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REVIEW ARTICLE

Case-control design as investigative approach to assessing cancer etiology: development and future perspectives

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Summary

The case-control method evolved out of analyses of series of cases. The analytic form of the case-control study can be found in the 19th century medical literature, but did not appear to be viewed as a special or distinct methodology. The first modern case-control study was the Janet Lane-Claypon's study of breast cancer in 1926, but the design was used only sporadically in medicine until 1950, when 4 published case-control studies linked smoking and lung cancer. These 1950s studies synthesized the essential elements of the case-control comparison, produced a conceptual shift within epidemiology, and laid the foundation for the rapid development of the case-control design in the subsequent half century. The powerful consistency of these case-control studies, and the replication of their findings in later prospective studies, promoted the general acceptance of the case-control study as a scientific tool in clinical research. Newer case-control studies have benefited from the advances in design, execution and analysis since 1950s. These advances include more rigorous selection and matching of case and control population, improved interviewing techniques, location of the design within a general framework of epidemiologic strategies for relating exposure to disease, understanding of the measures of effect, and application of increasingly sophisticated statistical procedures to findings. This review traces the development and future perspectives of the case-control design to assessing cancer etiology. With illustrations drawn primarily from the literature on its use and the value of its results to unravelling the etiology of malignant diseases, we tried to explore if the case-control approach firmly ensconced in epidemiology as investigational tool and rivals in importance the more straightforward cohort approach.

Key words: cancer etiology, cancer risk factors, case-control study, epidemiology

Introduction

The case-control study, a widely used method of observational epidemiological study, is an application of medical history-taking that aims to identify the cause of disease among a group of people, or the cause-effect relationships of a condition of interest. The underlying concept is simple. The past medical history, or history of exposure to a suspected risk or protective factor, of a group of persons with the disease or a condition of interest (the cases) is compared with the past history of another group of persons (the controls) who resemble them in as many relevant respects as possible, but who do not have the disease or the condition of interest. Statistical analysis is used to determine whether there is a stronger association of past exposure to the suspected risk or protective factor with the condition of interest among the cases than among the controls. An indirect estimate of the risk ratio, however, can be calculated. This measure is referred to as the odds ratio [1]. The method can be called "retrospective study" because it is concerned with events in the past. However, the cases are often collected prospectively, with cases added as they occur, so there exists possible confusion with what used to be called a prospective study but is now almost always called a cohort study. It has also been called case-compeer study and case-referent study, but case-control study is the most widely used term.

A computerised MEDLINE search did not find the term "case-control" in the title of a biomedical pa-

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per until 1967, and did not find it in the titles of more than two papers in a year until 1973. By 1980, 91 titles included the term, but in the year 2000, 1795 papers had "case-control" in the title or abstract [2]. This enormous increase is only partly a reflection of preferences in terminology, such as a shift from the term "retrospective study" to "case-control study" (probably by Philip Sartwell, 1908-1999) [3], and of the general increase in medical publications over the last 4 decades.

This review traces the development and future perspectives of the case-control design to assessing cancer etiology. With illustrations drawn primarily from the literature on its use and the value of its results to unravelling the etiology of malignant diseases, we tried to explore if case-control approach firmly ensconced in epidemiology as investigational tool and rivals in importance the more straightforward cohort approach.

A constellation of the case-control method development in medicine

A constellation of development in medicine had to be in place before the case-control study could be conceptualised and actualised. These include the definition of unique disease entities (cases), the assembling of case series, an interest in etiology at the individual level, and the practice of interviewing patients about past event. Most crucial has been the practice, refined over many years, of comparing cases of disease to cases of non-disease, so that factors that might account for the difference might be ascertained.

The method evolved out of analyses of series of cases. The concept was mentioned in the writings of the 19th century French physician Pierre Charles Alexandre Louis [4] on the heredity in tuberculosis, and a simple form of it was used by the 19th century English physician William Augustus Guy [5], who investigated the influence of occupation on health.

So, the analytic form of the case-control study can be found in the 19th century medical literature, but did not appear to be viewed as a special or distinct methodology.

A number of later clinical investigations by Whitehead in 1855 [6], Baker in 1862 [7], and especially by Broders [8] and Goldberger [9], both in 1920, can be described as case-control studies. These works in the first half of 20th century contained some or most of the essential elements of the case-control design.

As it emerged in the beginning of the 20th century, in the work of Goldberger and his colleagues [9] in South Carolina mill villages, the case-control study was but one part of a broader plan of attack to reduce the burden of the disease (pellagra), which also included experimental studies at the individual level, and investigating causes and interventions at a broader societal level [2]. Goldberger and his colleagues appear to have designed the first case-control study in which *a confounding factor* (income) was taken into account. The authors tried to take account of what they termed "disturbing or confusing factors".

Pioneering use of the case-control approach to assessing cancer etiology

The pioneering use of analyses close to modern case-control method concerning risk factors for malignant diseases was read to the Royal Medical and Chirurgical Society in 1862 by James Paget (of Paget's disease) but authored by W.M. Baker, entitled "Statistics of cancer" [7]. The data source was notes on 500 cases of cancer described by Paget between 1843 and 1861. Most of the paper was a listing of typical case-series statistics, such as the age distribution and duration of survival of cases of cancer, but in two instances the author provided a case-control type of comparison. The comparisons were of marital status and of prior pregnancy in women with breast cancer and in women with other cancers. The Baker's study appears to be *one of the first case-control approaches to the study of a chronic disease* [2], with an odds ratio for breast cancer of 1.2 for single state, and 3.0 for marital nulliparity. But Baker was conservative, stating that "the number is too small to allow for a very fair comparison being made between them and the cancers of the breast in this respect."

Broders of the Mayo Clinic in 1920 [8] described 537 cases (526 males) of squamous cell epithelioma of the lip, and investigated tobacco use, including the method of use (chewing, smoking, snuff-taking or any combination of them), and among smokers, the distribution of pipe, cigar, and cigarette use. In 500 "men without epithelioma of the lip" similar smoking data were tabulated. This study, sometimes cited as *an early case-control study*, makes no mention of the source of the controls, nor of the method of interview, and the mean age of cases and controls differed by more than 20 years. Though seemingly not much more advanced than the work of Whitehead in 1854 [6] or Baker in 1862 [7], the study did suggest a role for pipe-smoking in lip cancer (78.5% in cases vs. 38% in controls).

Not by accident, many of studies published in the first half of the 20th century, which have been identified as "early" case-control studies by a variety of authors, concerned the etiology of cancer [2]. During this period, many epidemiologists were aware of shifting

health profile in developed countries, and particularly of the increased frequency of cancer. There was some debate as to whether epidemiology should be extended from infectious to other etiologies. The position that it should be, was most fully articulated by influential Major Greenwood, who argued that cancer was, like infectious diseases, a "crowd-sickness", and therefore within the purview of the epidemiologist [10].

The era of modern form of case-control design

The first modern form of case-control study is most easily recognized in the Janet Lane-Claypon's study of breast cancer in 1926 [11], followed by the less well-known work of Lombard and Doering (1928) on cancer etiology in Massachusetts [12], and one case-control study of smoking and lung cancer of Müller in 1939 [13]. The modern form of case-control study is crystallised in the years following World War II in the work of Schrek and Lenowitz (1947) [14]. As we have mentioned above, particularly motivated by the increased frequency of cancer during this period, epidemiology extended from infectious diseases to cancer and other "crowd-sicknesses".

In 1926, the British Ministry of Health published a study entitled "A further report on cancer of the breast: reports on public health and medical subjects" [11]. This detailed and sophisticated investigation is often cited as the first case-control study [15]. Its author was Janet Lane-Claypon, a physician, laboratory investigator as well as epidemiologist, employed by the British Medical Research Council [16].

Lane-Claypon selected 500 hospitalised cases and 500 controls with non-cancerous illnesses from both inpatient and outpatient settings in London and Glasgow. The women were not matched on any characteristics, but proved quite similar in age and social class. Interviews were obtained by a small number of competent and accurate observers, following uniform methods which had been discussed with Dr. Lane-Claypon. The higher prevalence of the single state in breast cancer cases was noted, as well as the lower fertility of married cases. This paper deserves its landmark status in the history of the case-control study, even aside from providing the first solid evidence that low fertility raises the risk of breast cancer, a conclusion based on an analysis carried out by Mayor Greenwood, the project statistician [16]. A regression equation, based on age at marriage and duration of marriage, was developed to describe fertility in the case and the control series. The analysis was further refined by excluding cases who had pre-menopausal breast cancer, and whose fertility might therefore have been interrupted by the disease. The analysis showed 22% lower fertility in the case group.

Less well-known than the Lane-Claypon study, but in some ways similarly important and sophisticated, was the work of Lombard and Doering (1928) on cancer etiology in Massachusetts [12]. They analysed cases of cancer cared for by the Visiting Nurse Association in Massachusetts. This paper possibly provides the first use of sex and age matching in a case-control study, and also the first to concern itself with the need to have the same interviewer for cases and controls. Several of the nurses used themselves as "controls", a practice which modern epidemiologists would no doubt discourage.

Another US medical case-control study was published 20 years later by Schrek and Lenowitz in 1947 [14]. This modern form of case-control study is crystallised in the years following World War II. Cases were all 139 cases of penile carcinoma admitted to the Hines, IL VA Hospital from 1931 to 1944. No less than 6 different control groups were initially proposed [16], all from among admissions to the hospital, but distinguished from each other in sample size, years of admission, cancer/disease diagnosis and ethnic composition. Each control group was considered as a series; no matching was performed. Ultimately, however, only 3 groups were used for comparison of the prevalence of circumcision. For comparison to the 100 white cases, the authors assembled a series of white men admitted for any cancer in 1944 who had been interviewed for another study (minus 2 Jewish men and 4 men with penile cancer). To obtain controls for the 39 "coloured" cases, the authors interviewed all "coloured" men who were in the hospital on a single day in July 1945, which yielded a control group of 55 men with "tumor", and another of 113 men with "other diseases". While between 12.8% and 24% of the 3 control groups had been circumcised by the age of 3, none of the 139 cases had been circumcised at that age.

The German literature includes at least one case-control study of smoking and lung cancer [13]. Franz Müller, about whom little is known other than his membership in the Nazi party, mailed a questionnaire to family members of lung cancer victims requesting information about smoking history, including type (cigar, cigarette, pipe), daily consumption, and whether the victim had stopped or reduced smoking. A control group, of the same number, gender and approximate age as the series of 86 lung cancer cases for whom questionnaires had been returned, was similarly surveyed. While only 3.5% of the cases were non-smokers, 16% of the controls did not smoke, and heavy smoking was 6 times as common in lung cancer patients as in controls. This paper was cited by Wynder and Graham in 1950 [17], by the Surgeon General's 1964 report on Smoking on Health, and

in more recent discussions of historical epidemiology [18,19], but it otherwise seems to have been widely ignored [16].

Importance of the 1950 case-control studies on smoking and lung cancer

Following World War II, several investigators in England and in the United States adopted Müller's methods for case-control studies of smoking and lung cancer, which had become a very common and lethal malignancy 1950, a year that saw the publications of 4 case-control studies of smoking and lung cancer [15,18-20], was a watershed in the acceptance of this approach to assessing disease etiology. These 1950 studies established several features of the modern form of the case-control study [16]. The success of the 4 case-control studies in implicating smoking as a major risk factor for lung cancer led, in just over a decade, to major pronouncements on the health hazards of smoking from authorities on both sides of the Atlantic. The strong and consistent results that emerged from these early studies created confidence in the approach that was amplified when the findings were later confirmed by cohort studies.

For first of the US case-control studies of lung cancer and smoking [21], the population source was 5003 male admissions to the Hines, IL VA hospital from 1941-1948, all of whom had been surveyed upon admission for smoking history using a standard form. This data set permitted comparison of smoking histories in several case groups (lung cancer, other respiratory cancers, upper digestive tract cancers) and in different control groups (all other diseases, all other cancers). Schrek et al. (1950) noted that other cancers were a better comparison group, because cancer patients differed from other patients in that they were often referred from other VA hospitals [21]. Cigarette smoking, defined as smoking more than 10 cigarettes/day, was found in 71.2% of 82 lung cancer patients, 69.7% of 73 patients with cancer of the pharynx or larynx, 62.9% of 116 lip cancer patients, 54.8% of all 5003 admissions, and 48.8% of 522 cancers of sites other than the respiratory and upper gastrointestinal tract. Neither duration nor age of onset of smoking differed across the several case and control groups. Race, age and geographic origin of patients were assessed as potential confounders (in the terminology of the authors, "secondary factors"), and smoking rates were examined within strata of age and race. The authors concluded: "When age and race were equalized in the control and clinical groups, there still remained a statistically significant correlation between smoking and cancers of the lung and of the larynx and pharynx".

Smoking histories had been obtained routinely upon admission to Roswell Park Memorial Institute, Buffalo, NY, since 1938. In 1950 Levin et al. controlled for age by age-standardising the smoking prevalences to the age distribution of all 1650 men in the study [20]. No women were studied. The authors showed both the prevalence of smoking in cases and controls, and the proportion of lung cancer cases among smokers and non-smokers, the latter essentially a proportional morbidity analysis, since all study subjects were hospital admissions. Of lung cancer patients 54.1% had smoked for >25 years, compared to 34.9% of other cancer controls and 29.8% of non-cancer controls. The age-standardised proportion of lung cancer diagnoses among non-smokers was 8.6%, and among cigarette smokers of >25 years, 20.7%. Both of these early case-control studies of lung cancer [20,21] were in a sense nested case-control studies, since the smoking interviews had been obtained in the entire population from which cases and controls were selected.

Wynder and Graham [17] designed a survey instrument specifically for their study and used it to interview cases of lung cancer of both genders (but predominantly men) from hospitals in St. Louis and elsewhere, and from several private practices around the country. Controls were similarly heterogeneous. Recruited in several hospitals in St. Louis and in other parts of the country, they constituted a population different in age and geographic origin from the cases. The number of lung cancer cases (685) was considerably larger than in either the Levin et al. study (236) or the Schrek et al. Study (82) [20,21]. It is important to note that one subset of cases and controls (in two St. Louis hospitals) were interviewed prior to the diagnosis being established. As in the Levin et al. study [20], the smoking habits of controls were age-standardised. The commoner type of bronchogenic carcinoma (squamous, epidermoid or undifferentiated) was analysed separately from adenocarcinomas, and smoking history was graded from 0-5 based on a duration-intensity measure similar to pack-years, based mostly on cigarette consumption, but augmented by information on cigar and pipe-smoking. Cases of lung cancer consistently showed fewer non-smokers and more class 4 and 5 smokers (>20 cigarettes per day for $\geq$ 20 years) than did controls, whether from chest services or other hospital services, whether interviewed blind to diagnosis or not. Although there were few adenocarcinomas (52 cases), their relationship to smoking in men was similar to that of other bronchogenic cancers. In women, although heavy smoking was common in most bronchogenic cancers, it was found in only 2 of 13 adenocarcinomas. The Wynder and Graham's study was published in 1950, in the same issue of JAMA as the Levin et al. paper.

The Doll and Hill's study in 1950 [22] has come to

be viewed as a model of the case-control investigation. Notification of cancer cases (lung, colon, stomach, rectum) were received from 20 London hospitals, with the latter 3 cancers used as "contrasting groups". Each case was interviewed by a research almoner (social worker) who was also "instructed to interview a patient of the same sex, within the same 5-year age group, and in the same hospital at or about the same time" who did not have cancer. As in the Wynder and Graham's study [17], attention was paid to the duration of smoking, to histories of starting and stopping smoking, and to the amount smoked. This study devised the convention of setting the lower threshold for lifetime smoking at one cigarette per day for a year. A 6-month re-interview of a subset of subjects showed remarkable consistency in self-reported smoking histories. Contrast was made between cases of lung cancer and matched controls in overall smoking, in the amount smoked most recently, in the maximum ever smoked, in the age of onset of smoking and in the duration of smoking. Pipe smoking was shown to have a weaker relationship to lung cancer than cigarette smoking. Stratified analyses were used to deal with potential confounders, including urban/rural residence, cancer diagnosis of controls and potential interviewer bias. Unlike any other case-control study of the period, Doll and Hill (1950) used the distribution of smoking in lung cancer patients to develop "ratios" for lung cancer risk in London smokers, assuming a smoking distribution that paralleled that of the control population [16]. This yielded estimates of relative risk for lung cancer from smoking 10, 20 and 60 cigarettes per day of 19, 26 and 65; odds ratios were not calculated. The authors concluded, considerably more firmly than in the US studies, that cigarette smoking was "a factor, and an important factor, in the production of the carcinoma of the lung". In 1950, Doll and Hill in England [22] and Wynder and Graham in the United States [17] published large case-control studies of cigarette smoking and cancer of the lung almost simultaneously in the British Medical Journal and the Journal of the American Medical Association, respectively. Many more case-control studies of this and other kinds of cancer soon established the utility of the method.

These 1950 studies synthesized the essential elements of the case-control comparison, produced a conceptual shift within epidemiology, and laid the foundation for the rapid development of the case-control design in the subsequent half century.

Acceptance of the case-control study as a scientific tool in clinical research

Both the Royal College of Physicians' 1962 report entitled "Smoking and Health" [23], and US Surgeon General's Report of the same title, published in 1964 [24], relied heavily on "retrospective studies" in their assessment of the evidence. The Royal College of Physicians Committee cited 23 retrospective studies, all of which showed a relationship of smoking to lung cancer, and the Surgeon General's Report cited 29 such studies, all but one of which (a study in women) confirmed the association. The powerful consistency of these case-control studies, and the replication of their findings in later prospective studies, promoted the general acceptance of the case-control study as a scientific tool in clinical research [16].

Thus, using case-control design, several investigations regarding risk factors for some other health disorders, were performed: congenital malformations of the nervous system [25,26], thalidomide and congenital anomalies [27] and neural tube defects recurrences [28].

With the elaboration and wide application of this design over the subsequent half century, significant findings have been many. Diethylstilbestrol and vaginal adenocarcinoma [29], aspirin and Reyes syndrome [30], L-tryptophan and eosinophilia-myalgia [31], tampon use and toxic-shock syndrome [32] are examples of exposure-disease relationships widely accepted as causal that were uncovered in recent decades by case-control studies. Bearing in mind the rarity of the diseases under investigation in these studies, and the lack of strong exposure hypotheses at the time these studies were initiated, there is no realistic possibility that these associations could have been uncovered by any other epidemiologic strategy [16].

In 1971, the case-control work of Herbst et al. [29] showed that the design was useful in studying very rare conditions. During 1969 and 1970, 8 cases of adenocarcinoma of the vagina were seen in adolescent girls and young women in Boston, Massachusetts. This was, up till then, an extremely rare, almost nonexistent condition, and it was clear that these young women must have been exposed to some unusual cancer-causing agent. Each of the 8 cases was matched with 4 otherwise similar but healthy females of the same age. Their, and their mothers' past histories of many kinds of exposure to medications, vaginal douches, and other substances, were compared. Seven of the 8 cases had a history of their mothers having been given artificial estrogen to prevent miscarriage early in pregnancy (this had been a popular though unproven method of preventing threatened miscarriage since the 1950s; it has now been shown to be useless). None of the controls had a similar history. There was less than a 1 in 100,000 likelihood of this distribution occurring by chance. Adenocarcinoma of the vagina was caused by prenatal exposure of the de-

veloping female fetus to diethylstilbestrol, an artificial estrogen. Later studies showed that genital dysplasia in boys and young men was another consequence of prenatal exposure to artificial estrogen.

Evaluation and perspectives of the approach to unravelling cancer etiology

Generally, during previous years, case-control studies have undoubtedly been overused and many spurious associations have been reported. Yet the problems involved in locating a representative group of cases, selecting appropriate control groups, and collecting comparable information on cases and controls are often of such magnitude that the results of case-control studies are open to a variety of legitimate questions and objections, generally more so than the results of cohort studies. It relies on subjects' recall and/or completeness of existing records, there is incomplete allowance for extraneous factors, rates cannot be calculated, the mechanism of disease cannot be studied, and a proof of causation cannot be established. But very importantly, many of the shortcomings can be overcome by ingenious designs such as the use of a "nested" case-control study in which both cases and controls are drawn from the same large population that is being used in a cohort study.

Case-control studies are usually the most readily and cheaply carried out of all analytic epidemiologic studies. Many examples illustrate the value of the case-control study. For rare diseases they may be the only practical approach. It is a relatively rapid and reliable method of establishing evidence of an association between an exposure to a risk (or protective) factor and an unfavorable (or favorable) outcome. It can study several possible causes or exposures to risk simultaneously. It does not require study of large numbers - usually requires only a few cases. It is an excellent way to study diseases with long latency. It can often make use of existing records.

It is obvious that case-control studies have played a vital role in the development of many fruitful lines of study. For example, the relationship of cigarette smoking to lung cancer was demonstrated in case-control studies before any cohort studies of this question were carried out. Because of their relatively low cost, case-control studies should often be the first approach to testing of a hypothesis. They provide an excellent way to investigate whether any of several exposures is associated with a particular disease. This feature may facilitate an exploratory study (sometimes referred to as a "fishing expedition") to find clues and leads to further study [33].

Another cost-saving application is the nested case-control study. In a large cohort study, data collections that are difficult, expensive, or had not been thought of originally can be applied to the cases that develop and to only a subset of those that remain free of disease. For example, a nested case-control study was carried out in the Evans County cohort to determine whether vitamin A (retinol) level in the blood was related to the development of cancer [34]. Measurements of the concentration of vitamin A were made on the previously frozen serum specimens of the 135 persons who developed cancer and a sample of 237 cohort members who remained free of cancer through 1981. The high cost of measuring vitamin A in the entire cohort of 3102 persons was not justified by the small gain in statistical reliability that would have resulted. In that study, vitamin A level was not a useful predictor of cancer development.

In addition, a case-control study could be very suitable approach to evaluate the efficacy of a screening test (sigmoidoscopy) in the prevention of death from a disease (colorectal cancer) [35]. The northern California Kaiser Permanente settings were very suitable for a case-control study based on medical record review, because this maintenance organization's subscriber population of more than 2 million persons had many who died of colorectal cancer (the cases), had as many matched controls as desired, contained persons who did and did not receive sigmoidoscopic screening, and had all necessary information about screening and subsequent cancer in their medical records. The results showed that persons who died of colorectal cancer had received considerably fewer screenings by sigmoidoscopy than the controls. After control for confounding variables, this yielded a relative risk of 0.41 for fatal colorectal cancer for those who had received at least one screening sigmoidoscopy as compared with those who had received none. More persuasive, this 59% reduction in risk was confined to cancers potentially within reach of the sigmoidoscope; death from cancer higher in the colon was not prevented. This was a clear demonstration of the efficacy of screening sigmoidoscopy, to the extent possible in an observational study. The other good news was that performing the procedure every 10 years was about as efficacious as performing it at the generally recommended intervals of 3-5 years [35].

These examples, and many others, illustrate the value of the case-control study as investigative approach to assessing cancer etiology. Newer case-control studies have benefited from the advances in design, execution and analysis since 1950. These advances include more rigorous selection and matching of case and control population, improved interviewing techniques, location of the design within a general framework of epidemiologic strategies for relating exposure to disease, understanding

of the measures of effect, and application of increasingly sophisticated statistical procedures to findings [36-42].

Moreover, the concept is readily understandable, so members of the lay politics, political decision makers, and the media can easily grasp the significance of the findings, especially regarding new or serious health problems. Hopefully, future epidemiologists will enlarge the scope and purview of this elegant and useful design and use it to focus on the improvement of health in the population.

Conclusion

No other epidemiologic method has been so much discussed. During previous years, case-control studies have undoubtedly been overused, and many spurious associations have been reported. But many of the shortcomings can be overcome by ingenious designs such as the use of a "nested" case-control study. Most importantly, many examples illustrate the value of the case-control study as investigative approach to unravelling cancer etiology. It is now firmly ensconced in epidemiology, and rivals in importance the more straightforward cohort approach. The concept is readily understandable, so members of the lay politics, political decision makers, and the media can easily grasp the significance of the findings. Future epidemiologists will enlarge the scope and purview of this elegant and useful design and use it to focus on the improvement of health in the population.

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