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Prophylactic oophorectomy in *BRCA1* and *BRCA2* mutation carriers

T.R. Rebbeck*

Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, 904 Blockley Hall, 423 Guardian Drive, Philadelphia, PA 19104, USA

1. Introduction

The availability of genetic testing for inherited mutations in the *BRCA1* or *BRCA2* (*BRCA1/2*) genes provides potentially valuable information to women at an elevated risk of breast or ovarian cancer. Unfortunately, women who have inherited a mutation in *BRCA1/2*, have relatively few clinical management options available to reduce their risk of developing breast or ovarian cancer. Many high-risk women consider the option of bilateral prophylactic oophorectomy (BPO) which substantially reduces their risk of developing invasive malignancy. In general, these studies have been conducted on women who represent a heterogeneous group with respect to breast/ovarian cancer risk. In reports on BPO in women whose elevated cancer risk has been based on knowledge of inherited mutations in *BRCA1/2*, there is a 50–70% breast cancer risk reduction and a greater than 95% ovarian cancer risk reduction.

2. *BRCA1/2*-associated cancer risks

Risks in *BRCA1/2* mutation carriers estimated from high-risk pedigrees used for linkage analysis suggested a lifetime breast cancer risk of 80—90%, but these families were highly selected for the existence of multiple cancers occurring at an early age [1]. Population-based studies suggest that *BRCA1/2* mutation cancer risks may be substantially lower than those originally reported. For example, cancer risks may be no higher than 60% in population-based samples of Ashkenazi Jewish women who carry one of the commonly occurring mutations in *BRCA1/2* (i.e. 185delAG, 5382insC, 6174delT) [2]. Lifetime breast cancer risk associated with *BRCA2* in hereditary family (not population-based) samples appears to be similar to that of *BRCA1*, but the mean age of onset is shifted to a somewhat later age in the *BRCA2* mutation carriers. That is, while lifetime (total) risk may be similar, the age-specific penetrances or *BRCA1* and *BRCA2* may differ. More recent estimates of risk [3] suggest that populations routinely screened for *BRCA1/2* mutations in a high-risk clinical setting may have lifetime risks that are intermediate to those reported in Refs. [1,2].

3. Ovarian cancer risk reduction after prophylactic oophorectomy

With regard to ovarian cancer screening, clinical recommendations are limited. As in the general population, neither vaginal ultrasound nor CA-125 measurement has been shown to reduce morbidity or mortality from ovarian cancer in women with *BRCA1/2* mutations. Thus, these women are often advised to undergo BPO when childbearing is complete. Some authors suggest an additional gain of lifespan after BPO of 0.3–1.7 years [4,5]. BPO will at best reduce the risk of ovarian cancers: Intra-abdominal (peritoneal) carcinomatosis does occur in women who have undergone BPO [6–10]. While the origins of these cancers are poorly understood, it is hypothesised that either (1) clinically undetectable ovarian cancer cells remain in the peritoneum after removal of the ovaries, and/or (2) a 'field defect' is present in the peritoneum as the epithelial covering of the ovary (i.e. the origin of the epithelial ovarian cancer is in fact the peritoneal reflection onto the ovaries). One author suggests that BPO reduces ovarian cancer risk approximately 50%, but the residual ovarian cancer risk in post-oophorectomy subjects is still substantially

* Tel.: +1-215-898-1793; fax: +1-215-573-2265.

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higher (up to 30%) than that in the general population [11]. However, that study had too few patient-years of follow-up to reach a statistically significant conclusion.

Using a cohort of 551 women with disease-associated germline *BRCA1/2* mutations collected from 11 centres in North America and Europe, Rebbeck and colleagues [12] evaluated the effect of BPO on ovarian and breast cancer risk. 259 BPO subjects who underwent BPO were compared with 292 controls with no history of BPO. Post-surgery follow-up time for all groups was at least 8 years. Two women (0.8%) were diagnosed with papillary serous peritoneal carcinoma 4 and 11 years after BPO, respectively, and six women (2.3%) were diagnosed with ovarian cancer at the time of BPO. Excluding those six women diagnosed, at BPO, there was a highly significant reduction in ovarian cancer risk (adjusted Hazard Ratio (HR = 0.04; 95% Confidence Interval (CI): 0.01–0.16).

Morbidity following BPO exists with potentially deleterious effects on lipids, coronary artery disease, osteoporosis and other menopausal symptoms. Because it may affect the risk of breast cancer [13], concerns have arisen about hormone replacement therapy after BPO and hysterectomy to diminish these symptoms and address the increased risk of osteoporosis and cardiovascular disease. The extent to which the benefits of BPO outweigh these risks in *BRCA1/2* mutation carriers is not known. The availability of newer synthetic hormone replacement compounds such as raloxifene, which may confer cardiovascular and osteoporosis protection with no associated increase in breast cancer risk, are options that must also be considered.

Ovarian tumours tend to arise later than breast tumours in *BRCA1/2* mutation carriers. Cases have been reported in *BRCA1* mutation carriers in their thirties, although the median age of *BRCA1/2*-associated ovarian tumours is approximately 50 years [14–16]. Some suggest that BPO may be appropriate in very high-risk women after childbearing is complete or after the age of 35 years [17]. Using a decision analysis approach, a delay of BPO for 10 years in a 30-year old woman may not result in a substantial change in life expectancy [4].

4. Breast cancer risk reduction after prophylactic oophorectomy

With regard to breast cancer, recommendations for enhanced levels of screening using clinically established techniques include breast screening beginning at an earlier age, as well as more frequent exams (e.g. mammography and clinical breast exam every 6 months). Concerns include increased breast density in younger aged women. Other screening methods, such as breast imaging by magnetic resonance imaging (MRI) and digital mammography are being tested, but are not widely available outside of research protocols. Removal of ovarian tissue also reduces serum oestradiol levels. As a result, breast cancer risk may also be lowered [18]. In order to address this hypothesis, we have evaluated the effect of BPO on breast cancer risk reduction in 122 *BRCA1* mutation carriers [19]. Two groups of women were compared: those who had undergone BPO, and a matched set of women who did not undergo this surgery, but who were born at approximately the same time and were ascertained at the same study site as the BPO subjects. 43 BPO subjects were included, who had no history of breast or ovarian cancer before or at the time of their surgery, and no history of prophylactic mastectomy prior to or at the time of their BPO. Potential control women were selected if they had a confirmed *BRCA1* mutation, had both ovaries at the time of the surgical subject's BPO, were born before 1970, were born within 5 years of a BPO surgical subject (to control for potential cohort effects), and were ascertained at the same study location. Among these potential control subjects, 79 controls were selected who were alive at the time of the BPO subject's surgery, had no history of oophorectomy, no history of breast or ovarian cancer, and no history of prophylactic mastectomy at or before the time of the matched surgical subject's BPO. Women who had *BRCA2* mutations were excluded.

Surgical subjects were followed for an average of 9.6 years after BPO (range <1–36 years) and controls were followed for an average of 8.1 years (range <1–43 years) after BPO in the matched surgical subject. There was no differences in the lengths of follow-up in the two groups. BPO significantly reduced the risk of developing breast cancer in the whole sample (HR = 0.53, 95% CI: 0.33–0.84). Subjects who were followed at least 10 years after surgery and were parous (HR = 0.35, 95% CI: 0.13–0.95) or had BPO before the age of 50 years (HR = 0.34, 95% CI: 0.12–0.96) also experienced a substantial reduction in breast cancer risk. These results imply that risk reduction is greatest when a sufficient amount of time has elapsed after surgery.

These results have been more recently replicated in a superset of 99 BPO subjects with no breast or ovarian cancer, or prophylactic mastectomy prior to their BPO and 142 matched controls with no previous BPO, prophylactic mastectomy, and history of breast or ovarian cancer. 21 women in the breast cancer risk evaluation subset (21.7%) developed breast cancer after BPO, (HR = 0.47; 95% CI: 0.29–0.77).

The effect of hormone replacement therapy (HRT) on breast cancer risk after BPO has not been well studied. We reported that ever/never HRT use was not a significant independent predictor of breast cancer outcome in a multivariate Cox model that included BPO, and exclusion of women who had HRT exposure after BPO

did not significantly affect the risk reduction conferred by BPO [19]. However, this was a small sample, and additional information is required to guide women and their clinicians about the use of HRT after BPO.

5. Conclusions

Existing data suggest that BPO may reduce breast and ovarian cancer risk in women who have inherited *BRCA1/2* mutations. However, additional information about post-BPO mortality reduction, proper timing of surgery, and use of HRT are required. Recent recommendations include the use of BPO in postmenopausal women. For premenopausal women, the use of BPO should be weighed against age-related ovarian cancer risk, childbearing, and risk of complications that may arise as a result of surgically-induced menopause. In the absence of strong data to guide a decision, HRT use may be recommended after BPO until the age of 50 years. Until less surgically invasive options become available, including improved screening and chemoprevention regimens, the use of BPO is likely to remain a consideration for the clinical management of breast and/or ovarian cancer risk reduction in women who have inherited a *BRCA1/2* mutation.

Note added in proof:

Kauf et al. [20] have recently provided additonal information that BPO reduces both breast and ovarian cancer risk. Using a sample of 170 *BRCA1/2* mutation carriers followed for an average of 2 years, those authors reported a reduction in ovarian, fallopian tube, or primary peritoneal cancer risk with a hazard ratio of 0.15 (0.02–1.31), and in ovarian cancer risk of 0.32 (95% CI 0.08–1.20), with a 75% reduction in risk of any of these cancers. These results further support the use of BPO in cancer risk reduction for *BRCA1/2* mutation carriers.

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