Common Problems in Abortion-Breast Cancer Studies

Synthesis Paper: Induced Abortion and Breast Cancer

Many design errors can skew the results of epidemiological studies. Some of these biases and problems include:

1. Incomplete questionnaire, low user response, unsuitable circumstances for obtaining data

In the Nurses Study II, the basis of the Michels study, over half of respondents did not completely answer the study's question on induced and spontaneous abortion history. Rather than leaving these questions half-blank, the authors filled in the blank halves of their responses with "no." The Brauner study relied on a national survey to which over 60 percent of those invited to participate declined.

Many studies relied on interviews conducted in the home or over the telephone. Data obtained this way may be affected by some degree of reporting bias, because a respondent may be uncomfortable disclosing some information in front of a spouse or children or over the telephone. This bias may skew the study's results away from linkage of induced abortion and breast cancer.

To avoid: Studies with low response rates or in which large fractions of participants failed to complete surveys ought not to be employed as basis for analysis. Furthermore, surveys ought to be conducted in clinical settings as often as possible.

2. Health/ Survivor bias

Women who have died of breast cancer prior to the study time cannot be accounted for, and women who have been diagnosed with breast cancer prior to the study time are often deliberately excluded from its sample. Some studies exclude women with in situ[1)] breast cancer.[2)] This survivor or "health" bias may alter the results of the analysis concerned. It is somewhat higher in studies with representative population samples (rather than case-control studies), in studies whose populations are older (because breast cancer resulting from an induced abortion will most likely show up around a decade thereafter), and in studies that deliberately eliminate women with cancer history. (Depending on the age of the analysis, exclusion of controls with breast cancer may skew results away from or toward induced abortion-breast cancer linkage or have no effect.)

To avoid: Studies should commence with women who procure an induced abortion and track them for a minimum of eight to 10 years thereafter. This would eliminate health or survivor bias from studies. Researchers can also avoid introducing health or survivor bias, or reduce its effects, by not excluding any women who have, or who have had, invasive or in situ breast cancer and by limiting their analysis to women still in their reproductive years or just past them. Researchers should not exclude women who die of breast cancer; the relatives or friends of deceased women can be interviewed.

3. Incorrect Time Frame

An individual breast cancer cell requires around eight to 10 years to grow into a clinically detectable cancer one centimeter in diameter. However, some studies neglect this time frame. Some studies do not follow induced abortions for at least eight to 10 years after they are reported, and though they may eventually produce breast cancer, they do not do so in the too-brief follow-up time allotted. This skews the data away from linkage of induced abortion and breast cancer.

In analyses of the relationship between time of an induced abortion and breast cancer diagnosis, wrongly-bounded time frames may obscure induced abortion's effect.

To avoid: Studies should follow women long enough after an induced abortion—a minimum of eight to 10 years—for a resulting breast cancer to grow to a detectable size. Additionally, when studies design their analyses, their regressions' categories should be bounded so that they isolate the time frame in which a breast cancer resulting from an induced abortion is most likely to appear (e.g., zero to seven years after an induced abortion, eight to 15 years after, and 16 to 23 years).

4. Unsophisticated Analysis and Unsuitable Comparisons

Some analyses simply assess the influence of having any history of induced abortion on breast cancer risk. Such analyses are unsophisticated, because the number of abortions a woman procures, a woman's parity status at the time she has an induced abortion, and her age and the gestational stage at which she procures the abortion determine how harmful it may be.

Additionally, incorrect reference groups in analyses will obscure the influence of induced abortion on breast cancer risk. For example, the effect of induced abortion among nulliparous women will be muted if nulliparous women with induced abortions are compared to nulliparous women with no induced abortions (never-pregnant women). The breast cancer risk of never-pregnant women is greater than that of parous women; the risk associated with induced abortion will thus be muted.

To avoid: Rather than disregarding the differences between women with different reproductive histories, advanced research should parse out their effects. Researchers ought to conduct sophisticated analyses and assess the effect of the timing of an induced abortion in a woman's reproductive life (i.e., whether the induced abortion preceded or followed a first birth, if any, and the span of time between the abortion and any subsequent first birth). Researchers also ought to assess the influences of repeated induced abortions and maternal age and gestational period at induced abortion(s).

Additionally, the standard reference group in an analysis of breast cancer risk should be composed of women who are most protected against breast cancer. In an analysis of the effects of general abortion history, the preferred reference group is women who become pregnant early in their reproductive lives, who have had no abortions or second-trimester miscarriages, and who breastfed their children. In analyses of the effects of repeated induced abortions or of maternal age or gestational period at induced abortion, parous women with zero abortions should be the reference group. Women should not be divided by parity status.

5. Reporting and Abortion Law Changes

Changes in the legality of induced abortion pose challenges for researchers and academics attempting to assess induced abortion's effect on breast cancer. If the law regulating induced abortion changed markedly during the reproductive years of a study's participants, registry data might be incomplete and respondents could be inclined not to disclose illegal abortions in interviews. The Melbye study, whose start and end dates straddled a change in the nation's abortion law, controlled for the year in which an abortion was procured and thereby controlled for liberal abortion law and, by proxy, controlled out for induced abortion. They did not report the effect that using this control had on their analysis's results. It is likely that they eliminated the effect of induced abortion on breast cancer from their results with this control.

To avoid: Studies must take into account the influence that changing induced abortion laws will have on the number of induced abortions procured and on breast cancer rates. Researchers should not control for induced abortion's legality without reporting the influence of that control.

6. Omitted Variable Bias

Omitted variable bias is introduced when authors fail to fully specify (include all possible risk factors in) their model. The demonstrated importance of a given risk factor may be overinflated if a related risk factor is excluded. The models of the studies vary in their completeness, and all fail to include or to show the influence of some potential breast cancer risk factor(s) in their analyses.

To avoid: As much as possible, it is extremely important for studies to control for all potential factors for breast cancer in their analyses. Studies should avoid introducing omitted variable bias into their models by including all potential breast cancer risk factors. These factors may include the following:

- **Demographic factors.** Age, place of residence, place of birth (urban/rural), ethnicity, marital status, occupation, household income, race, educational attainment, religion.
- **Parity.** Ever pregnant/never pregnant, number of pregnancies, nulliparity/parity, number of full-term pregnancies, number of live births, age at first full-term pregnancy, ever had a premature birth.
- **Breastfeeding.** Ever lactated, breastfeeding duration.
- **Induced abortion.** Ever had an induced abortion, timing of induced abortion(s) relative to first full-term pregnancy, age at first induced abortion, number of induced abortions, gestational period (week) at induced abortions.
- **Spontaneous abortion.** Ever had a (first-/second-trimester) spontaneous abortion, timing of (first-/second-trimester) spontaneous abortion(s) relative to first full-term pregnancy, age at first (first-/second-trimester) spontaneous abortion, number of (first-/second-trimester) spontaneous abortions, gestational period (week) at spontaneous abortions.
- **Menstrual cycle.** Age at menarche, length of menstrual period, length of menstrual cycle, history of irregular menstruation.
- **Hormone use.** Hormonal contraceptive use, hormonal contraceptive use before first full-term pregnancy, duration of hormonal contraceptive use, age at initiation of hormonal contraceptive use, years since initiation of hormonal contraceptive use, years since last hormonal contraceptive use, physician refusal to prescribe hormonal contraceptives, use of hormonal contraceptives for menstrual periods, estrogen/progesterone use (so-called "hormone replacement therapy" use), duration of estrogen/progesterone use.

- **Menopause.** Menopausal status, age at menopause.
- **Family history.** Family history of breast cancer (first- and second-degree), mutation in BRCA1 or BRCA2 gene.
- **Breast health and gynecological history.** History of benign proliferative breast disease, history of oophorectomy, past breast biopsy, history of infertility drug use.
- **Other medical history.** (Major) medical condition(s), occupational exposures, diabetes mellitus 2, hypertension, smoking, alcohol intake, coffee consumption, caloric intake, beta-carotene intake, body mass index (height and weight), physical activity.

7. Incomplete Reporting and Distinguishing between Spontaneous and Induced Abortions

In some studies, the data referenced fail to distinguish or to distinguish completely, whether by women's intentional misreporting or not, between spontaneous and induced abortions. Other studies fail to distinguish induced and spontaneous abortions in their general or in their more sophisticated (if any) analyses.

To avoid: Data that does not distinguish abortion types is not suitable for use. Both general and sophisticated analyses must distinguish induced and spontaneous abortion.

8. Publication Bias

The Beral meta-analysis unsystematically excluded certain datasets and baselessly dismissed results that proceeded from re-analysis of case-control studies.

To avoid: To avoid publication bias, meta-analyses and re-analyses ought not to exclude studies unsystematically. Retrospective data or re-analyses thereof should not be dismissed where they contradict prospective data merely because they are retrospective.

9. Insufficient Sample Randomization

If a study's population is not representative (e.g., is of one socioeconomic class or race) of the general population, then the study's results are not generalizable to the general population.

To avoid: A study ought to ensure that its sample is representative of the general population. If a sample contains only urban, or white, or highly-educated women, its results are only applicable to these women.

10. Very Small Sample Size

If a study's sample size is too small, it may be difficult to ensure that it is sufficiently randomized, and its applicability to the general population may be limited. Furthermore, a too-small sample may inhibit

the distinguishing of women around various characteristics that assessment of the relationship between induced abortion and breast cancer requires.

To avoid: Researchers ought not to use too-small samples; this will enable them to distinguish women however necessary without generating subpopulations too small for any "signal" to be perceptible over fluctuations from other sources of error.

11. No Distinction between First- and Second-Trimester Spontaneous Abortions

It is common for studies to analyze first- and second-trimester spontaneous abortions in one category, though they generally have very different causes. The failure to analyze these separately will degrade the signal of any associated breast cancer risk, so a non-significant finding is more likely to result. Furthermore, spontaneous abortions not due to hormonal insufficiencies but to physical problems may increase risk of breast cancer, and the risk conferred is indirect evidence of the effect of induced abortion.

To avoid: Studies must distinguish between the two very different types of miscarriage (first-trimester vs. second-trimester), whenever the available data makes it possible.

12. Incomplete Explanation of Model

The Goldacre study compared the number of observed to expected breast cancer cases in a sample and included no explanation of how this expected number of cases had been derived.

To avoid: Researchers should not leave the reader without a clear explanation of their methods and model. Authors should note, for example, which women were included in a given category, and by what statistical means they derived their figures.

13. Proposed Research Agenda

We suggest a research data network be built from existing breast centers, which are FDA-regulated and which are accredited by the National Accreditation Program of Breast Centers. By making the data these centers already collect comprehensive and uniform with a form that included all potential breast cancer risks, a large database for breast cancer research could be generated. The proposed network database would permit the elimination of major gaps in the literature. Furthermore, researchers should endeavor to avoid the aforementioned biases in their analyses.

[1] There are invasive and in situ cancers of both the milk ducts and milk glands. When cancer cells form but do not penetrate the basement membrane, or outer layer of the duct or gland, a cancer is said to be an in situ cancer. These cancers are curable, because they cannot spread to other parts of the body. Invasive cancers have penetrated the basement membrane and can spread throughout the body, becoming metastatic and life-threatening. Most invasive cancers start as in situ cancers.
[2] *In situ* breast cancer will likely account for over 60,000 cases of breast cancer among women in 2013 in the U.S. and over 20 percent of breast cancer cases. (See American Cancer Society, "Cancer

Facts & Figures 2013" [Atlanta: American Cancer Society, 2013]: 9. "An estimated 232,340 new cases of invasive breast cancer are expected to be diagnosed among women in the US during 2013; about 2,240 new cases are expected in men...In addition to invasive breast cancer, 64,640 new cases of *in situ* breast cancer are expected to occur among women in 2013. Of these, approximately 85% will be ductal carcinoma in situ [DCIS]."") It is treated with surgery, radiation, and drugs, and it may be serious enough that a woman requires a mastectomy. Furthermore, most of these cancers develop into invasive breast cancers, though it may take 10 or more years for ductal carcinoma in situ to become invasive. (See Stephen P. Povoski and Sanford H. Barsky, "Chapter 10: In Situ Carcinomas of the Breast: Ductal Carcinoma in Situ and Lobular Carcinoma in Situ" in *The Breast: Comprehensive Management of Benign and Malignant Disorders*, eds. Kirby I. Bland and Edward M. Copeland III, 4th ed. (Philadelphia: Saunders Elsevier, 2009), 212: "Clearly the evidence is incontrovertible that DCIS can and often progresses to frank invasive adenocarcinoma.") Regardless: women with *in situ* cancer doubtless consider their condition to be "real" breast cancer, as do their doctors. Hence, to not account for these women is misleading.