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Cohort studies: history of the method II. Retrospective cohort studies

This article is the concluding part of an article on the history of cohort studies, the first part of which was published in SPM 2001; 46 (2): 75–86. The first part described early studies and dealt in detail with the development of studies in which relevant information about the members of the cohort is obtained directly from the members by the investigators, who then follow them forward to determine the frequency of the outcomes in which they are interested: that is, so called prospective cohort studies. This second part describes the development of retrospective cohort studies, in which the relevant information about the cohort members is obtained from the past records, as are some and perhaps all of the outcomes of interest.

Key-Words: Cohort studies – History.

Spread of tuberculosis in families

Retrospective cohort studies have almost as long a history as the prospective studies, for one was described by Frost in 1933[1], based on the black population of a small town in Tennessee. Interviews identified 556 persons living in 132 families, practically all of whom were examined clinically and radiographically, and 238 ex-members of the families, who were alive but had left the village or had died since the head of the household came into that position. From the information thus obtained, nearly 10000 person-years under observation were assembled and divided in five year age groups (though not apparently separately by sex) counting each person who entered the household in any given year or left in a given year as being under observation for half a year. Annual age-specific death rates from all causes and from tuberculosis were then compared with those for the black population of Tennessee and found to be closely similar, except at ages 20 to 49 years when the rates in the population under study were somewhat lower. The population was then divided according to whether there was a history of family contact with pulmonary tuberculosis and the annual attack rates of tuberculosis in the two groups were compared. In the presence of family contact the attack rate, standardised for age, was found to be about double that in the absence of such contact (12.9 per 1000 against 6.8 per 1000). Remarkably for that period, the attack rates were qualified by their standard deviations (respectively 1.7 and 0.64 per 1000).

Frost described this study not so much to provide evidence of the importance of family contacts in the spread of tuberculosis, for he realised that the number of persons involved was small, but as an illustration of the way records of past events could be used for the study of public health. The study is particularly notable for the clear description of the way person-years at risk can be calculated and for its success

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in gaining the co-operation of almost an entire population, for only three out of 135 known families were unwilling to be examined and consequently omitted from the study.

Nickel refiners' study

This technique of a retrospective cohort study is peculiarly well suited to the study of long-term occupational hazards and was, as far as I have been able to find out, first applied by Bradford Hill in a study of nickel refinery workers, which was not, however, reported publicly until he described it in the eighth edition of his textbook in 1966[2]. About 1000 nickel refinery workers and pensioners combined were identified from company records and followed for 10 years from 1929 to 1938. Sixteen were found to have died from lung cancer against one expected from national rates, 11 to have died from nasal cancer against less than one expected, and 67 to have died from other causes against 72 expected. The study was not published, as it had been carried out at the request of the local nickel refining industry for their information; but it was subsequently reported in brief as an example of how consistency in the results of different studies, though a useful characteristic in helping to conclude that an epidemiological association reflects causality, is not necessary for such a conclusion to be reached. Having described his findings, Hill continued in his text: "In 1923, long before any special hazard had been recognised, certain changes in the refinery had taken place. No case of cancer of the nose was observed in any man who first entered the works after that year, and in these men there was no excess of cancer of the lung. In other words, the excess in both sites is uniquely a feature in men who entered the refinery in, roughly, the first 23 years of the present century. No causal agent of these neoplasms has been identified. Until recently no animal experimentation had given any clue or any support to this wholly statistical evidence. Thus we have (or certainly had) to make up our minds on a unique event; and there is no difficulty in doing so. This situation very clearly makes nonsense of the assertion that if the evidence is 'only statistical' we cannot accept it for action."

Gas-workers' study

The first published application of the technique appeared in 1952, in a study of the mortality of men employed in the manufacture of coal gas[3]. This had been undertaken to test a hypothesis formulated five years earlier by Kennaway and Kennaway[4] who had analysed the occupations of men recorded on death certificates as having died from lung cancer in England and Wales over the period 1921–38 and compared the numbers in different occupations with the numbers of men classified in the same occupations in the national censuses of 1921 and 1931. Fifty six occupations were studied and the number of deaths attributed to lung cancer in each of seven groups of gas workers was found to be higher than the number expected from the total experience, the standardised mortality ratios varying from 129 to 184. This was certainly suggestive of a hazard, in view of the heavy production of coal tar fumes in the industry, but it was far from conclusive.

With the help of Dr R.E.W. Fisher, the medical officer of a large London gas company, a list was consequently drawn up of all the pensioners of the company other than salaried staff, who had reached 60 years of age and were in receipt of a pension on 1 January 1939, or who began to receive a pension in the succeeding 10 years. The date of birth, the date of entering the pension scheme, and, when applicable, the date and cause of death were recorded for each pensioner and the numbers of men at risk in each five-year age group were counted separately for each of the years 1939 to 1948, in the same way as Frost had counted his family members. Computers were not available at the time and the man-years at risk in each age and calendar year group for the 2000 odd pensioners were counted by hand. The term man-year, however, had not as yet come into general use and what would now be called a man-year (and had been called a man-year by Frost nearly 20 years before) was called simply a "unit". The units in each five year age group in each calendar year were then multiplied by the corresponding national sex- and age-specific mortality rates for all causes and for 18 specific causes or groups of causes and the numbers summed for all age groups and all 10 calendar years to give the total numbers expected. As, however, mortality rates were known to differ somewhat between London and the rest of the country, the expected numbers were multiplied by factors derived from a comparison between the London and the national rates, when appropriate data were available.

The results for seven causes of death are shown in Table 1. The excess mortality from lung cancer was not paralleled by other excesses and it was concluded that gas workers did

Cause of death	No. of deaths	Observed as a % of expected[a]
Cancers of lung and pleura	25	181[b]
Cancers of stomach and duodenum	32	139
Other cancers	99	100
Disease of cardiovascular system	322	97
Disease of respiratory system	120	94
Other diseases	222	96
Violence	20	65
All causes	840	98

[a] Expected in Greater London.
[b] $p < 0.01$.

Table 1 Mortality of retired gasworkers: A London Gas Company, 1939–48 (after Doll[3])

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suffer a moderately increased risk of developing lung cancer; but the number was too small to enable the risks associated with different occupations within the industry to be distinguished. By the time the results came to be published, the industry had been nationalised and the responsible authorities would not allow Dr Fisher's name to be listed as an author. Fortunately his epidemiological colleague was employed by the Medical Research Council and the report was published under his name alone[3].

Life span study of the atomic bomb survivors

The first really large retrospective cohort study was not undertaken until 1956 when the Atom Bomb Casualty Commission (ABCC) initiated the life span study of the survivors of the atomic bomb explosions. The history of its inception is of some interest, as it illustrates the way epidemiological techniques came to be accepted as important research tools in the decade that followed the end of the second world war. Following the atomic explosions, concern about the possible effects of irradiation was greatly increased. By far the greatest proportion of the approximately 180000 deaths was the direct result of blast and heat. Several thousand of the immediate survivors, however, died shortly afterwards as a result of acute radiation sickness and thousands more experienced acute symptoms and recovered. What might happen to those who recovered was unclear. It was recognised that knowledge of the long-term effects of substantial amounts of whole-body irradiation was incomplete and the joint commission of the US Army and Navy, which visited Japan shortly after the war, recommended a long-term study of the survivors to find out what they were. Large programmes of research were consequently initiated into the genetic and somatic effects of radiation, as seen in the survivors of the two explosions in January 1948.

The somatic effects programme started by conducting surveys and selecting a relatively small group of exposed survivors for regular clinical examinations; the so-called Adult Medical Survey. Survivors were identified in a radiation census in 1949 and a sample census carried out by the ABCC a year later; but there was, at the time, no prospect of obtaining estimates of individual doses. Exposed survivors were, therefore, classified according to their distance from the hypo-centre at the time of the explosion and the presence or absence of acute symptoms attributable to irradiation. The surveys quickly provided conclusive evidence that irradiation increased the risk of leukaemia[5], cataracts[6], and mental retardation in children heavily exposed *in utero*[7]; but the plan for repeated clinical examinations proved to be ill-conceived. By 1954, clinicians were seeking to examine regularly some 5000 people but the study was foundering in the face of negative findings and declining participation. There was, consequently, thought of closing it down[8].

Just then, however, another event occurred that altered the perspective of governments and their scientific advisers throughout the world. In June 1954, a hydrogen bomb was exploded over Eniwetok in the Pacific, which had 1000 times the power of the Hiroshima and Nagasaki bombs, and radioactive fallout was distributed worldwide. Further test explosions seemed certain to be carried out and determination of the quantitative effects of small doses of radiation became a burning issue. National committees were appointed in the UK and the USA to review the evidence. Their reports made it clear that no quantitative estimate of the risks could then be made[9,10] and an immense amount of research was initiated. Epidemiology by this time had been shown to be capable of contributing to knowledge of the aetiology of non-infectious disease and radioepidemiology moved from the wings to the centre of the stage.

An *ad hoc* committee under the chairmanship of Thomas Francis Jr recommended a plan to determine the cause specific mortality of a cohort of some 100000 persons (subsequently increased to about 120000) selected from nearly three times that number in Hiroshima or Nagasaki at the time of the national census on 1 October 1950 and whose history of exposure was known[11]. This was immediately accepted and the sample, with some minor modifications[12,13] became the basis for the Life Span Study, which has provided the principal evidence on which our current knowledge of the long term effects of radiation is based. To it was added a mortality study of 2800 individuals exposed *in utero* and non-exposed controls[14] and the registration of all cancers, irrespective of fatality[15] and research was begun to enable tissue doses to be estimated for each member of the cohort.

The population so defined has been followed to this day and still continues to be followed. By the late 1980s nearly 7000 deaths from cancer and over 8500 registered cases have been recorded in a population of some 76000 people with individually estimated doses. The results have shown a lifetime risk of fatal cancer of about 10% per Sv, with about a tenth of the deaths attributable to leukaemia, a dose-response relationship for leukaemia that is fitted significantly better by a linear quadratic relationship than a linear one, and a linear relationship with dose for fatal cancers other than leukaemia[16]. Some uncertainties remain, particularly about the trend with time in the excess relative risk for people who were irradiated in youth and the precise extent to which the findings for a Japanese population in 1945 can be generalised to other populations at later dates; but the general picture of both the qualitative and the quantitative effects

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of exposure to anything more than very small doses of low linear energy transfer radiation (that is gamma rays and x-rays) is clear.

Ankylosing spondylitis study

The Life Span Study is unique in the amount of effort that has been put into quantifying the extent of the exposure of individual members of the cohort to the agent of interest. With occupational hazards, which are perhaps the most common hazards that retrospective cohort studies are required to assess, retrospective investigation is seldom able to do much more than classify individuals according to whether they were process workers, and consequently regularly exposed, maintenance workers who were periodically exposed, and other staff who should not have been exposed at all, and then to divide men in each category according to the length of their employment. Rarely, detailed records exist which allow precise quantification. When they do exist, the records are likely to be complex and the task of estimating the exposure of thousands of individuals may be impossibly heavy, with the resources likely to be available.

This was the situation with which Court Brown and I were faced when, in July 1955, we were asked by the Medical Research Council to determine the nature of the relationship between exposure to ionizing radiation and the incidence of leukaemia, one year before the Life Span Study was initiated by the ABCC, and to provide the answer as quickly as possible. Patients who had received radiotherapy for ankylosing spondylitis seemed a suitable cohort to study, as they had been given a wide range of doses and spondylitis was a benign disease, so that the subsequent occurrence of leukaemia or of any other form of cancer would not be confused with a recurrence of the disease for which the treatment had been given, as might have been the case if an attempt was made to quantify the effects of radiotherapy given for a malignant disease. It was known, too, that some thousands of patients with spondylitis had been treated with radiotherapy over the previous 20 years. Such patients were consequently identified in 81 radiotherapy centres throughout the country by four teams of investigators, each of which included one epidemiologist and one radiotherapist.

Detailed accounts of the doses received by each of the 14000 odd patients identified, who had been treated before the end of 1954 would have been very time consuming and patients were therefore classified according to the number of courses of treatment they had received which ranged from one (the most common) to four or more. Random samples were then selected, stratified within treatment centres and calendar periods of treatment and weighted according to the number of courses so as to ensure about equal numbers in each category, which varied from 1 in 15 for patients who had received only one course to one in two for patients who had received four courses or more or who had been treated at two or more centres. Full details of these sampled treatments were then recorded and measurements were made of the doses received by these various treatments in three places in the spinal marrow of a human model. There was not time to follow each patient individually and we had to be satisfied with information about the development of leukaemia from the reports of physicians, the follow-up records at the cooperating centres, and the names of all individuals who had died from leukaemia in the records of the national vital statistics office over the previous ten years with which the names of the members of the cohort could be matched[17]. This limited procedure has subsequently been replaced by the individual follow-up of the entire cohort; but the initial crude follow-up proved adequate to discover nearly all the leukaemias that had occurred and provided a basis for concluding that the incidence of leukaemia bore a simple proportional relationship to the dose of radiation, that there was no threshold dose for the induction of the disease, and that the dose to the marrow that doubled the incidence of leukaemia was within the range of 30 to 50 r (0.3 to 0.5 Gy), at least as a working hypothesis for x-rays of the average energy used for the treatment of the disease – a doubling dose that has proved to be only slightly higher than that now estimated from the ABCC data with a similar postulated relationship (0.26 Gy).

Like the ABCC's Life Span Study, the cohort of spondylitic patients was subsequently followed forward, turning much of it into a prospective study. In this case, the follow-up has been continued from 1954 to the end of 1991, the radiotherapy data for the sampled cases have been used to estimate the distribution of doses to all the principal organs, and estimates have been made of the excess relative risk per Gy for a European population. The estimated overall effect has not been very different from that estimated for the Japanese atomic bomb survivors[18,19] but several notable differences were observed in the distribution of risk with time which may throw light on the way different aetiological agents interact with each other.

Later developments

In the last 25 years several innovations have been introduced, some of which have made cohort studies more flexible and more productive.

Age-period cohort studies

Generation cohort studies have come to be analysed in a complex way in an attempt to separate the effects of changes

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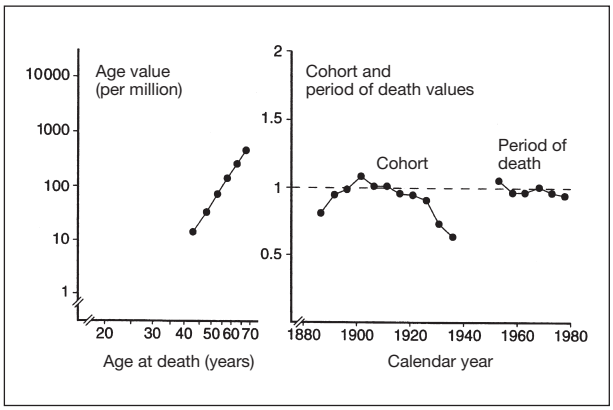

Figure 1 Mortality from bladder cancer in men in England and Wales analysed by age in years, cohort of birth, and period of death[20]

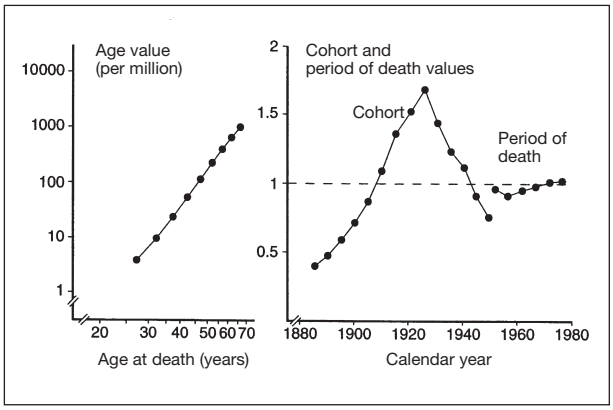

Figure 2 Mortality from lung cancer in women in England and Wales analysed by age in years, cohort of birth, and period of death[20]

in the risk to cohorts born at different periods, which commonly result from changes in behaviour, from changes in periods that have affected all generations simultaneously, whether due to environmental factors or, in the case of mortality rates, to new methods of treatment.

Osmond and Gardner first did this in 1982, using as examples the age-specific mortality rates in England and Wales from cancer of the bladder in men and cancer of the lung in women[20]. They recognised that there could be no unique solution for the variation in two dimensional space of the effects of age, cohort, and period, but suggested a means by which the relative contributions of cohort and period could be approximated by introducing a mathematical constraint that had the effect of partitioning the drift with time between period and cohort in a ratio that depended on the relative magnitude of the non-drift effects. With this technique they obtained the results shown in Figures 1 and 2. In both cases the greater part of the trend could be explained by cohort effects with peaks of bladder cancer for men born in 1900 and for lung cancer in women born in 1920 – both of which corresponded to the generations most exposed to cigarette smoke.

In a discussion of the various methods that have been suggested, Clayton and Schifflers[21] concluded „that the observation of incidence and mortality rates in populations over time does not provide sufficient information to ascribe smooth trends to period or cohort influences with any reliability." This is not to deny all uses for age, period, and cohort models; it is rather to stress that they must be examined and interpreted with some biological understanding of the mechanism by which the disease is being produced. As an example they cite the analysis of the trends in breast cancer mortality in Japan over the period 1955–1979. Three models fit equally well with grossly different implications regarding the separate period and cohort effects. One gives a reduction in age-specific rates above age 60 years, another gives a stabilisation of rates after the menopause, while the third gives a progressive increase in mortality to age 80 years, eliminating "Clemmesen's hook" in the increasing mortality with age which is a feature of all sets of data in relatively stable situations.

Nested case-control studies

A much more important development has been the conduct of case-control studies nested within a large cohort. This is an alternative to the technique adopted by Court Brown and Doll[17] when faced with the need to make complex estimates of the radiation dose to the bone marrow in their retrospective cohort study of the risk of leukaemia in patients irradiated for ankylosing spondylitis, to which I have referred, and it is usually simpler. To be efficient the technique requires the whole cohort to have been followed up with minimal lapse rate. The cohort can then be used as a population from which truly representative controls can be drawn at random, without risk of bias, for comparison with the members of the cohort who have developed the disease of interest. With a relatively small number of subjects, intensive efforts can then be made to quantify the exposure that cases and controls have experienced. Controls are chosen to match each case by surviving to the year when the affected member developed the disease of interest and by year of birth (the more exact the better) but they should not be required to match the affected member by year of entry to the cohort, as has sometimes been done, because this results in loss of important information relating duration of employment to the risk of developing disease. How many controls should be chosen to match each case, depends on the rarity of the cases and the complexity of the measures of exposure,

	Men dying from	
	Occupational cancers[a]	Other causes
Number	137	137
No. employed as topmen or hydraulics mains attendants	16	9
Mean years employed as above	18.2	10.4

[a] Cancers of lung (122), bladder (12), and scrotum (3).

Table 2 Employment in occupations heavily exposed to coal tar fumes among gas retort house workers (after Doll et al.[22])

but the more that are chosen the better, as greater numbers reduce the probability that any discovered differences could be due to chance.

In retrospect, it is surprising that so many years were to pass before this method came to be commonly used. A primitive form of it was described in 1972 in the study of the occupational hazards of gas-workers[22] when it was used to define the type of occupation within gas retort houses that was most likely to give rise to the specific hazards of cancers of the lung, bladder, and scrotum. Men were not easy to classify by type of occupation as they commonly changed from one to another and different names were given to the same jobs in different works. Two occupations, however, stood out as liable to result in much heavier exposure to tar fumes than others; namely, those of topman and hydraulic mains attendant. Information was consequently obtained about the length of time spent in these occupations for men who had died of one of the three types of cancer that had been shown to occur in excess in retort house workers and from controls who died of some non-occupational cause and were matched one to one for employer and age at death within the same five-year age group. The results are summarised in Table 2.

According to Liddell[23], the method became common only after about 1977. Two early examples of which I have personal knowledge were published in 1980. One is described later, when I consider the use of biomarkers. In the other, Peto[24] sought to relate the risk of lung cancer in an asbestos textile factory to cumulative exposure to asbestos dust measured in the modern terms of fibres ml^{-1} years. A cohort of 679 male workers was identified who entered the factory in 1933 or later, that is after dust had been controlled to the standards of the Asbestos Industry Regulations of 1931, it was then followed to the end of 1978, and special attention was paid to those who entered in 1951 or later, when ambient dust measurements were regularly carried out. In these men, eight deaths from lung cancer had occurred 20 or more years after first exposure with only 1.62 expected. The cumulative exposure of the eight men who died of lung cancer was compared with that of 42 men employed over the same period and no difference in the measured exposure to asbestos dust was seen. This finding, the author thought, implied that static samples of the ambient environment are not the appropriate indicator of personal risk, which may be more closely related to high transient exposures during certain activities, and these could be measured only by personal monitoring. This, Peto[24] noted had also been suggested from an earlier study of asbestos-related symptoms by Berry et al.[25] and had been concluded some time earlier about the measurement of dust in mines in relation to the risk of pneumoconiosis, when Oldham and Roach[26] introduced the concept of measuring the personal exposure each shift of randomly selected miners. That is not to say that static measurements of environmental pollution are no use – they have been shown to correlate with the incidence of lung cancer in other larger studies of the effects of exposure to asbestos[27,28] – but to warn that they may provide only crude estimates of an individual's exposure with a consequent need for large numbers if statistically significant differences are to be detected.

Nested case-control studies within retrospective cohorts have come to be a major tool of the epidemiologist's armamentarium and have, in some cases, been adapted to allow for personal rather than static measurements, as in Thériault et al.'s[29] study of the occupational hazards of leukaemia and brain cancer associated with exposure to 60 Hz electromagnetic fields produced by the passage of electricity. Many studies of such suspected hazards have been carried out in the last 16 years with inconclusive results, principally because of the lack of quantified information of the extent to which individuals in different occupations have actually been exposed. Faced with this problem, Thériault et al.[29] carried out a cohort study of 223000 men employed by Electricité de France-Gaz de France, Ontario Hydro, and Hydro-Québec, who were observed during the period 1970 to 1989. Cases of cancer were ascertained in France from company medical records during employment. In Canada they were ascertained by matching the names of employees with the records of local cancer registries and, in Quebec, from company medical records and death certificates. Over 4000 men were identified as having developed cancer. To compare with them, controls were selected randomly from members of the whole population matched for the same utility, year of birth, and alive on the date the affected employee developed cancer: four for each man with one of the cancers of special interest (defined in this study as any haematopoietic cancer, brain cancer, or melanoma) and one for each man with a cancer of another type.

Full occupational histories were built up for all members of both groups from company records. Measurements of the fields to which a sample of over 2000 men currently

Type of cancer	No. of cancers	Exposure equal to or above median		Exposure equal to or above 90th percentile	
Acute non-lymphoid leukaemia	60	2.41	(1.07–5.44)[b]	2.52	(0.70–9.09)
Acute myeloid leukaemia	47	3.15	(1.20–8.27)	2.68	(0.50–14.50)
All leukaemia	140	1.54	(0.90–2.63)	1.75	(0.77–3.96)
Astrocytoma	41	0.97	(0.34–2.80)	12.29	(1.05–143.5)
Malignant brain tumour	108	1.54	(0.85–2.81	1.95	(0.76–5.00)

[a] Compared to exposure less than median (3.1 μT years) and adjusted for socioeconomic status.
[b] 95% confidence interval.

Table 3 Odds Ratios[a] for specific cancers among electric utility workers by cumulative exposure to magnetic fields (after Thériault et al.[29])

employed were exposed were then made by means of personal dosemeters worn throughout a five-day week and jobs with similar mean exposures were collapsed into between 32 and 65 occupational groups, the number of groups varying between the different utilities. Allowance was made for procedural and power changes over the period of the men's exposures and each man's exposure was expressed in "μT years" by multiplying the mean exposure in each occupational group by the time spent in it. Odds ratios, adjusted for socio-economic status, were then calculated for 31 cancer types for men with exposures equal to or above the median and exposures equal to or above the 90th percentile in comparison with men whose exposures were less than the median. Only three of the cancers showed statistically significant excesses in one or other of the more heavily exposed groups: those for acute non-lymphoid leukaemia, acute myeloid leukaemia, and astrocytoma. The results are shown in Table 3 along with those for all leukaemia and all malignant brain cancers. Though not conclusive, these findings greatly strengthen belief in the idea that 60 Hz electromagnetic fields may cause occupational hazards of these two diseases. It was a major task to compute the occupational exposures of the 11000 men selected for a nested case-control study and it would have been quite impracticable, at the same level of detail, to have done so for 20 times as many men, which a simple cohort study would have required.

Use of biomarkers

Still better measures of exposure can sometimes be obtained by measurements of biological characteristics or biomarkers, as they have come to be called. The early example of a nested case-control study that I referred to previously, which used biomarkers, was that initiated by Wald et al., in 1975 and first reported in 1980[30]. The biomarker of greatest interest at the time was the blood level of retinol and a sample of serum was consequently obtained from each member of the cohort studied at the start of the investigation and stored (in a so-called serum bank) at –40°C.

The study population consisted of 16000 men aged 35–64 years who attended for a comprehensive health screening examination between March 1975 and December 1978. Apart from giving a sample of blood, which was used for a number of blood tests and to provide the sample of serum, all the men completed a standard health questionnaire, were examined clinically, and had an ECG and a chest x-ray. The National Health Service records of the men were flagged centrally and Wald and his colleagues were notified in the event of a man's death or registration as having developed cancer. By the end of 1979, 86 men were identified who had developed cancer and these were matched with double the number of controls who were alive and without cancer, of similar age and smoking habits, and whose blood was taken at approximately the same date (within four months). Analysis of the blood samples showed that the men who developed lung cancer had significantly low levels of blood retinol (a mean of 187 against 229 IU per dl) while men who developed other cancers did not. This seemed to confirm the relationship between low retinol intake and lung cancer that had been recorded from dietary histories and to accord with the evidence that vitamin A analogues could decrease the risk of cancer in animal experiments. It has not, however, been supported in subsequent serum studies. Later observations showed that low serum levels of b-carotene obtained in this[31] and other cohort studies using serum banks, predicted an increased risk of cancer better than the serum level of retinol; but this must now be interpreted as due to confounding with still another agent, as a controlled trial of the prophylactic value of b-carotene supplements continued for 12 years has shown that raising the serum level has no effect on the risk of developing either cancer of the lung or cancer of any other organ[32]. There remains, nevertheless, consistent evidence that a high level of consumption of green and yellow vegetables protects against the development of many cancers and further serum studies and controlled trials will be required to find out what the prophylactic agents are.

The results of nested case-control studies relating to serum sex hormones promise to be more productive. After years of conflicting reports, a relatively large study based on 130 cases of breast cancer and 251 matched controls, larger numbers than have been included in all the previous studies combined, supports the idea that high levels of available oestradiol (free and albumin bound) increase the risk of breast cancer as much as three-fold[33].

Urine banks have also been used. Ross et al.[34] used one in conjunction with a serum bank to test the importance of the combination of infection with the hepatitis B virus and the consumption of food contaminated with the fungal metabolite aflatoxin in the production of liver cancer in tropical climates. The cohort consisted of a little over 18000 men 45 to 64 years of age resident in four parts of Shanghai who volunteered to participate. Each man completed a standard questionnaire and gave samples of blood and urine, both of which were stored. After one to four years of follow up, liver cancer had been diagnosed in 22 men, and 120 controls were selected, matched within one year of age, within one month of sample collection, and for neighbourhood of residence, but otherwise at random. The results are summarised in Table 4. With blood positive for hepatitis B antigen and aflatoxin in the urine the relative risk of liver cancer was very much greater than when either marker was present alone and 60 times greater than when neither was present. These results are based on very small numbers and are preliminary and the study is being continued; but they provide the first objective evidence from observations on individuals of a synergism that has long been suspected from ecological observations, but has proved difficult to confirm by food frequency questionnaires.

Exposure to: HBV[a]	Aflatoxin[b]	No. of cases/controls	Relative risk (95 % CI)
–	–	4/74	1.0
–	+	6/51	1.9 (0.5, 7.5)
+	–	5/13	4.8 (1.2, 19.7)
+	+	7/2	60.1 (6.4, 561.8)

[a] HBs Ag in blood.
[b] Metabolite of aflatoxin in urine.

Table 4 Interaction of Hepatitis B infection and Aflatoxin in the production of liver cancer (after Ross et al.[34])

Conclusion

What then of the future? Cohort studies in the original sense of the generation studies introduced by Andvord in 1930[35] helped our understanding of the spread of tuberculosis and the aetiology of several cancers, but they are now of limited application and I doubt if they have much more to teach us. Cohort studies in the modern sense, both prospective and retrospective, have established themselves as essential tools for epidemiological research. The nested case-control study and the use of biomarkers, which will in the course of time involve the techniques of molecular biology, provide us with powerful weapons for testing hypotheses about both the genetic and environmental causes of disease and cohort studies have, I suspect, an even more important part to play in the future of medical research than they have had in the past.

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