Induced Abortion as an Independent Risk Factor for Breast Cancer: A Critical Review of Recent Studies Based on Prospective Data

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ABSTRACT

Although many case-control studies, based mostly on retrospective collection of data, have shown a statistically significant increase in breast cancer risk after induced abortion, especially before the first full-term pregnancy (FTP), this risk is denied by the National Cancer Institute and many researchers. The conclusions of ten recent studies based on prospective data collection are cited to buttress this position. These studies are examined in detail, with a focus on methodologic aspects. Collectively, these studies are found to embody many serious weaknesses and flaws, including cohort effects, substantial misclassification errors due to missing information in databases, inadequate follow-up times, inadequately controlled effects of confounding variables, and frank violations of the scientific method. These recent studies therefore do not invalidate the large body of previously published studies that established induced abortion as a risk factor for breast cancer.

Breast cancer incidence is increasing, as predicted from earlier studies. Disclosure of the probable contribution of induced abortion to the increase in risk should be part of the informed-consent process for abortion.

Introduction

In our 1996 “comprehensive review and meta-analysis” on induced abortion and breast cancer,1 we reported an overall, statistically significant odds ratio (OR) of 1.3. This result was based on all 21 extant published studies reporting data specifically on induced abortion and breast cancer risk, the earliest study dating back to 1957.2

However, far from accepting these results as establishing induced abortion as a risk factor for breast cancer, most researchers and public health authorities—such as the U.S. National Cancer Institute (NCI)—maintained a highly skeptical interpretation, describing the association variously as “inconsistent” and/or “inconclusive.”

Less than seven years later, the NCI determined and reported on its website3 as “well established” that “[i]nduced abortion is not associated with an increase in breast cancer risk.” This majority conclusion, reached after an NCI workshop in 2003, was based largely on several new studies that had used prospective data, studies that generally reported a null association. It was therefore concluded that previous indications of a significantly positive association, as we had summarized, were erroneous because they were based almost entirely on retrospective data, and thus subject to reporting bias.

The NCI’s conclusion was reinforced by a large “collaborative reanalysis” published in The Lancet in 2004.4 The Lancet reanalysis compared results of prospective data-based studies with those based on retrospective data. Its interpretation of the overall significant difference in the associations (significantly negative v. significantly positive, respectively) was that “collectively, the studies of breast cancer with retrospective recording of induced abortion yielded misleading results, possibly because women who had developed breast cancer were, on average, more likely than other women to disclose previous induced abortions.”

It is counterintuitive to arrive at such a definitive conclusion on the basis of a methodological problem that is acknowledged to be a mere possibility—especially since it requires the dismissal of such a substantial body of data reporting increased risk. Moreover, since induced abortion is an exceedingly common and overwhelmingly elective surgical procedure, and since breast cancer is such a common life-threatening disease, the possible causal association between induced abortion and breast cancer bears further scrutiny. Critical analyses of the Lancet reanalysis5 and of several of the large recent prospective studies have been published separately,6–14 but an overall review and careful examination of the body of recent prospective data-based studies, taken as a whole, has not previously appeared.

Prospective vs. Retrospective Data: Methodologic Considerations

That the widely observed positive association between abortion and breast cancer could be an artifact resulting from reporting bias (also variously referred to as response bias and recall bias) was suggested in 1991 by Lindeffors-Harris et al.11 The group had previously published both a retrospective case-control study12 (based on interview data), and the only cohort study then extant13 (based on computerized medical records) to report data on induced abortion and breast cancer risk. As the two studies included the same Swedish women, the authors compared the results of the two studies and claimed to have found direct evidence of reporting bias. They stated that there was a significant difference “between underreporting of previous induced abortions among controls relative to overreporting among cases.”11 The authors subsequently retracted the nonsensical claim of “overreporting”115 upon which their significant evidence of reporting bias depended, although they continued to cling to reporting bias as an explanation—as have many others, even in the absence of any significant positive evidence. On the contrary, evidence of the lack of such reporting bias has been produced repeatedly, most recently by Tang et al.15

Because of the absence of even the possibility of reporting bias, prospective data are considered more reliable than retrospective data. Prospective studies, however, are prone to their own particular weaknesses, for example, cohort effects and lack of adequate follow-up time.
Induced abortion was legalized and widely available to women only fairly recently, in about the last 30-35 years. Consequently, the inclusion of women in a study cohort who spent most or all of their reproductive years before abortion was widely available will move the results toward the null association, especially since such women would be the oldest members of the study cohort and therefore comprise the majority of the breast cancer cases.

This cohort effect can also be understood as resulting in a comparison of two essentially different populations: the younger one, which had experienced most of the abortions, and the older one, which had developed most of the breast cancers. The statistics generated by this sort of analysis would be invalid.

Additionally, cohort analyses are often conducted after a relatively short period of exposure, in contrast to case-control studies that begin with a population of breast cancer patients. Since the induction of breast cancer typically takes several years, the presence of many as-yet-unaffected women in a given cohort who had an induced abortion only within the previous few years will result in an understimation of the effect.

In addition to the strengths and weaknesses particular to cohort v. case-control studies, there are of course potential weaknesses and flaws common to all types of studies. Even though the possibility of reporting bias is limited to retrospective databases, other defects can also result in substantial misclassification of subjects in terms of exposure category (e.g., women who had abortions being misclassified as not having had any abortions), causing large errors in the final results. Confounding by other variables not adequately controlled for, missing vital information on study subjects, and even gross errors in study design or violations of scientific principles, may also serve to invalidate the results of any type of study.

**Analysis of Specific Prospective Studies**

Between 1996 and August 2005, ten epidemiological studies reporting results based on prospective data on induced abortion and breast cancer have been published. Five of them are case-control studies nested in a prospective database, and one includes a study of each type on the same population. One additional cohort study by Lash and Fink published in 2004, is not included in the present analysis because the authors did not distinguish between induced and spontaneous abortion, oddly using the term “pregnancy termination” for both exposures. The current review is restricted to induced abortion, since induced and spontaneous abortion are clearly different events, and because the lack of association between spontaneous abortion and breast cancer is indeed well established, as we have previously observed.

The 1997 study by Melbye et al. is by far the largest of the studies, comprising all 1.5 million women born in Denmark between 1935 and 1978, and including more than 300,000 abortions and more than 10,000 cases of breast cancer. The single conclusion listed is: “Induced abortions have no overall effect on the risk of breast cancer.”

Melbye’s inclusion of abortions from 1973 onward suggests a substantially cohort effect, as women born in 1935 were 38 years old in 1973 when—according to the authors—abortion was legalized in Denmark. However, since abortion had in fact been legalized in 1939, many of the oldest members of the cohort—60,000 of them were misclassified as not having had an abortion, even though they had a legal abortion on record. In addition, Melbye et al. used the breast cancer registry (the outcome variable) starting in 1968, while not counting abortion (exposures) until 1973. Hence they violated the fundamental rule of temporality, with outcomes preceding exposures in time.

Despite these huge errors, the calculation of the overall raw rate still yielded 1.44, which when adjusted was reduced to 1.00 (95% CI: 0.94-1.06) because of so many of the older subjects being misclassified. Nevertheless, Melbye et al. still observed a statistically significant trend of increasing risk with increasing gestational age at abortion, with a relative risk (RR) of 1.89 reported for abortions beyond 18 weeks gestation. That the authors would decide not to include these significant positive findings among their official “conclusions,” as other authors have noted, is also troubling.

The cohort analysis of the 2000 Iowa Women’s Health Study by Lazovich et al. represents a sizable cohort (more than 37,000 women) with ample follow-up time (subjects were 65-74 years of age at time of data analysis). Nevertheless, it is statistically a very small study, as the women in the study were at least 55 years of age at baseline in 1986, and almost all of the 653 reported abortions took place before their legalization in 1973. Consequently, the statistical confidence intervals (95% CI) are very wide, with the overall RR = 1.1, (95% CI: 0.8-1.6).

Interestingly, higher RR’s are reported for subgroups previously reported to be at higher risk, specifically women with abortions under age 20 (RR = 1.5) or at age 30 or more (RR = 1.7), and women who remained nulliparous (RR = 1.7). Since the small numbers precluded statistical significance for any of the findings, Lazovich et al. claimed to have “observed no excess risk among women who reported having an induced abortion,” and further emphasized that their “data do not provide support for” a causal link between abortion and breast cancer. However, it is also clear that their data are in no way inconsistent with such a link.

The 2000 case-control analysis by Tang et al. involved a population in the area of Seattle, Washington, a population overlapping those of two previous retrospective studies by some of the same researchers. However, the Tang study was restricted to parous women, since its prospective database was drawn from birth certificates representing the last birth prior to breast cancer diagnosis. Both of the earlier studies had reported significantly increased risk among women with a history of induced abortion, and the prospective study was specifically designed “to examine the possible association of induced abortion and breast cancer while avoiding the possibility of differential underreporting.”

From the overall result of the prospective analysis of 463 cases and 2,201 controls (RR = 0.9, 95% CI: 0.7-1.2), the authors concluded that there is no real association, at least in women in whom abortion is “followed at some later time by pregnancy and childbirth.” One would therefore conclude that the earlier positive findings by this group were indeed false indications resulting from reporting bias. However, in yet another 2000 study of the same population, Tang et al. concluded that their results “did not suggest that controls are more reluctant to report a history of induced abortion than are women with breast cancer.” Moreover, one of the other earlier studies also had tested for and found no evidence of reporting
The very large 2001 study of Goldacre et al. comprised 28,616 cases and 325,456 controls. Based on records for both abortion and breast cancer from the British National Health Service (NHS) database on residents of Oxford, UK, over a 30-year period (1968-1998), it appeared to provide a robust analysis. Indeed, the results (expressed as Observed/Expected, instead of RR) were reported with very tight confidence limits: O/E = 0.83, 95% CI: 0.74-0.93.

However, the database showed that scarcely more than 1% of patients (300 out of 28,616) had a record of induced abortion over the entire 30-year period, whereas the recorded abortion rate for the whole UK exceeded 1% per year for that period. Hence, more than 90% of women in the study who had had an abortion were misclassified as abortion-negative. Even the authors admitted that their “data on abortion are substantially incomplete.”

While it should be unarguable that a study based on such egregiously deficient data is virtually useless for ascertaining any link between abortion and breast cancer, the authors still saw fit to conclude unequivocally, based on their analysis, that induced abortion “does not increase the risk of breast cancer.” This dubious publication represents the second time that a research team at Oxford University (i.e. a group with overlapping authorship) has seen fit to exonerate induced abortion from a link to breast cancer using an inappropriate data set. In 1982, the Oxford group claimed their results to be “entirely reassuring,” even though “only a handful of women” in that study had reported having an induced abortion. An Oxford group with overlapping authorship is also responsible for the "collaborative reanalysis" discussed above, as well as the 2005 study of Brewster et al., discussed below.

The 2002 study of Ye et al. included both a cohort analysis of more than 267,000 women from Shanghai, China, born between 1925 and 1958, and a case-control study drawn from that cohort, in which most (652) of the 702 cases incident within the study period (1989-1995) were age-matched with a similar number (694) of controls. Data on reproductive history were obtained by questionnaire at entry into the cohort between 1989 and 1991.

The results of the two analyses were virtually identical, with an adjusted odds ratio (OR) of 1.06 (95% CI: 0.91-1.25 and 0.84-1.33 for the cohort and the case-control analysis, respectively). The authors concluded: “Abortions as they have been performed in China are not an important cause of breast cancer.” This wording reflects the unusual pattern of induced abortion in China, where more than 90% of induced abortions occur after first FTP. This is in marked contrast to the United States and most other Western nations, in which most abortions precede the first FTP. In addition, the Chinese “one child policy” of the last quarter century has made the prevalence of induced abortion very high: 51% of the Ye cohort reported at least one induced abortion. It is noteworthy that, although the numbers were very small, women who had an abortion before first FTP were at elevated risk (OR = 2.16), as were those with first abortion beyond the first trimester (OR = 1.95). There is also reason to believe that the overall OR of 1.06 was underestimated, owing to the high prevalence of abortion in China. In any epidemiological study, the potential effect of some exposure is calculated by observing a difference in outcome between those exposed and those not exposed. However, when the prevalence of the exposure is very high, the unexposed group may no longer represent a typical population, and may represent a high-risk subgroup instead. Hence, adjustment for other variables may be inadequate for their confounding effect, and the OR (or RR) may be underestimated.

Considering abortion in China specifically, women with no abortions are likely to be those with no children, or those who began having children at a later age, both risk factors for breast cancer. Importantly, both of these features of reproductive history were indeed observed to be risk factors in the Ye study. Because Ye et al.
had such a large cohort to work with, this question could have easily been answered by conducting another case-control analysis wherein the control group was matched for parity and age at first childbirth, as well as maternal age. However, Ye et al. rejected our suggestion that they do so."

The 2003 case-control study by Erlander et al. was based on the linkage of the birth registry and the cancer registry of Sweden, during the period 1973-1991, yielding 1,759 case-control pairs for the analysis. The overall reported OR was 0.84 (95% CI: 0.72-0.99). As noted above, the use of the same time period for both induced abortion exposures (which were recorded in the birth registry from antenatal interviews) and breast cancer diagnoses would tend toward underestimation of the RR, as follow-up time for the more recent abortions would be inadequate to allow for cancer to appear, and the more recent births would add the confounding, short-term effect of FTP.

A much more serious concern is that there was no record of abortions that took place after the index birth and before the breast cancer diagnosis. It is troubling that the authors trivialized this defect, merely acknowledging that they “had no means of adjusting for pregnancies that took place after the time of interview, but before diagnosis of breast cancer.”

They further suggested: "Such pregnancies among parous women, however, should have little impact on breast cancer risk," not mentioning abortion in this context, and citing a study that dealt only with FTPs. Of critical importance, however, is the fact that in Sweden abortions are used more for limiting family size than for postponing first childbirth. Consequently, the majority of women in the Erlander study who had an abortion were misclassified as not having had any abortions. Hence, as in the studies of Melbye et al. and Goldacre et al., the database is simply unsuitable for examining the link between induced abortion and breast cancer. But like Melbye et al., the database not only used an inadequate database but also violated a fundamental rule of scientific methodology: In any case-control pair in which the older of the pair had an abortion after the date of the antenatal interview for the younger of the pair, the older subject was deliberately misclassified as not having had an abortion. Moreover, the number of such illicit manipulations was not divulged.

The 2003 report of Paoletti et al. provided an analysis of abortion-breast cancer data from the large scale “E3N Study,” in which approximately 100,000 French women aged 40-65 were enrolled during 1990-91, with follow-up questionnaires every two years. Only the first two questionnaires contained data on reproductive events. The 2003 report is based on breast cancer data (2,646 cases of invasive cancer) reported approximately through the year 2000.

The authors “conclude that there is no relationship between breast cancer and induced abortion,” based on their overall finding of RR = 0.91 (95% CI: 0.82-0.99). The authors note, however, that abortion was legalized in France in 1975, which means that women over age 55 at enrollment were over age 40 when abortion was legalized. Naturally, these women (about 40% of the population) would also comprise the vast majority of the breast cancer patients. Hence, the comparison in the Paoletti analysis is mostly between abortions among the older members of the cohort, and breast cancers among the older members, i.e., it reflects a major cohort effect, seriously inflating the statistical power of the study and causing an underestimation of the true relative risk. Had the authors restricted their analysis to cohort members under age 55 at enrollment, a more accurate picture would have emerged.

In 2004 Palmer et al. reported a cohort analysis of the Black Women’s Health Study (BWHS), a cohort comprising 59,000 African-American women enrolled in 1995. As in Paoletti’s E3N study, participants completed follow-up questionnaires every two years. But in marked contrast, the BWHS cohort age range at enrollment was very wide (21-69 years; median 38). Separate results were reported for nulliparous and parous women (incidence rate ratio [IRR] = 0.9, 95% CI: 0.5-1.4 and 1.1, 95% CI: 0.8-1.4, respectively), based on both breast cancer incidence and induced abortions reported through the 1999 questionnaire.

Note that the wide age range means a wide range in follow-up time, the older women in the study having a longer follow-up time than the younger ones. It would therefore be among the youngest members of the cohort that one would expect the IRR to be most underestimated, especially with the analysis including abortions reported in the 1999 questionnaire.

This pattern actually shows up in the report, which includes stratified data for women under age 45 v. age 45 or older. Among nulliparous women, the IRR for the women under 45 is 0.7, compared with 1.2 for the women 45 or older. Among parous women, no such trend is apparent (IRR = 1.2 and 1.0 for the under 45 and 45 or older women, respectively). It is, however, among the parous women that the IRR would be underestimated owing to the confounding effect of FTP.

The authors concluded that their “findings indicate that induced abortion does not increase breast cancer risk in African-American women.” A more accurate analysis of their data would exclude women too old to have been exposed to legal abortion (the oldest women were over 45 when abortion was legalized in 1970-73), and, even more importantly, exclude women who had reproductive events reported after the baseline in 1995.

The 2005 case-control study of Brewster et al. was nested in a nationwide database of Scottish NHS records of reproductive history and cancer diagnoses, which were computerized in 1981. Controls (9,888 women) were matched to all breast cancer cases under age 55 (2,833 women), for the period 1981-1998. In addition, records placed in the database in 1981 included full reproductive histories antedating 1981. Moreover, the authors present evidence to support their claim that their data on induced abortion “seem likely to be reasonably complete.”

It appeared that researchers, finally, had a prospective database that was simultaneously large and essentially complete, and that spanned the entire time frame since abortion was legalized. Such a database would be eminently suitable to determine with accuracy and precision a relationship between induced abortion and breast cancer, if one exists.

But inexplicably, the authors restricted the inclusion of women with any pre-1981 reproductive history to “those with some reproductive events occurring before 1981, and (for whom) number of pregnancies equaled number of births—that is, no miscarriages or induced abortions before 1981.” This arbitrary application of selection bias meant the wholesale elimination of women for whom abortion preceded the first live birth.
The resulting distortion is easily demonstrated by comparing the characteristics of Brewster's study population with the known patterns of the prevalence of abortion in Scotland. In Scotland, abortion is used primarily as a means to delay childbearing, and 58% of abortions are performed on nulliparous women. In extreme contrast, in the Brewster study only 155 women—5.6% of the study population—had an abortion while nulliparous. Hence it is clear that the Brewster study's population is wholly unrepresentative of the Scottish female population. In other words, the most suitable prospective database yet to become available for the study of induced abortion and breast cancer was deliberately distorted beyond recognition. Hence, the authors' conclusion that induced abortion is not a "substantive risk factor" for breast cancer is without credibility.

Discussion

In the nine years since we reviewed the abortion-breast cancer literature, the ten published studies based on prospective data were widely touted as resolving the controversy in favor of no abortion-breast cancer association. Yet, as is clear from the present review, none of them has provided credible evidence to back up the oft-repeated claim of no association.

In addition to the present chronicle of studies with huge proportions of study subjects misclassified, inadequate follow-up periods for the latent effect of breast cancer to develop, inadequate control for cohort effects, and the confounding effect of FTP, among other flaws, as well as frank violations of proper methodology, these reports contain numerous misrepresentations of the published literature.

One common example is the absence of mention, in the context of discussing the paucity of prospective database studies, of the excellent 1989 study by Howe et al. The Howe study was a case-control study nested in a prospective database of the New York State fetal death registry, begun in 1970 with the legalization of abortion. Considering breast cancers diagnosed between 1975 and 1980, the authors correctly restricted the analysis to patients under age 40, with controls for all 1,451 patients pair-matched for age and residence. They reported a statistically significant association (OR = 1.9, 95% CI: 1.2-3.0). Yet the recent prospective reports largely ignore the Howe study, and two even flatly declare that no study such exists.

Meanwhile, the earlier work by Howe et al. is expunged from Howe's own "Annual Report to the Nation on the Status of Cancer," a detailed analysis of trends in major cancers in the United States during the last quarter of the 20th century, published in 2001. It is noteworthy that the analysis showed an overall decrease in cancer incidence for men and women combined, but only because the incidence for men decreased by 3% per year during the index period 1992-1998. In fact, cancer incidence among women increased 0.3% per year during the same period. The word "abortion" does not appear in the report.

A closer look at the report reveals that almost the entire increased cancer incidence in women is in breast cancer. (The upward trend in lung cancer in women, which soared in the 1970s and 1980s, had leveled off by 1992, and the annual incidence, though not the death rate, was slightly decreasing by 1998.) Moreover, virtually all the increase in breast cancer incidence between 1986 and 1998 occurred in women under age 65 in 1998, i.e., in women under age 40 in 1973, the year induced abortion was legalized nationwide by the Roe v. Wade decision. It is not unreasonable, therefore, to attribute a substantial portion of the increase in breast cancer incidence since 1986 to induced abortion. Such an attribution is in complete agreement with predictions made in our 1996 review and meta-analysis.

We predicted at least 24,500 abortion-attributable cases of breast cancer per year in the United States alone by the fourth decade of the 21st century. Incidence is still rising, with the number of total cases expected to reach almost 270,000 in 2005. It is more than ironic that, despite denials of the abortion-breast cancer link, most authors of the recent literature freely admit the protective effect of FTP, which is abrogated by abortion. It is therefore unarguable—as recently acknowledged by Thorp et al.—that any reasonable standard of informed consent for abortion should include the fact that a woman's long-term breast cancer risk will be higher if she consents to the abortion than if she does not.

Researchers also widely admit to the biological plausibility of abortion as an independent cause of breast cancer, through the estrogen-mediated stimulation of breast growth in the absence of differentiation. This was demonstrated experimentally in rats in the landmark experiments of Russo and Russo. In fact, the biological plausibility of abortion as a risk factor has been strengthened by recent work of Melbye et al., showing the risk-increasing effect of very early premature birth (before 32 weeks) as well as very recent confirmation of the carcinogenic effect of estrogen-progestagen contraceptives and replacement hormones, which is acknowledged by the World Health Organization.

Conclusion

It is only reasonable to conclude, from all extant evidence, that induced abortion is indeed a risk factor for breast cancer, despite the strong and pervasive bias in the recent literature in the direction of viewing abortion as safe for women. Recent prospective studies, widely touted as refuting the abortion-breast cancer link, are found to embrace many serious methodologic flaws sufficient to invalidate their findings.

It is deplorable that in an era in which women's rights appear so prominently on the political and public health landscape, women should be denied the right to know about the breast cancer risk-increasing effect of such a common matter of choice as induced abortion.

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