International Journal of Epidemiology
© International Epidemiological Association 1988

Vol. 17, No. 3
Printed in Great Britain

A Collection of 56 Topics with Contradictory Results in Case-Control Research

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Mayes L C (Child Study Center, Yale University School of Medicine, New Haven, Connecticut, USA), Horwitz R I and Feinstein A R. A collection of 56 topics with contradictory results in case-control research. *International Journal of Epidemiology* 1988, 17: 680–685.

This research was done to learn more about the frequency and characteristics of conflicting research in case-control studies. In a survey of the epidemiological and medical literature, we found 56 topics in which the results of a case-control study were in conflict with the results from other studies of the same relationship. Cancer was the associated disease for 30 of the controversial topics. We suggest that much of the disagreement may occur because a set of rigorous scientific principles has not yet been accepted to guide the design or interpretation of case-control research. Consequently, the investigator's 'judgement' is the main precaution against scientific hazards and distortions in the validity of evidence. To correct this deficiency, we propose using the principles of an experimental trial to develop the scientific standards for case-control research.

The contradictory results that can arise from epidemiological studies of the same cause-effect relationship were recently emphasized when a single issue of a leading medical journal contained two reports with opposing conclusions.[1,2] In those reports, the relationship of post-menopausal oestrogen therapy and subsequent coronary artery disease was examined in a large group of women, followed prospectively (or longitudinally) as cohorts. Despite the similar use of the cohort method, the two studies obtained contradictory results.

In the many circumstances in which a cohort study cannot be done, the most popular epidemiological approach has been to use retrospective case-control studies. Because they are so relatively easy to do, they have been applied to study a large number of relationships, and have produced a vast literature of conclusions regarding diseases that were presumably caused or protected against by diverse pharmaceutical, environmental, or other agents. Because the ease of the investigation is accompanied by some major scientific hazards in the validity of the evidence, case-control studies can regularly be expected to produce conflicting results.[3]

Several years ago, in an analysis of some of the methodological problems and standards in case-control studies, two of us[3] reported 17 relationships in which the results of a case-control study conflicted with the results of at least one other epidemiological investigation. Because the 17 relationships had been noted in a casual review of the literature, our survey was regarded as possibly inadequate or biased. Suggestions were made that the contradictions were relatively uncommon events, and that the 17 instances we cited were an atypical collection of 'outlyers', which differed from the usual agreements found in case-control studies.[4]

The current research was done to investigate the subject in a more comprehensive manner and to find any other relationships, beyond the 17 previously cited, in which contradictory results had occurred. Our purpose in the review was not to describe or evaluate methodological sources of the contradictions, but simply to note the characteristics and frequency of relationships in which the conflicts had occurred.

METHODS

For the research, a *topic* was defined as a relationship between an alleged causal agent, such as *reserpine*, and

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the disease associated with that agent, such as *breast cancer*. The topic would be cited as *reserpine/breast cancer*. With the key words of 'case-control', 'controversy', 'case', or 'control', a computer search of the *Index Medicus* for the years 1979–83 generated titles and abstracts for a list of 154 topics.

After all publications identified in this list were examined, the topics selected for further review were those in which either a case-control study had been done or in which the results seemed to contradict previous studies. After examination of the additional studies identified from the corresponding bibliographies, a topic was deemed to have conflicting results if (1) it had received at least two studies, one of which was in the case-control format; and (2) the conclusions of at least one case-control study conflicted with the conclusions of other studies of the same topic. For example, in investigations of the relationship between polyvinyl chloride (PVC) and breast cancer, the results were negative with a case-control study, but positive with a cohort design.[227,228]

Our search of the literature was thorough, but not intended to be exhaustive. Our 'index' publications covered only a five-year period (1979–83) and we included only those topics in which conflicting results were clearly apparent. In addition, we excluded the many topics in which contradictory studies existed for various relationships between sexual hormones and birth defects. The latter relationships could have added more than 40 additional topics to our list, because of the diverse ways in which individual birth defects and individual sexual hormones had been studied separately or in various combinations.

Each publication on each selected topic was classified according to whether the proposed association between agent and disease was regarded as causal or protective, and whether the investigators had interpreted their results as supporting or not supporting the proposed association. We also noted the particular period of calendar years that were covered for the patients under investigation.

RESULTS

The 56 topics that were noted and cited in this review are listed in Table 1. The table is organized according to the proposed agents, with subsidiary entries listed for each disease associated with that agent. The studies for which the proposed relationship was protective rather than causal are shown with an asterisk. The studies marked 'supportive' were those that supported the proposed relationship, whether it was causal or protective. The studies marked 'non-supportive' showed either no distinctive relationship, or a relationship going in the opposite direction. The 17 topics noted in our previous research are also included here, and (for the convenience of readers) we have cited the individual references for the contradictory studies of those topics.

Table 1 shows that 50 of the proposed relationships were causal and 6 were protective. Although the individual results are not cited in Table 1, the 262 studies that are referenced in that table contain 185 case-control studies, 64 cohort studies, and 13 with other designs, such as ecological association (or 'heterodemic') research. Overall, cancer was the associated disease for 30 of the controversial topics, including 13 of the 27 medical or pharmaceutical exposures, 9 of the 16 biological exposures, and 8 of the 14 occupational or environmental exposures. The earliest case-control study included among the 56 controversial topics was published in 1929,[151] and the longest interval between studies for any single topic was 39 years (lactation and breast cancer).

DISCUSSION

This review has led to the identification of 39 additional topics, beyond the 17 cited earlier, in which the results of a case-control study are in conflict with results from other studies of the same relationship. The number of topics would have been substantially higher if we had included studies of birth defects and antecedent exposure to sexual hormones.

The results are particularly impressive because we did not try to find every possible example of these conflicts. The prevalence of contradictory results in case-control research is doubtless much higher than we have cited. In fact, since completing our computer search and review of the topics listed in Table 1, we have heard of about 20–30 additional topics that could have been added to the list of contradictions.

The problem of contradictory results is not unique to case-control research. Contradictions can arise whenever causal relationships are investigated in studies where the compared agents did not receive randomized experimental assignment, and where the groups and data are collected without deliberate strategies to avoid or reduce bias. The frequency of the problem may be increased in case-control studies, however, because the case-control format is both easy to use and easily affected by important biases. The bias can be either innate in the assembled evidence, or induced by the investigative decisions and methods.

Although often conceived and interpreted as a statistical exercise in sampling from an available 'pool' of cases and controls, a case-control study is done as a substitute for the experimental trial that was scien-

TABLE 1 *Controversial topics by agent and disease*

	Years spanned by studies	Number supportive	Reference listing	Number non-supportive	Reference listing
I. *Medical or pharmaceutical exposures*					
A. *Oral contraceptives*					
1. *Benign breast disease	1971–1976	4	6,7,8,9	2	7,10
2. Breast cancer	1975–1983	2	5,11	3	12,13,14
3. Cervical cancer	1965–1972	3	15–17	4	18–21
4. Melanoma	1977–1980	1	22	1	23
5. Multiple births	1977–1981	1	24	2	25,26
6. *Ovarian cancer	1981–1983	6	27–32	2	33,34
7. Prolactinomas	1979–1982	1	35	2	36,37
8. *Rheumatoid arthritis	1978–1983	3	38–40	1	41
9. Stroke	1969–1973	3	42–44	1	45
10. Thromboembolism	1968–1971	4	43,44,46,47	1	48
B. *Other contraceptives*					
1. IUD and limb deformities	1976–1983	2	49,50	3	51–53
2. Spermicides and Down's syndrome	1980–1982	2	54,55	2	56,57
C. *Other pharmaceutical substances*					
1. *Aspirin and myocardial infarction	1974–1975	2	58	1	59
2. Anesthesia and abortion	1971–1984	3	60–62	3	63–65
3. Oestrogens and breast cancer	1962–1982	3	11,66,67	5	68–72
4. Oestrogens and endometrial cancer	1967–1978	5	73–77	2	78–80
5. Diazepam and birth defects	1975–1983	2	81,82	1	83
6. Reserpine and breast cancer	1974–1977	3	84–86	8	87–94
D. *Surgical/Radiographic Procedures*					
1. Appendectomy and cancer	1964–1974	3	95–97	5	98–102
2. Cervical biopsy and preterm delivery	1969–1979	1	103	1	104
3. Cholecystectomy and large bowel cancer	1978–1982	3	105–107	1	108
4. Circumcision and cervical cancer	1954–1967	2	109,110	6	111–116
5. Gastrectomy and amyotrophic lateral sclerosis	1969–1979	2	117,118	1	119
6. Mammography and breast cancer†	1976–1984	5	120–124	2	125,126
7. Tonsillectomy and Hodgkin's disease	1971–1975	2	127,128	3	128–130
E. *Radiotherapy*					
1. I^{131} and breast cancer	1974–1983	1	131	1	132
2. Leukaemia	1958–1968	7	133–139	5	139–143
II. *Biological exposures*					
A. *Infections or vaccines*					
1. Bacteraemia and adverse pregnancy outcomes	1960–1981	1	144	2	145,146
2. Herpes and cervical cancer	1969–1971	1	147	1	148
3. Pertussis vaccine and infantile spasm	1981–1983	1	149	1	150
4. Tuberculosis and cancer	1929	1	151	1	152
B. *Biological exposures*					
1. Aflatoxin and Reye's syndrome	1972–1980	3	153–155	1	156
2. *Breast feeding and infantile eczema	1953–1981	5	157–161	2	162,163
3. Serum cholesterol and colon cancer	1967–1981	3	164–166	2	167,168
4. Menarche and breast cancer	1956–1971	3	169–171	3	172–174
5. *Parity and colorectal cancer	1981–1982	1	175	1	176
6. Pregnancy risk factors and cleft palate	1975	1	82	1	177
C. *Other diseases*					
1. Allergy and malignancy	1955–1975	4	178–181	4	180,182,183, 184
2. Benign prostatic hypertrophy and prostatic cancer	1974	2	185	1	186
3. Lactation and breast cancer	1931–1970	2	187,188	4	169,170,189
4. Sickle cell disease and glaucoma	1967–1983	2	190,191	1	192
5. Thyroid disease and breast cancer	1976–1981	1	193	4	194–197
6. Birth characteristics/child abuse	1971–1983	2	198,199	2	200,201

TABLE 1 *Continued*

	Years spanned by studies	Number supportive	Reference listing	Number non-supportive	Reference listing
III. *Occupation, life style, or environment*					
A. *Alcohol and bladder cancer*	1980–1983	2	202,203	1	204
B. *Coffee*					
1. Bladder cancer	1968–1975	3	205–207	2	208,210
2. Congenital defects	1980–1983	1	209	2	210,211
3. Myocardial infarction	1972–1976	2	212,213	3	214–216
C. *Home, occupation, chemical*					
1. Dogs and multiple sclerosis	1977–1982	4	217–220	3	221–223
2. Iron oxide and lung cancer	1970–1979	1	224	1	225
3. Organic solvents and glomerulonephritis	1972–1980	5	226–229	1	230
4. PVC and breast cancer	1980–1981	1	231	1	232
5. Textile work and oral cancer	1961–1982	2	233–235	1	236
6. Rubber work and lung cancer	1976–1982	2	237,238	1	239
D. *Saccharin and bladder cancer*	1974–1983	1	240	8	241–248
E. *Smoking*					
1. Cervical cancer	1980–1983	2	249,250	1	251
2. Diabetic retinopathy	1977–1983	2	252,253	3	254–256

* = protective
† = diagnostic association

tifically preferable but logistically unfeasible. In statistical reasoning, a rigorous set of principles has been developed and can be applied for the inference used to interpret results when a sample substitutes for the desired population that could not be examined. In scientific reasoning, however, an analogous set of principles has not yet been generally accepted and applied. No established standards of 'scientific inference' are used to interpret results when a case-control study substitutes for the randomized trial that could not be conducted.

In the absence of rigorous scientific principles, case-control studies depend on arbitrary decisions by the investigator. The decisions may seem justified by entrenched tradition, authoritative convention, or personal reputation—but not by established standards of scientific inference. In such circumstances, conflicts, contradictions, and controversies will be inevitable and abundant.

We have suggested elsewhere[257,258] that scientific standards for non-experimental research can be attained by using the principles of an experimental trial to choose groups, obtain data, and analyse results. Many of the principles of a scientific experiment—such as appropriate eligibility criteria for admission and suitable standards for detection of disease—can be employed despite the lack of randomization. In addition, suitable prognostic stratifications or other adjustments can be used to deal with the susceptibility bias that may arise in the absence of randomization. Other scientific principles can be applied to avoid transfer bias in the collected groups, ascertainment bias produced by investigators or patients, or exclusion bias created by the investigators' choice of groups.

The use of these scientific principles may not be promptly welcomed by investigators who have long worked without them and who have relied instead on authoritative customs, traditions, or beliefs. Since science has always depended on suitable evidence and suitable logic, rather than authoritative beliefs, an improved scientific quality and 'stability' of results in case-control studies will require the development and application of rigorous standards for scientific, rather than statistical inference.

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(Revised version received July 1987)