EDITORIALS

Induced Abortion, Bias, and Breast Cancer: Why Epidemiology Hasn’t Reached Its Limit

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Once again we are faced with the difficult task of judging a body of epidemiologic evidence. The issue, induced abortion and breast cancer, is about as thorny as it gets in modern American medicine (1). For us, the task at hand is more a matter of separating statistical association from spurious coincidence than of separating causal associations from noncausal. Making these judgments in the face of considerable uncertainty and complexity is a serious matter, requiring prudence and the superimposition of qualitative methods on quantitative. And it is a necessary matter, underscoring the importance of epidemiology for public health and for the practice of medicine.

Epidemiologic studies are sometimes the only practical (or ethically acceptable) way to link exposures to human disease. Perhaps because epidemiology is so important, it often undergoes intense scrutiny from editors, journalists, and from its own practitioners (2-5). In the most recent spate of critique, a familiar theme has resurfaced: Epidemiologic studies are subject to bias, systematic influences creating the illusion of relationships when none exist. For epidemiologists, bias calls for great care in inference-making. For the public and the press, bias is very unsettling, conflicting results and interpretations even more so.

Bias, for example, has been touted by a Science news reporter as the reason why epidemiology has reached its “limit” in its capacity to understand the determinants of disease in human populations (3). Judging from the report by Rookus and van Leeuwen (6) in this issue of the Journal, nothing could be further from the truth. In a creative and fortuitous way, Rookus and van Leeuwen examine bias in a study of abortion and breast cancer, joining others who have found similar results in the complex relationships among hormones, pregnancies, women’s choices, and breast cancer risk (7-9). Their work and the work of others (10) give credence to the idea that the modest relationship reported in studies stretching back four decades can be explained, at least in part and perhaps even in large measure, by reporting (recall) bias. The bias arises when women are asked whether they have ever had an abortion. For very personal and perhaps even subconscious reasons, women—especially healthy women—underreport this emotionally laden decision.

Bias is not the whole story. A judgment of epidemiologic evidence requires many parallel considerations: the extent to which confounders have been controlled and the study designs employed, such as case-control, cohort, or randomized trials. In addition, judgments take into consideration the magnitude of the effect, consistency, temporality, biologic plausibility, dose-response, and an overall sense of coherence (11). An assessment of bias is also important, and recall bias is but one of many types. A recent addition to the list is “wish” bias, the extent to which a reviewer believes a priori that the hypothesis is true (12). In its most extreme form, wish bias becomes a belief maintained regardless of what the evidence shows. The philosopher Quine has pointed out that experience can never force one to reject any particular belief (13).

Typically, inferential judgments appear in reviews, editorials, textbook chapters, and reports of organizations (14). The judgments in these publications reflect the scientific values of the author, which may differ as a result of training, professional development, and other factors (15). Put another way, the evidence does not “stand alone,” not in medical science and not in journals that report its results. There is no proof akin to that found in theoretical mathematics (16). Evidentiary assessments, even when expressed in quantitative terms, are more qualitative than most lay persons appreciate. Although quantitative concepts are undeniably relevant, in the end our judgments are qualitative. Even strength of association, a very quantitative idea, enters into judgments in terms of the very qualitative consideration of the extent to which unknown (and therefore unmeasurable) confounders exist. Meta-analyses, which combine several studies in a quantitative algorithm, cannot solve the basic epistemological problem. Meta-analyses may increase statistical precision and narrow confidence intervals around estimates of effect, but they cannot correct for confounders or for biases. In the end, meta-analyses provide an assessment of consistency, one—but only one—of the many parallel considerations important in inference-making. And even consistent findings may hide systematic error.

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Two recent reviews of the evidence on induced abortion and breast cancer (17,18) illustrate these ideas. Published 1 month apart, they reveal contradictory conclusions. In September, Michels and Willett (17) wrote that the current evidence is "inadequate to infer...a relationship between induced...abortion and breast cancer risk." For them, the relationship may be "nonexistent." In October, Brind and colleagues (18) wrote that induced abortion is a "significant independent risk factor." For what they call a "public health tragedy," excess breast cancer cases attributed to induced abortion were calculated.

How can two reviews, published so close together, produce such different assessments? The answer does not lie in selection of studies reviewed. Both reviews carefully describe their search techniques and exclusion criteria. Moreover, nearly the same sets of studies were included: those which distinguished induced abortions from spontaneous abortions. The most obvious difference between the two reviews is that the one by Brind et al. (18) includes a meta-analysis which produced a statistically significant, modest elevation in risk associated with induced abortion (a weighted odds ratio of 1.3). Brind et al. included the results of a cohort study among 20 case-control studies; they made no attempt to constrain the analysis on the basis of quality criteria. We take greater issue, however, with their interpretation of the results, dismissal of the study's limitations, and their blurring of association with causation.

Our concerns go beyond the fact that the overall odds ratio is small. One issue is how easily Brind et al. (18) dismiss bias. They argue that any bias is unlikely to have been responsible for their finding because there is "consistency across the independent studies," as reflected in the overall result of the meta-analysis. This argument ignores the possibility that a systematic bias may affect all (or nearly all) studies. For Michels and Willett (17), recall bias remains a viable explanation for the finding of slightly increased risk. They cite survey data (10) and a Swedish study (8) using a registry-based gold standard to show that healthy women consistently and widely underreport their history of induced abortion. Brind et al. (18) discount this same evidence. They also jump from the finding of an association to the conclusion of cause and effect—a leap beyond the bounds of inference.

In the end, the difference between the conclusions found in these two recent reviews is inescapably bound to the notion of judgment itself and therefore to the values each reviewer brings to the examination of scientific evidence in all its complexity.

Do the results by Rookus and van Leeuwen (6) reported in this issue of the Journal resolve the matter of induced abortion and breast cancer risk once and for all? Simply put, they don't. Nevertheless, they offer tantalizing insight into the issue of reporting bias. Rookus and van Leeuwen find an elevated (1.9) adjusted relative risk overall among those reporting induced abortion in this Netherlands study. But their most striking finding is a large geographic variation in that elevated risk (1.3 in "liberal" areas of the country versus 14.6 in "conservative" regions) that is difficult to explain without considering the possibility of differential recall. They provide evidence of this possibility by finding the presence of recall bias within these same regions in regard to another reproductive matter: oral contraceptive use.

As editors, we believe that peer-reviewed studies should be published independent of the direction of the results. In fact, 2 years ago, the Journal published an article linking breast cancer and induced abortion (19). This is all part of the scientific process. The tapestry of accumulating information never ceases its growth, and it is rare that any single stitch changes the entire pattern.

We also offer our overall assessment of the relationship between induced abortion and breast cancer (17,18,20-23). We believe that there is as yet insufficient evidence to claim that a true association exists between induced abortion and breast cancer. Attribution of causation to specific numbers of cases is, therefore, not appropriate.

Where we go from here is less a matter of prediction than of preparation. In general, the future lies in our ability to overcome the epistemological and ethical difficulties inherent in inference-making (24). One task is to examine the potential role of recall bias in studies of induced abortion, following the methodologic work of others (6,8,10,25,28). Another task is to study "wish" bias itself. A formidable strength of epidemiology is its capacity to study carefully not only what causes and prevents disease but also what muddies the path to scientific understanding. Finally, we suggest that investigators and funding agencies develop cohort studies on induced abortion, which are less susceptible to differential recall bias. Simply repeating case-control studies subject to repetition of the same biases is less likely to provide substantially more information.

Because bias impedes our vision and is subject to sound inquiry, we are far from reaching a scientific "limit." Indeed, after this excursion into the issue of abortion, bias, and breast cancer, it seems our future has as much to do with human behavior as with human biology (29).

References

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Search for Genes That Suppress Cancer Metastasis

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In this issue of the Journal, Lee et al. (1) report the isolation of a novel gene termed KiSS-1 that is involved in controlling the metastatic potential and thus the progression of human malignant melanoma. An accurate perspective on the importance of this work requires a review of the current understanding of the biology of cancer metastasis. The pathogenesis of cancer metastasis consists of a series of linked, sequential, and selective steps. Metastasis begins with the detachment of tumor cells from the primary neoplasm and the invasion of the surrounding stroma by single cells or a group of cells with increased motility and secretion of degradative enzymes. Once the invading cells penetrate the lymphatic or vascular channels, they may grow there or a single cell or clumps of cells may detach and be transported within the circulatory system. Tumor emboli must survive the host’s immune and nonimmune defenses and the turbulence of the circulation. Moreover, they must arrest in the capillary bed of receptive organs, extravasate into the organ parenchyma, proliferate, and establish a micrometastasis. Growth of these small tumor lesions requires the development of a vascular supply and continuous evasion of host defense cells. When the metastases grow, they can shed tumor cells into the circulation and thus produce metastasis of metastases (Fig. 1) (2).

In 1889, Paget (3) proposed that metastasis was not random and occurred only when certain favored tumor cells (the “seed”) interacted with certain specific organs (the “soil”). A modern definition of the “seed and soil” hypothesis embraces three principles. First, neoplasms are biologically heterogeneous and contain subpopulations of cells with different metastatic properties. Second, the process of metastasis is selective for cells that pre-exist in the parental neoplasm (5). Third, the outcome of metastasis, as shown in human and rodent tumors, depends on multiple interactions of metastatic cells with homeostatic mechanisms shown to influence growth, vascularization, invasion, and drug sensitivity (2,6,7).

The recognition that neoplasms are heterogeneous for metastatic properties prompted the selection–isolation of clones or variant lines whose metastatic properties differed from each other’s (2). The availability of these congenic cell populations and the recent development of transgenic mice (8) have facilitated studies on the genetic and epigenetic regulation of the metastatic phenotype.

Two mutually exclusive mechanisms can be proposed for the genetic regulation of the metastatic process. The first mechanism suggests that a few master genes, such as the homeobox family of transcription factors, coordinate the multiple genes that regulate different steps of metastasis (9,10). No available data support this possibility. The second mechanism proposes that each discrete step of metastasis is regulated by transient or permanent changes in different genes at the DNA and RNA levels (11). As stated above, to produce metastases, metastatic