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Origins and early development of the case-control study: part 2, The case-control study from Lane-Claypon to 1950

Summary

The first modern case-control study was Janet Lane-Claypon's study of breast cancer in 1926, but the design was used only sporadically in medicine and the social sciences until 1950, when four published case-control studies linked smoking and lung cancer. 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.

Keywords: Case-control study – Epidemiology – History.

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."* (Lane-Claypon 1926a). This detailed and sophisticated investigation (12 chapters totaling 84 pages, plus 51 pages of appendix tables) is often cited as the first case-control study (Cole 1979). Its author was Janet Lane-Claypon, a physician employed by the British Medical Research Council, and an excellent laboratory investigator as well as an epidemiologist, who had previously been principally engaged in studies of child health, including nutrition (Lane-Claypon 1916) and stillbirth (Lane-Claypon 1926b). Lane-Claypon's investigation contended with issues that have come to be seen as central to the modern case-control study.

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 characteristic, 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. Recall bias was weighed in assessing histories of past "breast troubles":

> " … in the event of any divergence between the two series showing a higher incidence among the cancer series, objections might fairly be raised on psychological grounds. It is evident that a woman who has suffered from a trouble so serious as to require the removal of the breast and the surrounding tissues will be likely to search in her memory for some antecedent causative agent, or event."

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 interesting analysis, carried out by Major Greenwood, the project statistician. A regression equation, based on age at marriage and duration of marriage, was developed to describe fertility in the case series, and was then applied to 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 their disease. The analysis showed 22% lower fertility in the case group.

Less well-known than the Lane-Claypon study, but in some ways similarly sophisticated, was the work of Lombard and Doering (1928) on cancer etiology in Massachusetts. This paper provides a rationale for the use of controls in words hard to improve upon:

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> "We feel that any study of the habits of individuals with cancer is of little value without a similar study of individuals without cancer. To know that a large percentage of patients with cancer have certain habits is of little value for inference unless we know what percentage of the community at large has the same habit."

They analysed cases of cancer cared for by the Visiting Nurse Association in Massachusetts. In fulfilling their self-stated desire for a control group, they arranged to have:

> "the same investigator who collected the record of the patient with cancer fill out a similar record for an individual without cancer, of the same sex and approximately the same age."

This is the first use we have been able to find in the medical literature 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 (unblinded, however) for cases and controls. Interestingly, "several of the nurses used themselves as controls", a practice which modern epidemiologists would no doubt discourage.

We have not located another US medical case-control study until a study of penile carcinoma published 20 years later (Schrek & Lenowitz 1947). This study too was distinguished by an attention to the control population, with the authors stating that an objective of their study was:

> "… to illustrate the use of control groups in a statistical study. The use of controls is routine in experimental work and every experimental group is checked by one or more controls. In statistical studies on cancer, however, control groups are not as frequently used. This paper exemplifies several types of control groups and considers the necessity and advantages in the use of controls in statistical work."

Cases were all 139 cases of penile carcinoma admitted to the Hines, Il VA Hospital from 1931 to 1944. No less than six different control groups were initially proposed, 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 three 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 two Jewish men and four 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 three control groups had been circumcised by the age of three, none of the 139 cases had been circumcised at that age.

Case-control studies in social sciences prior to 1950

A number of investigations in sociology and psychology in the first half of this century were case-control in design. Ernest Greenwood (1945) summarised five such studies from sociology and three from psychology. Accurately, if somewhat wordily, he named the design "ex-post facto effect-to-cause experiments". In six of the eight examples, the cases were juvenile delinquents. Although one might have expected social and psychological factors to be emphasised, four of the studies focused on birth order as the major causal variable of interest. In discussing methodologic issues in such studies, Ernest Greenwood noted, as the central problem, that cases remote in time from the exposure must be a selected set of all cases because of death and other losses, a concern echoed in contemporary discussion of case-control studies in epidemiology (Kelsey et al. 1986).

In survey research it is apparent that there can be a close relationship between the case-control and cross-sectional designs. Indeed, if a cross-sectional survey simultaneously ascertains caseness and interviews individuals about their historical experiences, the raw materials of a case-control study are present, albeit with prevalent cases, and, depending upon the specific exposure and disease, perhaps without a clear sense of directionality from outcome to exposure (Kramer & Boivin 1989). Before the modern refinements in case-control methodology, the difference between the two approaches would have been primarily in feasibility and efficiency; a cross-sectional design would greatly oversample controls, and it is hard to imagine that a cross-sectional design could be used to demonstrate the etiology of a disease as rare as lung cancer.

The "ex-post facto effect-to-cause experiment" has, however, not taken hold in sociology and psychology to anything near the extent it has in epidemiology. The central role of caseness in medicine and epidemiology certainly favors the case-control design. In addition, the design is not readily applied when the outcome variable of interest is continuous, as it so often is in the social sciences.

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Lung cancer, smoking and the case-control study

A leap forward in the use and acceptance of the case-control study came with the studies that implicated cigarette smoking in cancer of the lung published in 1950 in the United States (Levin et al 1950; Wynder & Graham 1950; Schrek et al. 1950) and in Britain (Doll & Hill 1950), the latter study more fully developed in the authors' 1952 publication. These 1950 studies established several features of the modern form of the case-control study, and therefore deserve detailed examination. The success of the four 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.

Before discussing the 1950 studies, we must note that the German literature includes at least one case-control study of smoking and lung cancer (Müller 1939). Franz Müller, about whom little is known other than his membership in the Nazi party, was in conformity with Hitler's abhorrence of smoking when he 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 cases were non-smokers, 16% of controls did not smoke, and heavy smoking was six times as common in lung cancer patients as in controls. This paper was cited by Wynder and Graham (1950), by the Surgeon General's 1964 report on Smoking on Health, and in more recent discussions of historical epidemiology (Susser 1985; Davey-Smith et al. 1994), but it otherwise seems to have been widely ignored.

Schrek et al. – 1950

The Hines, IL VA hospital was again featured in the annals of case-control history as the source of the January 1950 publication of the first of the US case-control studies of lung cancer and smoking (Schrek et al. 1950). 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 (see Fig. 1).

This data set permitted comparison of smoking histories in several case groups (lung cancer, other respiratory cancers, upper digestive cancers) and in different control groups (all other diseases, all other cancers). The authors 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. 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 (or, in the terminology of the authors, "secondary factors"), and smoking rates were examined within strata of age and race. Schrek et al. (1950) concluded: "When age and race were equalized in the control and clinical groups, there still remained a statistically significant correlation between smoking and cancer of the lung and of the larynx and pharynx."

FORM USED IN TAKING THE HISTORIES
OF THE SMOKING HABITS OF PATIENTS

SMOKING HABITS

	Light	Moderate	Heavy	Duration
Cigarette	10 or less	10–20	More than 20	
Cigar	2 or less	2–4	More than 4	
Pipe	3 or less	3–6	More than 6	
None				

Figure 1 Survey instrument used to ascertain smoking history (in Schrek et al. 1950

Levin – 1950

Smoking histories had been obtained routinely upon admission to Roswell Park Memorial Institute, Buffalo, NY, since 1938. Levin et al. emphasised that "Special attention with respect to the history of smoking has not been paid to any single group of conditions, so that these records may be presumed to be free from bias which might result from preconceived ideas as to relation between smoking and a particular form of cancer." Levin et al. controlled for age by age-standardising the smoking prevalences to the age distribution of all 1650 men in the study. No women were studied. Levin et al. (1950) 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. 54.1% of lung cancer patients 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 (as defined at hospital admission) was 8.6%, and among cigarette smokers of > 25 years, 20.7%.

It is notable that both of these early case-control studies of lung cancer (Schrek et al. 1950; Levin et al. 1950) 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 – 1950

Wynder and Graham's study, published in the same issue of JAMA as the Levin et al. paper, designed a survey instrument specifically for their study (see Fig. 2) 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 cases of lung cancer (685) was considerably larger than in either the Levin et al. study (236) or the Schrek et al. study (82). An interesting feature of this study is 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, 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/day for ≥ 20 years) than did controls, whether from chest services or other hospital services, whether interviewed blind to diagnosis or not.

Name:..... Age: .....

1. Have you ever had a lung disease? If so, state time, duration and site of disease:
   Pneumonia Asthma Tuberculosis Bronchiectasis
   Influenza Lung Abscess Chest Injuries Others
2. Do you or did you ever smoke? Yes ☐ No ☐
3. At what age did you begin to smoke?
4. At what age did you stop smoking?
5. How much tobacco did you average per day during the past 20 years of your smoking?
   Cigarettes..... Cigars ..... Pipes .....
6. Do you inhale the smoke? Yes ☐ No ☐
7. Do you have a chronic cough which you attribute to your smoking, especially upon first smoking in the morning? If so, for how long?
   Yes ☐ No ☐
   Duration.....
8. Do you smoke before or after breakfast? Before ☐ After ☐
9. Name the brand or brands, and dates, if any given brand has been smoked exclusively for more than five years.
   Change frequently? ☐

First brand – from 19 . . . . to 19 . . . .
Second brand – from 19 . . . . to 19 . . . .

10. What kind of jobs have you held? Have you been exposed to dust or fumes while working there? (Use back of page for detailed description of possible exposure)

From	To	Position	Dust or Fumes

11. Have you ever been exposed to irritative dusts or fumes outside of your job? In particular have you ever used insecticide spray excessively? If so, state time and duration.
    Yes ☐ No ☐ Type..... Duration .....
12. How much alcohol do you or have you averaged per day? State time and duration in years.
    Whiskey..... Beer ..... Wine.....
13. Where were you born and where have you lived most of your life? State the approximate time span you have lived in a certain locality. Up to what grade did you attend school?
    Birthplace ..... Home ..... Educational Level .....
14. State the cause of death of your parents, and of brothers and sisters, if any.
15. *Site of Lesion* *Microscopic Diagnosis* *Papanicolaou Class* *Etiological Class*

Interviewer .....

Figure 2 Survey instrument used to ascertain smoking history (in Wynder et al. 1950)

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.

Doll and Hill – 1950

This classic study has come to be viewed as a model case-control investigation. Notifications of cancer cases (lung, colon, stomach, rectum) were received from 20 London hospitals, with the latter three 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 five-year age group, and in the same hospital at or about the same time" who did not have cancer. As in Wynder and Graham (1950), 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 six-month re-interview of a subset of subjects showed remarkable consistency in self-reported smoking histories.

Contrasts were made between cases of lung cancer and matched controls in overall smoking, in amount smoked most recently, in maximum ever smoked, in age of onset of smoking and in 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. This yielded estimates of relative risks for lung cancer from smoking 10, 20 and 60 cigarettes per day of 19, 26 and 65; odds ratios were not calculated. However, 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 carcinoma of the lung".

A retrospective account of the events surrounding the publications of these articles has been provided in recent papers in the American Journal of Epidemiology (Armenian & Szklo 1996; Wynder 1997; Terris 1997).

Both the Royal College of Physician's 1962 report entitled "Smoking and Health", and the US Surgeon General's Report of the same title, published in 1964, 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, impressed the committee members who authored the reports, notwithstanding the scarcity of epidemiologists among them. Jeremiah Morris in the UK and Leonard Schuman in the US were the only epidemiologists on these two important official committees examining smoking and health. Nonetheless, the smoking and health reports promoted the general acceptance of the case-control study as a scientific tool in clinical research.

Record and McKeown – 1949, 1950

The studies of smoking and lung cancer are rightly viewed as setting the stage for the modern era of the case-control study. Their influence was no doubt accentuated by the pressing and controversial question they addressed. Also, as we have seen, epidemiologic studies of cancers have been important to the development of the case-control design since the 19th century.

It would be unfair, however, to neglect the contemporaneous, though less well remembered, use of the case-control paradigm in the studies of birth defects by Record and McKeown (1949 and 1950) in Birmingham. Like the studies of lung cancer and smoking, this work was motivated by the shifting health patterns of the time, in this case, the increasing prominence of congenital malformations among infant deaths as other causes of infant mortality declined. In Record and McKeown's case-control study of risk factors for congenital malformations of the nervous system, the first of many such investigations on this topic from the Birmingham group, the design is clearly articulated.

Using vital records of Birmingham 1940–1947, this two-part study identified 930 consecutive cases of congenital nervous system malformation and selected a control group of approximately equal size. The controls were every 200th birth over the seven year period. Exposure data were obtained from vital records and from a home visit in which a maternal interview was conducted. Cases and controls were compared on numerous exposures, including maternal health during pregnancy, season of birth, birth order, and family history of congenital malformations. Though the findings were less immediately salient than those of the smoking and lung cancer studies, the Record and McKeown study stimulated further work on neural tube defects in Birmingham. As Ian Leck has emphasised, the work of another Birmingham investigator – W. H. Smithells – which strongly implicated folic acid deficiency in this disorder (Smithells et al. 1983) "can be traced back to these case-control studies" (Leck 1996).

Arguably, the articulation and execution of this case-control design was better developed – though certainly less influential – than in some of the smoking and lung cancer studies. Indeed, it would be hard to improve upon the design even now. The selection of all cases within a region, and the use of a random sample of all births in the study base as controls, were remarkable for their time. It should be noted too that the cross-sectional and case-control design tend to intersect in this research on congenital malformations, where cases are of necessity ascertained at birth (and are therefore prevalent) rather than at conception.

The co-occurrence of this work with the case-control studies of smoking and lung cancer serves to demonstrate that the case-control design was not an accidental discovery in one field of research; it evolved from the context of the time. The timing of the breakthrough reflected several underlying and interrelated developments: the shifting health profile of the developed countries in the first half of the twentieth century; the corresponding evolution within epidemiology to consider not only infectious diseases, but also cancer and other chronic conditions as falling within its purview; the development of applied statistics; and the social conditions of the years immediately following World War II.

Conclusions

While the first modern case-control study was performed in the 1920's, it was only at mid-century that the press of interest in the relationship of smoking to health provided a problem that could be addressed through the case-control method. A specific chronic disease (lung cancer) was hypothesised to be caused by an individual exposure of long duration (smoking) that was ascertainable through personal interview. 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. In the years since 1950, case-control studies have been greatly refined, but much of their popularity can be attributed to their initial success in linking smoking and cancer.

With the elaboration and wide application of this design over the subsequent half century, significant findings have been many. Diethylstilbestrol and vaginal adenocarcinoma (Herbst et al. 1971), aspirin and Reyes syndrome (Hurwitz et al. 1987), L-tryptophan and eosinophilia-myalgia (Martin et al. 1991), and tampon use and toxic-shock syndrome (Kehrberg et al. 1981) are examples of exposure-disease relationships widely accepted as causal that were uncovered in recent decades by case-control studies. Most importantly, because of 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.

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 populations, 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.

We noted at the end of part I of this paper that the case-control work of Goldberger and Sydenstricker (1920) on pellagra was characterised by the integration of this study form into public health action. More recently, the case-control design has been fitted squarely into the focus on individual level risk factors for noninfectious disease which became the dominant form of epidemiology from 1950 until the end of the century. This focus has been accompanied by a trend towards separating this form of research from a broader multilevel public health agenda. 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.

Zusammenfassung

Ursprünge und frühe Entwicklung der Fall-Kontroll-Studie: Teil 2, die Fall-Kontroll-Studie von Lane-Claypon bis 1950

Janet Lane-Claypon's Brustkrebsstudie im Jahr 1926 war die erste moderne Fall-Kontroll-Studie. Das Design wurde jedoch in den medizinischen und den Sozialwissenschaften nur sporadisch angewendet, bis 1950 vier Fall-Kontroll-Studien über den Zusammenhang von Rauchen und Lungenkrebs veröffentlicht wurden. Diese Studien vereinigten die wesentlichen Bestandteile des Fall-Kontroll-Vergleiches, lösten eine konzeptuelle Verschiebung in der Epidemiologie aus und legten den Grundstein für die schnelle Entwicklung des Fall-Kontroll-Designs in den darauffolgenden 50 Jahren.

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Résumé

Origines et premiers développements de l'étude cas-témoins. Partie 2, de l'étude cas-témoins de Lane-Claypon à 1950
La première étude cas-témoins moderne est celle de Janet Lane-Claypon sur le cancer du sein en 1926. Ce plan d'étude n'a cependant été utilisé que sporadiquement en médecine et en sciences sociales jusqu'en 1950, lorsque quatre études cas-témoins portant sur le tabac et le cancer du poumon furent publiées. Ces études de 1950 synthétisent les éléments essentiels de la comparaison entre cas et témoins et induisent une évolution conceptuelle en épidémiologie. Elles établissent les fondations à partir desquelles le plan d'étude cas-témoins se développera rapidement au cours de la deuxième moitié du siècle.

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