Invited Commentary

Invited Commentary: Reproductive Organ Surgeries and Breast Cancer Risk—Apples, Oranges, or Fruit Cocktail?

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Case-control and cohort studies are almost always complicated by nonrandom exposure allocation, which must be minimized in the design and analysis phases. Tubal sterilization is a common gynecological procedure that may be associated with other reproductive organ surgeries, which in turn may be associated with breast cancer risk. In this issue of the Journal, Gaudet et al. (Am J Epidemiol. 2013;177(6):492–499) argue successfully that tubal sterilization is unassociated with breast cancer risk. Scrutiny of the heterogeneous studies included in their meta-analysis underscores the role of confounding and effect modification in observational epidemiologic studies. Specifically, tubal sterilization is unassociated with breast cancer risk, but either oophorectomy or hysterectomy, or both, and the timing of these procedures warrant careful consideration in the design, analysis, and interpretation of observational research on reproductive factors.

breast neoplasms; case-control studies; cohort studies; hysterectomy; meta-analysis; oophorectomy; tubal sterilization

Abbreviations: CARE, Contraceptive and Reproductive Experiences; CPS-II, Cancer Prevention Study II.

In this issue of the Journal, Gaudet et al. (1) report that tubal sterilization is not associated with breast cancer risk by using data from their Cancer Prevention Study II (CPS-II) Nutrition Cohort (2), and they provide a meta-analysis of previous case-control (3–6) and cohort (7–9) studies. Given the widespread use of tubal sterilization (10, 11) and the high burden of breast cancer nationwide (12), the work by Gaudet et al. to compile the collective evidence to date is an important contribution. The results of the present analysis may give investigators the clearest evidence that tubal sterilization is unrelated to breast cancer risk. However, we caution readers to carefully consider the complexities inherent in—and across—this series of studies as they have differentially managed the added impact of various reproductive organ surgeries, which may have occurred after tubal sterilization (13, 14) and which are associated with breast cancer risk (5). The paper by Gaudet et al. brings together the findings of previous work on tubal sterilization and allows one to consider why results differ. Such an exploration provides epidemiologists an excellent example of comparing apples and oranges.

Exposure to circulating ovarian hormones affects breast cancer risk (15). The pronounced protective effect of bilateral oophorectomy on breast cancer risk is well established, particularly among women who receive the surgery at younger ages (5, 16–18). Possible independent effects of hysterectomy or partial oophorectomy have also been studied. These reproductive organ surgeries possibly reduce breast cancer risk by affecting ovarian function and, hence, circulating ovarian hormones, yet the evidence on partial oophorectomy and hysterectomy on breast cancer risk has been mixed and inconclusive (5, 19–23). Women who have had tubal sterilization are more likely than other women to undergo subsequent hysterectomy, yet there is no known biological explanation for the increased likelihood of hysterectomy following tubal sterilization (14). Furthermore, approximately half of hysterectomies are accompanied by bilateral oophorectomy (24, 25), resulting in ovarian removal for 15% of women by age 60 years (18). Hysterectomy or oophorectomy, or both, performed at younger ages may be more protective than those procedures performed at older ages (5).
Given these findings, one would expect studies that investigate tubal sterilization irrespective of oophorectomy or hysterectomy, or both, to obtain possibly biased risk estimates, because their baseline reference groups in different populations may contain a higher proportion or a lower proportion of women with previous oophorectomy or hysterectomy, or both, among women who have undergone tubal sterilization. Additionally, because the cumulative impact of reproductive organ surgeries is the association of interest, studies that partially adjust for oophorectomy or hysterectomy, or both, without respect to the timing of the procedures may also obtain possibly biased risk estimates. Of the 8 studies included in the present meta-analysis, 1 did not adjust for or stratify by oophorectomy or hysterectomy, or both (3); 2 studies excluded women who underwent oophorectomy or hysterectomy, or both, from their analysis (8, 9); 2 studies adjusted for oophorectomy or hysterectomy, or both, in their multivariate models (1, 7); 2 stratified by oophorectomy or hysterectomy, or both, to determine possible independent effects of tubal sterilization (4, 5); and it is unclear how 1 handled oophorectomy or hysterectomy, or both (6). Possible misclassification of exposure for hysterectomy or oophorectomy, or both, may be a limitation for the cohorts included in the studies, because cohorts typically assess exposure at 1 point in time, and information on reproductive surgeries or other noncancer endpoints may not be updated during follow-up or may not be included in the analyses. Confounding by indication for surgery has also been implicated in the potential for biased risk estimates, although recent evidence indicates that breast cancer risk reductions conferred by bilateral oophorectomy are not strongly confounded by failure to account for nonmalignant indications for surgery, such as uterine fibroids or endometriosis (18). It is unclear whether confounding by indication for surgery may be a problem for BRCA mutation status, since BRCA mutation carriers are candidates for prophylactic organ surgeries (26).

As an example of the importance of full consideration of previous oophorectomy or hysterectomy, or both, in the analyses of the Women’s Contraceptive and Reproductive Experiences (CARE) Study (5), a population-based case-control study of women diagnosed with breast cancer (4,490 cases and 4,611 controls) between the ages of 35 and 64 years (1994–1998) in 5 areas of the United States, we explored a possible association between breast cancer risk and tubal sterilization, irrespective of other reproductive organ surgeries and evaluated subgroups that differed as to whether they had undergone other reproductive organ surgeries. Although we failed to find an association with tubal sterilization overall, we did find a statistically significant protective effect for tubal sterilization before age 28 years and before calendar year 1980. However, results were likely dominated by the cumulative impact of other reproductive organ surgeries, such as oophorectomy (bilateral or with at least part of an ovary remaining) and hysterectomy. Further analysis examining risk separately for women with and without other reproductive organ surgeries and using a reference group of women who had no reproductive organ surgeries revealed that tubal sterilization alone was unrelated to breast cancer risk. Among the 1,820 women who had tubal sterilization alone, neither age at sterilization nor calendar year of tubal sterilization was associated with breast cancer risk. Our study demonstrated how complexities in women’s histories of reproductive organ surgeries, particularly when performed at younger ages, may influence the association between tubal sterilization and breast cancer risk.

It is informative to note that the proportion of women reporting tubal sterilizations in the studies included in the present meta-analysis varies widely: 9% (1), 12% (9), 15% (4), 23% (7), 28% (5), 34% (3), and 50% (8). The most recent nationwide estimate for tubal sterilization among married women is 21.1%, but this varies by race, socioeconomic status, education, and age (10). Reproductive factors associated with tubal sterilization include higher parity and a history of unintended pregnancy, which may explain some of the observed racial and socioeconomic variation (11). The annual number of tubal sterilization procedures and the methods and invasiveness used to accomplish these procedures have changed over the decades spanned by these studies (27, 28); furthermore, the rates of hysterectomy or oophorectomy, or both, vary across time and age (24, 25, 29). Because the number of tubal sterilizations increased dramatically during the 1970s (27), birth cohort effects may have resulted in lower proportions of tubal sterilization among older samples. As noted by Gaudet et al. (1), among the women in their sample who were born between 1903 and 1920, 2.8% obtained tubal sterilizations compared with 21.5% for those born between 1941 and 1952. Similar birth cohort effects are likely to have also impacted the proportions of women obtaining oophorectomy or hysterectomy, or both, which may have confounded or modified breast cancer risk estimates in those studies that differentially handled oophorectomy or hysterectomy, or both.

Another important consideration is that the studies included in the present meta-analysis used different study designs, used different questions to capture tubal sterilization history, and had different age distributions and distributions of sociodemographic characteristics. Each of these studies assessed the association between tubal sterilization and breast cancer risk as secondary analyses or as part of multiple analyses, but the original aims of these studies did not address this question specifically. The CPS-II is a cohort study using data collected in 1982. It used self-reported age at or years since tubal sterilization as a proxy for whether or not the participant received a tubal sterilization under the assumption that women who did not respond to this item had not had the procedure. The Women’s CARE Study asked participants whether they had ever had a tubal sterilization and, if so, the interviewer marked the date of the procedure on a calendar of life events, where other reproductive organ surgeries, pregnancies, types of contraceptives used, and use of hormone therapy were obtained by month, year, and age at exposure. Among Women’s CARE Study control participants, we found statistically significant differences in the distributions of several risk factors (including age, race, study site, and age at menarche) when classified by the women’s premenopausal reproductive organ surgery status. Both CPS-II and the Women’s CARE Study concluded that tubal sterilization
does not impact breast cancer risk, and the meta-analysis also shows no association. Moreover, the variation in risk factors and different age distributions and birth cohorts in the published studies could account for some of the observed heterogeneity of results, making it difficult to definitively rule out an association between tubal sterilization and breast cancer, although by using different approaches the collective evidence does not suggest that such an association exists.

In light of our Women’s CARE Study findings of the importance of considering other reproductive organ surgeries, defining an appropriate reference group, and noting the observed heterogeneity across prior studies in considering other reproductive organ surgeries (3–9), the study by Gaudet et al. (1) serves as a platform to emphasize that a woman’s history of reproductive organ surgeries plays a key role in breast cancer etiology, may modify the effects of other related factors such as tubal sterilization, and must be considered as a potential confounder in observational studies. Although we agree with Gaudet et al. in the conclusion that tubal sterilization is unrelated to breast cancer risk, we underscore the message that oophorectomy or possibly hysterectomy, or both, and the timing of these procedures warrant careful consideration in the design, analysis, and interpretation of etiologic studies of reproductive factors including tubal sterilization.

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REFERENCES


