Induced Abortion and Breast Cancer Risk: A Critical Analysis of the Report of the Harvard Nurses Study II

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An April 24th paper by Harvard researchers Karin Michels et al.[1] reported the widely disseminated conclusion: "Among this predominantly premenopausal population, neither induced nor spontaneous abortion was associated with the incidence of breast cancer."

This conclusion was based on the results of 10 years of follow-up of participants in the Harvard Nurses Study II, between 1993 and 2003. Data were gathered from baseline questionnaires returned by more than 105,000 women in 1993, and every two years thereafter by women who were 39–56 years of age in 2003. Results from this cohort analysis were presented as Hazard Ratios (HR), with the overall, covariate-adjusted HR for induced abortion being 1.01, 95% confidence interval (CI): 0.88–1.17.

This conclusion appears to be straightforward and unambiguous. However, several serious methodological concerns cast doubt on the validity of the overall result.

Prospective v. Retrospective Studies

The overall significant positive association between induced abortion and breast cancer incidence that we observed in our 1996 meta-analysis of published data[2] has been disputed. Since most of those data were derived from retrospective studies, many attempted to attribute the observed association to reporting bias. Studies based on prospective data, not subject to even the possibility of reporting bias, have been widely viewed as more credible for that reason. During the past decade, about 12 studies based on prospective data have appeared in the literature, the first ten of which I reviewed in 2005.[3] As noted in that review, such studies are prone to other flaws that may weaken studies of any design. I concluded that, owing to a host of methodologic weaknesses and flaws, even including frank violations of the scientific method,[4-6] none of the ten provided credible evidence to support their universal claim of a null association between induced abortion and breast cancer.

Inadequate Length of Follow-up

One weakness in prospective studies is the relatively short period of follow-up, in contrast to most retrospective case-control studies. Since the induction of breast cancer by an exposure such as induced abortion typically takes 8 to 10 years, the inclusion of women with very recent abortions will artificially lower the observed association. Three of the recently reviewed studies suffer from this defect.[4,7,8]

In the present case, since all questionnaires filed since 1993 were used to update the abortion data, and since cohort members were relatively young (39–56 years old in 2003, and 66% premenopausal), a relatively small but significant segment of the study population will have had abortions occurring with as little as zero follow-up time. How much this defect contributed to lowering the observed association cannot be determined. However, it could easily have been avoided by including only those women with abortions reported on the 1993 questionnaire, and breast cancer diagnoses reported only on the more recent questionnaires, thereby providing adequate follow-up time for all women included in the analysis. Indeed, the authors do show data stratified (in four strata) by age at first induced abortion, and only 21% of patients with any abortions had their first induced abortion at age 30 or older. Hence it is only among this age stratum that inadequate follow-up time applies. Therefore, the proper exclusion of the subjects with recent abortions would not have substantially decreased the statistical power of the study, yet it would have eliminated an obvious source of error.

Confounding Factors

One possible confounding factor in a relatively young study cohort is the transiently increased risk of breast cancer following full-term pregnancy (FTP). It is a weak association, first appearing in women over age 25 at FTP, with the odds ratio rising with maternal age at FTP, having a maximum magnitude of about 1.4, and disappearing within 15 years post partum.[9] In the relatively young, mostly parous (more than 80%) Harvard cohort, many of the parous women were still within the 15-year period following FTP. Hence, the observed HR for induced abortion is depressed by an unknown amount because the women without abortion were at elevated risk. This known source of error could have been eliminated by statistical adjustment for age at last FTP. However, there is no evidence that the authors considered the transient risk increase due to FTP at all.

Another important adjustment, but one which the authors applied only selectively, is for spontaneous abortion. Although this study reconfirms yet again the absence of a significant association between spontaneous abortion and breast cancer, in this particular population a small negative overall association (HR = 0.89) that almost achieved statistical significance (95% CI: 0.78–1.01) was observed. This adjustment was applied to the whole cohort in which results are stratified for maternal age at first induced abortion, and the final, covariate-adjusted HRs are seen to rise. However, it is inexplicably omitted from adjustment variables for the overall HR, which is seen, instead, to fall upon adjustment for the combination of all the other such variables (i.e., from an age-adjusted HR of 1.05 to 1.01).

Fortunately, the magnitude of the error resulting from this inappropriate omission can be calculated, by pooling all the HRs of the four age strata according to a weighted average, in the same way that cumulative odds ratios were calculated in our 1996 meta-analysis.[2] When this calculation is applied, the overall HR rises from 1.05 to 1.10, instead of decreasing to 1.01. It is also likely, considering the size of the overall population, that were this adjustment for spontaneous abortion applied to the raw data, the HR of 1.10 would be close to statistical significance.

The same error of omission appears in the presentation of the data separately for nulliparous and parous women. In this case, the overall covariate-adjusted HR for induced abortion in nulliparous women decreases with adjustment from 1.26 to 1.19 (95% CI: 0.90–1.58). However, the HR for spontaneous abortion among nulliparous women is even lower than for the entire cohort (0.82); hence, adjusting for number of spontaneous abortions would assuredly raise the HR for induced abortion substantially, probably to at least 1.3, again close to statistical significance. Unfortunately, the magnitude of this error cannot be calculated since no HRs adjusted for number of spontaneous abortions are shown specifically for nulliparous women.

Carcinoma in situ

One other omission that may reduce the observed HR for induced abortion in the Michels study concerns the exclusion of cases of carcinoma in situ. Curiously, no reason is given for this exclusion, although the authors claim that "results including in situ cases were comparable to those for invasive cases only." This is odd, considering that inclusion of the 399 in situ cases would have boosted the statistical power of the study. Indeed, data concerning the incidence of in situ carcinoma—since it is an early form of breast cancer—should be less vulnerable to error from lack of adequate follow-up interval after exposure. That is, the observed HR should be less depressed by this source of error, but no HRs are given at all for in situ carcinoma; nor is any quantitative definition given for the descriptor "comparable."

A Pattern of Denial

The study by Michels et al. therefore fits a pattern that is disturbingly familiar. A perfectly good data base from a relatively large cohort of women followed for 10 years, most well into middle age, such as the Harvard Nurses Study II, would be expected to provide sound, meaningful data on the relation between induced abortion and breast cancer, at least in premenopausal women. Yet the presence of several methodologic flaws in analyzing the data, including failure to exclude recent exposures, coupled with failure to include many appropriate cases and to apply appropriate statistical adjustments, all combine to lower the observed association. I have previously characterized this trend as a "strong and pervasive bias" in the recent literature concerning induced abortion and breast cancer.[3]

Ironically, this trend is most clearly indicated by the persistent claim of reporting bias to discount or discredit studies based on retrospective data, despite the lack of credible evidence of such reporting bias in abortion-breast cancer studies. In fact, the one group that claimed to produce direct evidence of such bias, in comparing data on the same Swedish women obtained both retrospectively and prospectively,[10] were only able to obtain a significant measure of reporting bias by invoking the dubious phenomenon of "overreporting," a claim they later retracted.[11] Michels herself was an early[12] advocate of the reporting bias explanation for the observed association, still suggesting in this latest study that "women with breast cancer may be more likely to reveal a history of abortion."[1] This is all the more surprising in light of the fact that a 1995 retrospective case-control study on women in Greece, a study which Michels coauthored, reported a significant overall positive association (odds ratio: 1.51, 95% CI: 1.24–1.84),[13] and specifically discounted any attribution of their findings to reporting bias, with the conclusion "that healthy women in Greece report reliably their history of induced abortion."

In the Michels study, as demonstrated above, the mere inclusion of a single appropriate adjustment (for number of spontaneous abortions) would have served to raise the overall HR to at least 1.1 (and higher for nulliparous women). It is difficult to imagine that proper analysis of these cohort data would not produce a result that is in the range of the modest significant positive overall association (odds ratio in the range of 1.2 to 1.5), as documented by our previous review and meta-analysis.[2]

For such a common elective exposure as induced abortion, and such a common, potentially life-threatening disease as breast cancer, it is deplorable that this biologically plausible association—whose documentation in the medical literature has now passed its 50th anniversary[14]—should remain largely unknown to women.

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