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Editorial

Reproductive Surgery, Menopause and Breast Cancer Risk

C. La Vecchia

Istituto di Ricerche Farmacologiche 'Mario Negri', 20157 Milan; and Istituto di Statistica Medica e Biometria, Università degli Studi di Milano, 20133 Milan, Italy

A ROLE for hysterectomy and/or ovariectomy on subsequent breast cancer risk has long been described [1], but the issue remains open to discussion. This is due to at least three reasons, including: (i) the difficulties of obtaining reliable and valid histories on type of surgery (i.e. hysterectomy only versus mono- or bilateral ovariectomy); (ii) the different impact of various types of reproductive surgery on menopause at various ages; and (iii) the potentially complex modifying effect and interaction of age at menopause and hormone replacement therapy (HRT) on the risk estimates for reproductive surgery and their influence on breast cancer risk at various ages [2].

The large Canadian dataset reported by Kreiger and colleagues, in this issue of the *European Journal of Cancer* [3]; pp. 97–101, provides further relevant information on the issue of reproductive surgery and breast cancer risk and has two major advantages, i.e. its record-linkage prospective design, together with the type of information available which minimises the possibility for misclassification of exposure, and the large number of cases and events, together with the long observation period.

In summary, the data of this large dataset confirm that bilateral ovariectomy at an early age reduces subsequent breast cancer risk, possibly by inducing early menopause. They also indicate that other common reproductive surgical procedures, including tubal ligation, hysterectomy only and unilateral ovariectomy, reduce breast cancer risk, possibly by affecting in some general way ovarian function, and hence circulating ovarian hormones. The risk reductions, however, were moderate, of the order of 15–25%, in the absence of clear age- and time-related patterns.

Monolateral ovariectomy may affect breast cancer risk in premenopause by altering female hormone levels. Hysterectomy may also modify ovulation, ovarian blood flow and cause ovarian failure [4–6]. Thus, it is conceivable that hysterectomy without ovariectomy in premenopause may reduce the risk of breast cancer. The data on the issue are still controversial [7], suggesting that, if these gynaecological procedures do change ovarian function in a way that modifies breast cancer risk, the strength of the association is moderate. In the study by Kreiger and colleagues, the relative risk for hysterectomy only was 0.87, based on 1427 cases and that for unilateral ovariectomy was 0.74, based on 152 cases.

These reproductive surgical procedures may also modify age at menopause. Age at menopause is a recognised risk factor for breast cancer, the risk increasing with later age at menopause [8–10]. Several questions on the issue remain unanswered. These include quantitative assessment and comparison of risk estimates across various studies, which have often used different reference categories and have shown a variable strength of the association. For instance, among women with a natural menopause, the relative risk of breast cancer for women aged under 40 years compared with those aged 50 years or more differed by approximately a factor of 4 in a large case–control study including data from the U.S.A., Canada and Israel [11], but only a 20% excess risk was reported from an American case–control study derived from a nationwide screening programme [12]. The effect of age at diagnosis and other time factors is also unclear, since variable latency periods before the establishment of an effect of age at menopause have been suggested [8, 12, 13]. It is also important that age at diagnosis is adjusted in strict (i.e. single year) terms for evaluating the effect of age at menopause [2]. Thus, the most precise and reliable estimate of the influence of age at menopause on breast cancer risk is given by the collaborative re-analysis of individual data from 51 epidemiological studies of 52 705 women with breast cancer [14], which estimated an increased risk of 2.8% per year of delayed menopause.

There are also difficulties in understanding and in disentangling the potential effect of type of menopause. Trends similar to those observed for all menopausal types together were detected in women experiencing a surgical menopause in some studies [8, 11, 15], although the association was weaker in others [12, 16]. This is probably attributable to the inclusion of cases with hysterectomy alone and with monolateral ovariectomy in the definition of age at menopause. It has been shown, in fact, that inclusion of women with simple hysterectomy leads to an underestimate of the effect of age at menopause as well as of HRT on breast cancer risk [2]. When bilateral ovariectomy was considered, a consistent reduction in risk with decreasing age at operation was generally reported [11, 12, 17], but latency effects following surgery are yet unclear.

Pooled data from two case–control studies conducted between 1983 and 1994 in major teaching and general

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hospitals from six Italian geographical areas [18] on 3576 postmenopausal women with incident, histologically confirmed breast cancer and 3578 postmenopausal controls admitted to hospital for acute, non-neoplastic, non-hormonal, non-gynaecological conditions provided relevant information on the role of age and type of menopause. When all types of menopause were considered together, the floating absolute risks (FARs) (which avoids the definition of an arbitrary reference category [19]) were 0.49 for < 45 years of age, 0.81 for 35–39 years, 0.82 for 40–44 years, 0.88 for 45–47 years, 1.02 for 48–50 years, 1.23 for 51–53 years and 1.24 for 54–56 years, with a significant linear trend in risk. A stronger association was observed in women reporting a natural menopause, with FARs of 0.14 for women with menopause < 35 years of age versus 1.20 for those with menopause at 54–56 years (ratio between extreme FAR estimates = 8.6). No trend emerged in the overall surgical menopause group, including hysterectomy alone or with monolateral ovariectomy and bilateral ovariectomy. However, when only women reporting a bilateral ovariectomy were considered, a significant and strong linear trend in risk was observed [18]. No heterogeneity emerged when risks were evaluated in separate strata of age at diagnosis/interview.

Thus, the protective effect of bilateral ovariectomy in premenopausal women appears to be largely explained by the effect of anticipating menopause. In other words, the causal factor seems to be early age at menopause, and the inverse relationship with bilateral ovariectomy can be largely accounted for by earlier age at menopause. This explains why in the study by Kreiger and colleagues [2] there was strong protection for women who had undergone bilateral ovariectomy under the age of 45 years, but not for those reporting bilateral ovariectomy at an older age.

An independent protective effect of hysterectomy alone and/or with monolateral ovariectomy on breast cancer risk has been reported using the Canadian dataset of Kreiger and colleagues, as well as by the Cancer and Steroid Hormone (CASH) study [17], but is still open to evaluation [7, 9–12]. This effect has been interpreted as being at least partly due to the induction of early menopause by hysterectomy. However, women who underwent hysterectomy only could not indicate the exact age at menopause, thus leaving the possibility of confounding by age at menopause. Some additional confounding is also possible, because the most common indication for hysterectomy without ovariectomy in premenopause is uterine fibroids, which share similar risk factors, such as nulliparity, with breast cancer [20].

In particular, an unavoidable limitation of the study by Kreiger and colleagues [3], common to most record linkage studies, is the lack of information on covariates. Among these, age at menopause and HRT use would be of major importance in order to avoid relevant confounding or modifying effects [2] and, hence, allow the formulation of causal inference. Some of the associations observed in the study could, in fact, be at least partly modified by a different age at menopause and/or prevalence of use of HRT in women who had undergone reproductive surgery, since both later menopause and HRT use are associated with breast cancer risk [9, 14].

Consequently, this study, because of its prospective design and uniquely large dataset, provides an accurate description of the association between various types of reproductive surgery and breast cancer risk, but leaves open the issue of quantification and, mostly, of its interpretation in terms of causal inference and understanding potential underlying pathogenic mechanisms.

1. Hyrayama T, Wynder EL. A study of the epidemiology of cancer of the breast. II. The influence of hysterectomy. *Cancer* 1962, **15**, 28–38.
2. Pike MC, Ross RK, Spicer DV. Problems involved in including women with simple hysterectomy in epidemiologic studies measuring the effects of hormone replacement therapy on breast cancer risk. *Am J Epidemiol* 1998, **147**, 718–721.
3. Kreiger N, Sloan M, Coterchio M, Kirsh V. The risk of breast cancer following reproductive surgery. *Eur J Cancer* 1999, **35**, 97–101.
4. Souza AZ, Fonseca AM, Izzo VM, Clauzet RM, Salvatore CA. Ovarian histology and function after total abdominal hysterectomy. *Obstet Gynecol* 1986, **68**, 847–849.
5. Stone SC, Dickey RP, Mickal A. The acute effect of hysterectomy on ovarian function. *Am J Obstet Gynecol* 1975, **121**, 193–197.
6. Janson PO, Janson L. The acute effect of hysterectomy on ovarian blood flow. *Am J Obstet Gynecol* 1977, **127**, 349–352.
7. Parazzini F, Braga C, La Vecchia C, Negri E, Acerboni S, Franceschi S. Hysterectomy, oophorectomy in premenopause, and risk of breast cancer. *Obstet Gynecol* 1997, **90**, 453–456.
8. Trichopoulos D, MacMahon B, Cole P. Menopause and breast cancer risk. *J Natl Cancer Inst* 1972, **48**, 605–613.
9. Lipworth L. Epidemiology of breast cancer. *Eur J Cancer Prev* 1995, **4**, 7–30.
10. Kelsey JL, Gammon MD, John EM. Reproductive factors and breast cancer. *Epidemiol Rev* 1993, **15**, 36–47.
11. Helmrich SP, Shapiro S, Rosenberg L, *et al*. Risk factors for breast cancer. *Am J Epidemiol* 1993, **117**, 35–45.
12. Brinton LA, Schairer C, Hoover RN, Fraumeni JF Jr. Menstrual factors and risk of breast cancer. *Cancer Invest* 1988, **6**, 245–254.
13. Alexander FE, Roberts MM. The menopause and breast cancer. *J Epidemiol Community Health* 1987, **41**, 94–100.
14. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet* 1997, **350**, 1047–1059.
15. Ewertz M, Duffy SW. Risk of breast cancer in relation to reproductive factors in Denmark. *Br J Cancer* 1988, **58**, 99–104.
16. Carter CL, Jones DY, Schatzkin A, Brinton LA. A prospective study of reproductive, familial, and socioeconomic risk factors for breast cancer using NHANES I data. *Public Health Rep* 1989, **104**, 45–50.
17. Irwin KI, Lee NC, Peterson HB, Rubin GL, Wingo PA, Mandel MG and the Cancer and Steroid Hormone Study Group. Hysterectomy, tubal sterilization, and the risk of breast cancer. *Am J Epidemiol* 1988, **127**, 1192–1201.
18. Braga C, Negri E, La Vecchia C, Franceschi S. Age at menopause and breast cancer: estimation of floating absolute risks. *The Breast* 1998, **7**, 27–32.
19. Easton DF, Peto J, Babiker AGAG. Floating absolute risk: an alternative to relative risk in survival and case–control analysis avoiding and arbitrary reference group. *Stat Med* 1991, **10**, 1025–1035.
20. Parazzini F, Negri E, La Vecchia C, Chatenoud L, Ricci E, Guarnerio P. Reproductive factors and risk of uterine fibroids. *Epidemiology* 1996, **7**, 440–442.

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