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POINT-COUNTERPOINT

Bias in the Evaluation of Low-Magnitude Associations: An Empirical Perspective

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In nonexperimental research, the possible existence of bias can never be entirely eliminated, and our ability to infer causation is correspondingly limited (1). If, however, in any reasonably well-conducted study the magnitude of an association is large relative to any plausible biases that may be present, we may judge that it would persist even if those biases could be eliminated (2). In cancer epidemiology, for example, it is no accident that one of the early associations to be identified was between smoking and lung cancer (3), the presence of bias notwithstanding. Both the disease and the exposure were common, and the association was exceedingly strong. That association was correctly identified despite clear evidence (in retrospect) of selection bias (the inclusion of controls with smoking-related disorders such as chronic bronchitis) (4, 5).

By contrast, if an association is of relatively low magnitude (defined here as a relative risk estimate of less than 2.0), it may not be possible to judge whether or not it can be entirely accounted for by bias. Yet, we are confronted by the dilemma that in the evaluation of the risk of common diseases in relation to common exposures, even small relative risk increments, well below 2.0, may have profound public health implications. If, for example, the current use of estrogens for 5 or more years increases the risk of breast cancer by some 1.35-fold, as has been suggested (6), that association would pose a major public health problem: The baseline incidence of the disease is high, and the relative increment in the risk would translate to a high absolute risk among exposed women.

As modern epidemiology has evolved, improved insight into potential sources of bias and refinements of statistical and epidemiologic methodology have enabled us to design more rigorous studies and to analyze them with greater precision. In addition, to come to grips with whatever biases may still be present despite such refinements, techniques of sensitivity analysis have been developed to quantify the impact of residual biases under various assumptions and, thus, to help guide us in our judgment (7). Other approaches have also been suggested (8–13). Such advances may sometimes improve our ability to evaluate the validity of smaller associations than was previously feasible. For example, an association that becomes stronger when it is assessed in a population at low baseline risk or when nondifferential misclassification is reduced would favor causation (11). However, the difficulty may remain unresolved when all that exists is a weak association or a series of weak associations (9). In practical terms, a point in the gradient of declining relative risk must be reached at which the amount of bias that may result in a spurious effect becomes so small that it cannot realistically be ruled out. It is the purpose of this essay to explore where that point may be, empirically, by reference to the "real life" example of breast cancer risk in relation to the use oral contraceptives (14, 15).

ORAL CONTRACEPTIVES AND BREAST CANCER

In 1996, findings were reported from a meta-analysis (or collaborative reanalysis, the designation used by

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the investigators) of 54 studies of breast cancer risk in relation to the use of oral contraceptives (14, 15). The "raw" data from the individual studies were suitably recoded when necessary, pooled, and reanalyzed; 53,297 cases (more than 90 percent of all cases evaluated epidemiologically anywhere in the world) and 100,239 controls were compared. Most of the data were derived from case-control studies; prospective studies were included by means of a nested case-control design with four randomly matched controls for each case. Relative risks (odds ratios) adjusted for confounding were estimated by a modification of the Mantel-Haenszel method.

Overall, 41 percent of the cases and 40 percent of the controls had ever used combined oral contraceptives, and the relative risk estimate was 1.07 ($2p$ = 0.00005). In a subset of 46,330 cases and 85,464 controls for whom the relevant data were available, the relative risks according to intervals after stopping oral contraceptives were as follows: among those who were still using them or who had stopped less than a year previously (current users), 1.24 (95 percent confidence interval: 1.15, 1.33) and among those who had stopped 1–4, 5–9, and 10 or more years previously, 1.16 (95 percent confidence interval: 1.08, 1.23), 1.07 (95 percent confidence interval: 1.02, 1.13), and 1.01 (95 percent confidence interval: 0.96, 1.05), respectively. The trend within users was statistically significant ($p <$ 0.00001). The findings were interpreted as indicating that "women who are currently using combined oral contraceptives or have used them in the past 10 years are at slightly increased risk of having breast cancer diagnosed" (14, p. 1713).

Consider the possible effects of bias. With regard to possible information bias (a problem in the case-control studies), it is unlikely that awareness of the hypothesis would have induced the cases to report exposures that did not actually take place. Bias could more readily have occurred if the controls tended more commonly than the cases to forget having been exposed. Such underreporting would probably have been greatest among women who stopped their use of oral contraceptives many years previously, especially those who were short-term users.

With regard to possible selection bias, good medical practice requires that oral contraceptive users should undergo regular breast examinations. They are also advised to continue to do so after they stop using oral contraceptives and to have mammograms as they become older. In both the case-control and the follow-up studies, more intensive screening among ever users could thus have given rise to bias (16). First, there could have been a tendency for screening to result more commonly in the detection of additional cases of otherwise occult breast cancer among exposed than among nonexposed women. If so, such otherwise occult cases could have been detected both among current users who, presumably, would have been under the most intensive surveillance and among ex-users in whom the prevalence of potentially detectable breast cancer was higher because of their more advanced age. Second, exposed cases could have tended to be diagnosed earlier than otherwise, so that the time since last oral contraceptive use was reduced.

Below, two questions are explored for which it is assumed that there is no association between the use of oral contraceptives and breast cancer. First, under the most parsimonious assumptions, how much information or selection bias would result in an overall relative risk estimate of at least 1.07? Second, could such bias also result in an estimate of at least 1.24 for current users of oral contraceptives, followed by a decline as the interval since last use increases?

AN ARITHMETICAL EXERCISE

In the collaborative reanalysis (14, 15), the percentage rates of exposure to oral contraceptives among the cases of breast cancer were as follows: currently exposed, 5 percent; and last exposed 1–4, 5–9, and more than 10 years previously, 6, 9, and 19 percent, respectively. Here, those proportions are approximated.

Consider a hypothetical, population-based case-control study (table 1) in which 100 cases are identified and compared with 100 controls; 40 cases have ever used oral contraceptives, five of them currently, and five, 10, and 20, respectively, stopped 1–4, 5–9, and more than 10 years previously. Within each category, the dates of diagnosis are equally distributed over time. On the null, the distribution of oral contraceptive use among the controls is the same as that among the cases. Make the following assumptions (table 2):

TABLE 1. Oral contraceptive use and breast cancer, hypothetical distribution of exposure among 100 cases and 100 controls

Oral contraceptive use	Cases	Controls	Relative risk
Never	60	60	1.00*
Ever	40	40	1.00
Time since last use (years)			
0–1	5	5	1.00
1–4	5	5	1.00
5–9	10	10	1.00
≥10	20	20	1.00
Total	100	100	

* Reference category.

TABLE 2. Oral contraceptive use and breast cancer, separate and combined effects of information and selection bias on overall relative risk estimates

Information bias (no. of controls misclassified)	Selection bias (no. of additional exposed cases diagnosed)	Oral contraceptive use	Cases	Controls	Relative risk
0	0	Never	60	60	1.00*
		Ever	40	40	1.00
1	0	Never	60	61	1.00*
		Ever	40	39	1.04
2	0	Never	60	62	1.00*
		Ever	40	38	1.09
0	1	Never	60	60	1.00*
		Ever	41	40	1.03
0	2	Never	60	60	1.00*
		Ever	42	40	1.05
1	1	Never	60	61	1.00*
		Ever	41	39	1.07
2	1	Never	60	62	1.00*
		Ever	41	38	1.11
1	2	Never	60	61	1.00*
		Ever	42	39	1.09
2	2	Never	60	62	1.00*
		Ever	42	38	1.14

* Reference category.

1. Information bias. None of the cases misreport their exposures; one to two exposed controls report that they were not exposed. That is, none of the exposed cases and 2.5–5 percent of the exposed controls are misclassified as nonexposed.
2. Selection bias. Screening among women who have used oral contraceptives results in the identification of one or two additional cases of breast cancer in the study base, increasing the total number of exposed cases to 41 or 42 and the overall total to 101 or 102. That is, selection bias results in the augmentation of the total of exposed cases by 2.5–5 percent and of the total of exposed plus nonexposed cases by 1–2 percent.

Overall relative risk estimates

Under these assumptions, table 2 gives separate and combined relative risk estimates. If only information bias is present and one or two controls are misclassified, the relative risk estimates are 1.04 and 1.09, respectively. If only selection bias is present and one or two additional exposed cases are identified in the study base, the estimates are 1.03 and 1.05, respectively. For the combination of information bias affecting one control and selection bias resulting in the identification of one additional case, the relative risk estimate is 1.07. All other combinations yield estimates that are higher.

Time-specific relative risk estimates

Consider the combination in table 2 in which information bias results in the misclassification of one control, selection bias results in the identification of one additional exposed case, and the overall relative risk estimate is 1.07. Make the following further assumptions (table 3):

1. Information bias. The control who forgets her exposure last used an oral contraceptive 10 or more years previously.
2. Selection bias. The additional exposed case identified as a result of screening is divided equally among the four time categories. In addition, among the exposed cases, screening also advances the time of diagnosis of breast cancer, so that within each category of time since last use, the most recently exposed case shifts to the adjacent earlier category. Thus, in the category of last use 10 or more years previously, one case is lost; in each of the categories of last use 1–4 and 5–9 years previously, one case is lost and one is gained; and among the currently exposed cases, one case is gained. In the close-ended time categories, these shifts translate to aggre-

TABLE 3. Oral contraceptive use and breast cancer, combined effects of information* and selection* bias on time-specific relative risk estimates

Oral contraceptive use	Cases	Controls	Relative risk
Never	60	61	1.00†
Ever	41	39	1.07
Time since last use (years)			
0–1	6.25	5	1.27
1–4	5.25	5	1.07
5–9	10.25	10	1.04
≥10	19.25	19	1.03
Total	101	100	

* Assumptions: information bias: one control last exposed ≥10 years previously misclassified as nonexposed; selection bias: 1) one additional exposed case identified in the study base and assigned equally to each time category, 2) time of diagnosis among exposed cases advanced by one case per category.

† Reference category.

gate advances in the time of diagnosis of 6 months or less; if the open-ended category of last use 10 or more years previously is assumed to be 10–29 years, the advance is again 6 months.

Under these assumptions (table 3), for current oral contraceptive users and those who stopped 1–4, 5–9, and 10 or more years previously, the relative risk estimates are 1.27, 1.07, 1.04, and 1.03, respectively.

Finally, under analogous assumptions, for all associations with overall relative risk estimates greater than 1.07, the relative risk estimates for current oral contraceptive users are 1.24 or greater and are higher than the estimates in the remaining time categories (table 4).

DISCUSSION

In the collaborative reanalysis of oral contraceptive use in relation to the risk of breast cancer (14, 15), the overall relative risk estimate for ever users of oral contraceptives was 1.07. For current users, it was 1.24, and it declined with increasing time since last use to a value of 1.01 among women who stopped 10 or more years earlier. In this exercise, the null has been assumed, and under parsimonious assumptions concerning the possible combined effects of information and selection bias, that pattern has been closely replicated. If it is assumed that the only source of information bias was the underreporting of oral contraceptive use by 2.5 percent of the exposed controls and that the only effect of selection bias was augmentation of the number of exposed cases by 2.5 percent (and of the total case series by 1 percent), that combination would also have yielded an overall relative risk estimate of 1.07. If surveillance for breast cancer among oral contraceptive users also advanced the aggregate time of diagnosis by 6 months, the estimate for current users would have been 1.27, and there would again have been a decline to an estimate of 1.03 among women who stopped 10 or more years earlier. Are these assumptions plausible?

Information bias

In the collaborative reanalysis, about 25 percent of ever users had taken oral contraceptives for less than 1 year, and among those last exposed 10–19 and 20 or

TABLE 4. Oral contraceptive use and breast cancer, separate and combined effects of information* and selection* bias on overall and time-specific relative risk estimates

Information bias (no. of controls misclassified)	Selection bias (no. of additional exposed cases diagnosed)	Oral contraceptive use	Years since last oral contraceptive use						Total		
			0–1			≥1					
			Cases	Controls	Relative risk	Cases	Controls	Relative risk	Cases	Controls	Relative risk
1	0	Never	60	61	1.00†	60	61	1.00†	60	61	1.00†
		Exposed	6	5	1.22	34	34	1.02	40	39	1.04
2	0	Never	60	62	1.00†	60	62	1.00†	60	62	1.00†
		Exposed	6	5	1.24	34	33	1.06	40	38	1.09
0	1	Never	60	60	1.00†	60	60	1.00†	60	60	1.00†
		Exposed	6.25	5	1.25	34.75	35	0.99	41	40	1.03
0	2	Never	60	60	1.00†	60	60	1.00†	60	60	1.00†
		Exposed	6.5	5	1.30	35.5	35	1.01	42	40	1.05
1	1	Never	60	61	1.00†	60	61	1.00†	60	61	1.00†
		Exposed	6.25	5	1.27	34.75	34	1.04	41	39	1.07
2	1	Never	60	62	1.00†	60	62	1.00†	60	62	1.00†
		Exposed	6.25	5	1.29	34.75	33	1.09	41	38	1.11
1	2	Never	60	61	1.00†	60	61	1.00†	60	61	1.00†
		Exposed	6.5	5	1.32	35.5	34	1.06	42	39	1.09
2	2	Never	60	62	1.00†	60	62	1.00†	60	62	1.00†
		Exposed	6.5	5	1.34	35.5	33	1.11	42	38	1.14

* Assumptions: information bias: 0–2 controls misclassified as nonexposed; selection bias: 1) 0–2 additional exposed cases identified in the study base; 2) time of diagnosis among exposed cases advanced by one case per category.

† Reference category.

more years previously, the proportions were 35 and 62 percent, respectively; 50 percent of these short-duration exposures were for 3 months or less (15). Underreporting of such short episodes, especially if they took place many years earlier, could readily have occurred more commonly among the controls, since they may not have been as motivated as the cases to remember their exposures.

In the collaborative reanalysis, the great preponderance of the data was from case-control studies, and the investigators acknowledged that they could not rule out information bias (15). To assess its possible effects, they performed sensitivity analyses in which women who used oral contraceptives for less than 1 year were reclassified as never users; the relative risk estimates were hardly changed. Those analyses, however, may not have eliminated information bias, since memory loss could also have been greater among controls than among cases who used oral contraceptives for more than 1 year, particularly if the total durations comprised multiple episodes of use, each relatively brief.

Validation studies (or more properly, replication studies) have been interpreted as suggesting that current or recent oral contraceptive use is reported reasonably accurately (17–19). However, the studies have varied in their definition of what constitutes adequate replication among data sources. None of them have excluded misclassification of exposure of the order of 2.5 percent, even for recent use, and even if such use was of long duration. With regard to use that ended in the distant past, whether of short or long duration and whether in single or multiple episodes, there have been no satisfactory studies. With regard to replication of reported never use of oral contraceptives, there have been no studies at all. It is important to stress this latter point, since inflation of the reference category of nonexposed controls, as a result of the misclassification of exposed controls, is the postulated source of information bias.

Most of the case-control studies in the collaborative reanalysis were interview based or they used mailed questionnaires, and there was widespread and well-publicized concern about breast cancer risk from the time oral contraceptives were introduced. Some degree of information bias was thus unavoidable and was likely to have been in the same direction among the studies. Some of the studies were egregiously biased. For example, in one study (20), each of the cases was questioned in a face-to-face interview by a single male physician, while the controls were interviewed by telephone by two female nurses—circumstances that rendered bias all but inevitable. In another study (21, 22), the hypothesis was announced on the facing page of a questionnaire mailed to cases and controls—again a circumstance that made bias virtually inevitable.

Other case-control studies attempted to minimize information bias, by the use of structured questionnaires, for example, with contraceptive histories recorded in relation to a calendar of reproductive events (23). However, on the basis of the above considerations, it would be impossible to demonstrate that even the most rigorous of them could have excluded greater underreporting of oral contraceptive use by controls, relative to cases, of the order of 2.5–5 percent.

Selection bias

It is established that screening facilitates the early detection of breast cancer (16, 24) that might otherwise remain clinically silent for many years. Indeed, it is specifically because the most effective screening tool, mammography, advances the time of diagnosis that it has been advocated as standard public health policy since the late 1960s. Thus, in many of the studies included in the collaborative reanalysis, more intensive screening among exposed women would likely have resulted in the selective identification of an excess of cases that might otherwise not have been diagnosed or might only have been diagnosed after the studies were completed (16). By the same token, more intensive screening among oral contraceptive users would also have advanced the aggregate date of diagnosis among exposed cases.

If screening accounts wholly or partly for the associations with oral contraceptive use, those associations should be strongest among women with the least advanced tumors. This was the case in the collaborative reanalysis (15): Among women with cancer localized to the breast and those with spread beyond the breast, the relative risk estimates for current oral contraceptive users were 1.24 and 1.10, respectively. The corresponding estimates among women who stopped 1–4, 5–9, 10–14, and 15 or more years previously were, respectively, 1.16 and 1.08, 1.06 and 0.96, 0.97 and 0.91, and 1.13 and 0.95.

The authors stated that these differences "...offer only indirect evidence about the possible effects of different surveillance patterns, and merit further investigation. They do not, however, provide an explanation for the elevated risk of breast cancer among recent users" (15, p. 205). As shown here, that conclusion is incorrect: It is precisely among the most recently exposed women that bias due to more intensive screening among oral contraceptive users would tend to produce the highest apparent elevation in the risk. Moreover, that pattern would be evident even if no other bias were present and even if the only effect of

screening was to advance the date of diagnosis among the most recently exposed women.

As opposed to information bias, a problem confined mainly to the case-control studies, selection bias due to screening could have affected both the case-control and the follow-up studies. Indeed, such bias might well have been more severe among the latter. In the three largest follow-up studies, the Nurses Health Study (25), the Royal College of General Practitioners' Oral Contraception Study (26), and the Oxford Family Planning Study (27), the participants were aware of the hypothesis, and differential screening for breast cancer according to exposure status could have been more intense than in the population at large.

Based on the above considerations, there is a strong likelihood, supported by quantitative evidence, that more intensive screening among oral contraceptive users gave rise to selection bias in the collaborative reanalysis. Such bias could also have contributed to the overall relative risk estimate of 1.07, and it could readily have accounted for estimate of 1.24 among current oral contraceptive users, followed by a decline as the interval after stopping increased to 10 or more years.

In this exercise, only two specific sources of bias, information bias due to underreporting of exposure by the controls and selection bias due to differential screening among oral contraceptive users and nonusers, have been considered. In practice, of course, there could also have been multiple additional sources of bias. To give just two examples, information bias could also have occurred if the cases and controls tended to remember the dates of last exposure to oral contraceptives differently, and selection bias could have occurred in case-control studies with poor enrollment rates or in cohort studies with poor follow-up rates. Confounding could also have biased the results; socioeconomic status, for example, is a well-established indicator of breast cancer risk (28), and it is also a determinant of oral contraceptive use, is difficult to measure, and, hence, is difficult to control.

Each of these additional potential sources of bias might have either increased or attenuated the overall and time-specific relative risk estimates, depending on their direction. The point, however, is that their possible existence renders the interpretability of the small relative risk increments identified in the collaborative reanalysis all the more opaque. In this specific example, for relative risk estimates on the order of 1.07 or 1.24, it is simply not possible to distinguish between bias and causation as explanations for the observed associations. In addition, it is unlikely that refinements of epidemiologic or statistical methods, sensitivity analyses, validation studies, etc., can get around the difficulty.

Thus far, this essay has focused on the specific example of the relation of oral contraceptive use to the risk of breast cancer. The wider implication, however, is that we can seldom, if ever, be completely confident about inferring causality for any low-magnitude association identified in observational data except perhaps when a high-magnitude relative risk can be identified in a study of a population at low baseline risk or in a study that has minimal nondifferential misclassification (11). Nonexperimental methods excel at the documentation of large associations, not small ones. To be sure, the particulars concerning potential sources of bias may vary from study to study, but quantitative exercises analogous to this one would consistently reveal how little bias it takes to produce associations of low magnitude.

To illustrate that point, consider the relation of hormone replacement therapy (predominantly unopposed estrogens) to breast cancer risk, also analyzed in the collaborative reanalysis (6). Among current users or those who stopped 1–4 years previously, the relative risk increased by a factor of 1.023 for each year of use. For women exposed for 5 or more years, the relative risk was 1.35 (95 percent confidence interval: 1.21, 1.49). The only major difference between this analysis and that of oral contraceptive use (14, 15) is that for hormone replacement therapy, there appeared to be a duration effect—a difference that is not surprising since oral contraceptives are used intermittently at times when women do not wish to become pregnant, while hormonal replacement therapy tends to be continuous. That distinction apart, the assumptions concerning information and selection biases evaluated in this exercise are readily applicable to the analysis of hormone replacement therapy. Again, for a relative risk estimate of 1.35, it is not possible to distinguish between bias and causation.

Next, some broader generalizations. One advantage (or possibly, a disadvantage) of having access to massive amounts of exposure and outcome data is that it becomes possible to document low-magnitude associations within narrow confidence intervals and, thus, for practical purposes, to rule out chance. It might perhaps be argued that a meta-analysis is less reliable in that regard than a single, massive study because of the potential for multiple biases in multiple studies. However, given the persistence of any systematic bias, augmentation of the sample size simply increases the statistical robustness of any observed association, regardless of whether it is derived from a single, large study or a meta-analysis.

These considerations are especially germane as they apply to claims that associations such as those observed, for example, between passive smoking and

lung cancer (relative risk = 1.26) (29), trans fatty acids and myocardial infarction (relative risk = 1.50) (30, 31), or alcohol and breast cancer (relative risk = 1.24) (32) are causal. It is sometimes argued that it is important to interpret such small risk increments as "real" because the diseases are common, and hence, the absolute risks are high. Thus, even in the absence of full reassurance about the absence of bias, it may be prudent policy to act as if such associations are indeed causal. How to act in the public interest in the face of marginal evidence is, of course, a matter of judgment. However, neither importance nor prudence nor judgment is a criterion of scientific validity. As a matter of good science, these considerations cannot be invoked as if they constitute bolstering evidence, in conjunction with a low-magnitude associations, to justify causal inferences.

Finally, this exercise serves to demonstrate that relative risk point estimates derived from nonexperimental studies are, by their nature, crude and imprecise. Given the small amounts of bias that it takes to distort such estimates, their expression to more than one decimal place is pseudoprecision. Yet, for low-magnitude associations such as in the collaborative reanalysis and in the examples mentioned above, this practice is common, perhaps in the mistaken belief that such pseudoprecision somehow confers validity to associations that are not, in fact, demonstrably valid.

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