterscheiden (zum Beispiel Wohnort, Beruf, Verhalten oder Umweltexposition) und die weiterverfolgt werden, um zu sehen, ob die Inzidenz- oder Mortalitätsraten in Abhängigkeit der gewählten Variablen variieren. Dieser Studientyp ist heute eine der wichtigsten epidemiologischen Forschungsmethoden. Anfangs wurden diese Studien als prospektive Studien bezeichnet, da die Information, welche die Individuen in den Kohorten charakterisiert, vor Eintritt der Krankheit erfasst wurde. Heute werden sie bevorzugt Kohortenstudien genannt und man unterscheidet zwischen prospektiven und retrospektiven Kohortenstudien. Bei prospektiven Kohortenstudien wird die Individuen betreffende Information zum Zeitpunkt des Studienbeginns erhoben und dann weiterverfolgt. Bei retrospektiven Kohortenstudien hingegen wurde die Individuen charakterisierende Information irgendwann in der Vergangenheit erfasst (z.B. eine frühere Strahlentherapie oder der Eintritt in einen spezifischen Beruf).

Diese verschiedenen Studienarten haben alle den grossen Vorteil, dass sie die wichtigsten Ursachen für Bias vermeiden, die Fall-Kontroll-Studien beeinflussen könnten. Von Nachteil ist allerdings, dass aufgrund eher geringer Inzidenzraten, aber insbesondere geringer Mortalitätsraten, sehr viele Personen für einige (wenn nicht sogar viele) Jahre beobachtet werden müssen, um statisch signifikante Resultate zu erzielen.

Einige frühe prospektive Studien werden beschrieben, im Einzelnen jene von 34000 Britischen Ärzten, 190000 Amerikanischen Bürgern und Bürgerinnen mit verschiedenen Rauchgewohnheiten, etwa 5000 Bewohnern mittleren Alters aus Framingham mit unterschiedlichen Blutdruckwerten, Blutcholesterinspiegeln etc. und 13000 Kindern mit unterschiedlichem familiären Hintergrund, die alle während einer Woche im Jahr 1946 in Grossbritannien geboren wurden.

Résumé

Etude de cohorte, histoire de la methode:

I. Etude cohorte prospective

Le terme „étude de cohorte" a été introduit par Frost en 1935 pour décrire une étude qui comparait la survenue de la maladie chez les individus nés à des périodes différentes. Il s'agissait en particulier de l'incidence de la tuberculose, spécifique pour le sexe et l'âge. La méthode a été étendue à l'étude des maladies non transmissibles par Korteweg qui l'utilisa 20 ans plus tard pour analyser l'épidémie de cancer du poumon aux Pays-Bas. Ce type d'études est à présent mieux caractérisé par les termes d'études de génération ou d'études de cohortes générationnelles. Cette dénomination les distingue du type d'étude plus communément réalisé actuellement, dans lesquelles on définit des groupes d'individus qui se distinguent par une variable donnée (tels que le lieu de résidence, la profession, un comportement ou une exposition environnementale), que l'on suit dans le temps afin de voir si leurs taux d'incidence ou de mortalité varient. Ce type d'études, devenu un des outils les plus importants de la recherche épidémiologique, a été initialement dénommé étude prospective, parce que l'information caractérisant les individus dans les cohortes était mesurée avant l'apparition de la maladie. A présent, elles sont préférablement appelées études de cohorte et classées en études de cohorte prospectives si l'information a été obtenue des sujets au moment où l'étude débute, suite à quoi ces individus sont suivis dans le temps, ou études de cohorte rétrospectives, si l'information caractérisant les individus a été mesurée dans le passé (par exemple, la prescription de radiothérapie, ou le début d'une activité professionnelle).

Ces deux types d'études ont le grand avantage d'éviter les sources les plus importantes de biais qui peuvent affecter les études cas-témoins, mais elles ont aussi le désavantage de requérir un grand nombre d'individus à suivre pendant plusieurs (si ce n'est de très nombreuses) années pour obtenir des résultats statistiquement significatifs, étant donné que les taux d'incidence, et plus spécifiquement les taux de mortalité, sont en général bas.

Plusieurs des premières études prospectives sont décrites: en particulier celles des 34000 médecins britanniques, des 190000 citoyens et citoyennes américains ayant différentes habitudes tabagiques, des quelques 5000 résidents d'âge moyen de Framingham ayant différentes pressions artérielles, taux de cholestérol plasmatiques, etc. et des 13000 enfants nés en Grande-Bretagne au cours d'une semaine de 1946 ayant différentes origines familiales.

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