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The impact of risk-reducing hysterectomy and bilateral salpingo-oophorectomy on survival in patients with a history of breast cancer – a population-based data linkage study

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Novelty and impact statement: Our data challenges the belief that modern medical endocrine treatment is as effective as prophylactic surgery for endocrine ablation in breast cancer survivors. If our data can be replicated in another independent dataset, hysterectomy plus removal of the ovaries should be considered by premenopausal women diagnosed with breast cancer and could reduce their risk of death by 50%. Prophylactic surgery does not seem to be of benefit to postmenopausal women diagnosed with breast cancer.

Abstract

Prophylactic surgery including hysterectomy and bilateral salpingo-oophorectomy (BSO) is recommended in BRCA positive women, while in women from the general population, hysterectomy plus BSO increases the risk of overall mortality. The effect of hysterectomy plus BSO on women previously diagnosed with breast cancer is unknown.

We used data from a population-base data linkage study of all women diagnosed with primary breast cancer in Queensland, Australia between 1997 and 2008 (n=21,067). We fitted flexible parametric breast cancer specific and overall survival models with 95% confidence intervals (also known as Royston-Parmar models) to assess the impact of prophylactic surgery (removal of uterus, one or both ovaries). We also stratified analyses by age 20-49 and 50-79 years, respectively.

Overall, 1,426 women (7%) underwent prophylactic surgery (13% of premenopausal women and 3% of postmenopausal women). No women who had prophylactic surgery, compared to 171 who did not have prophylactic surgery developed a gynaecological cancer. Overall, 3,165 (15%) women died, including 2,195 (10%) from breast cancer. Hysterectomy plus BSO was associated with significantly reduced risk of death overall (adjusted HR = 0.69, 95% CI 0.53-0.89; P =0.005). Risk reduction was greater among premenopausal women, whose risk of death halved (HR, 0.45; 95% CI, 0.25-0.79; $P < 0.006$). This was largely driven by reduction in breast cancer-specific mortality (HR, 0.43; 95% CI, 0.24-0.79; $P < 0.006$).

This population-based study found that prophylactic surgery halved the mortality risk for premenopausal breast cancer patients. Replication of our results in independent cohorts, and subsequently randomised trials are needed to confirm these findings.

Introduction

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females globally, accounting for 23% of total cancer cases and 14% of cancer deaths in 2008 [1]. Breast cancer incidence has been rising in Asia and Africa [2, 3], while rates have largely stabilised in North America, Europe and Australia [4, 5], although in young women (25-39 years) an increase in breast cancer with distant involvement has been observed (United States SEER data 1996-2009; [6]).

Risk factors for breast and uterine cancers are well described and include prolonged exposure to and higher concentrations of endogenous estrogen [7, 8]. Women in Queensland (QLD), Australia (including mutation carriers), who were diagnosed with breast cancer subsequently have a more than 150% increased risk of developing uterine cancer and also a higher than 40% increased risk of developing ovarian cancer compared to the general population [9]. Prophylactic hysterectomy and bilateral salpingo-oophorectomy (BSO) could reduce the risk of subsequent gynaecological and breast cancers in these patients.

In breast cancer susceptibility gene (BRCA) carriers, prophylactic risk-reducing BSO significantly reduces ovarian cancer risk [10] and incidence of new breast cancers in premenopausal women [11-13]. Consequently, in BRCA carriers BSO decreases all-cause, breast cancer-specific, and ovarian cancer-specific mortality[11-13]. However, only 5 to 6% of all breast cancers are directly attributable to inheritance and the cumulative risk of developing breast cancer by age 70 for a mutation carrier in Australia is approximately 40% [14], less than had been estimated from studies in other countries [15]. Furthermore, the cumulative risk of ovarian cancer by age 70 is estimated at 40 to 50% for BRCA1 mutation carriers and 10 to 25% for BRCA2 carriers [16-19].

In women at average cancer risk without a previous diagnosis of breast cancer, two large prospective studies and one retrospective population-based cohort study found that BSO reduced risk of ovarian cancer by more than 96% and the risk of breast cancer in women 45 years or younger by 40%. However, these benefits were counteracted by a significantly increased risk of death from other causes (e.g. cardiovascular disease) compared with women who preserved their ovaries, particularly among premenopausal women [20-27]. In a meta-analysis of 12 case-control studies and a recent case-control study, hysterectomy alone without BSO was reported to reduce the risk of ovarian cancer by 34% [28] and breast cancer risk by 16% [29], respectively.

The exact mechanism of this is unknown but it is suspected to be induced by reduced follicle stimulating hormone levels.

For patients diagnosed with breast cancer, the benefits and risks of BSO are unknown, especially for the majority (>90%) of patients who are BRCA1/2 negative. We therefore used a population-based data linkage approach to examine if patients with a personal history of breast cancer who had prophylactic BSO with or without hysterectomy experienced different overall and breast cancer specific survival compared to women with breast cancer who did not have prophylactic gynaecological surgery.

Methods

Data

All cases of invasive breast cancer (ICD-O-3 code C50) diagnosed among women 20-79 years, in Queensland (QLD) between 1997 and 2008 were selected from the population-based QLD Cancer Registry (QCR). Cases based on autopsy or death certificate only were excluded. Other data items available from the QCR included breast cancer cell type (morphology), Indigenous status (self-identified), laterality and size of the tumour, number of lymph nodes surgically excised, number of lymph nodes positive, as well as information regarding second primary cancers. Cause of death was ascertained through routine matching with the Australian National Death Index, with follow up to the 31st December 2009.

The QCR also holds a record of the most recent admission to every public and private hospital within QLD for each cancer patient. This facilitated a deterministic linkage between the QCR data and the QLD Hospital Admitted Patient Data Collection for all admissions on or after the date of diagnosis of breast cancer until the end of 2009 as well as any gynaecological surgery that occurred between 1995-2009. Matching was performed using a unique hospital record number that was stored in both datasets. Once this link was in place we could then identify all admitted episodes of care for each woman during the study period. In particular, we were able to obtain details of breast-cancer related surgical treatment as well as any gynaecological surgery (BSO +/-hysterectomy). Data on selected comorbidities (atherosclerosis,

cerebrovascular disease, cholesterol (hypercholesterolemia), dementia, deep vein thrombosis, diabetes, heart disease, osteoporosis/bone fractures and pulmonary embolism) that were documented during admission were also obtained (see Table 1 for definitions). After the data linkage was completed, de-identified data was extracted by the data custodians for analysis.

Surgical procedures

Relevant gynaecological and breast-cancer related surgical codes are shown in Table 1, classified by type of procedure. For the aim of this study we defined "prophylactic" gynaecological surgery as those surgical procedures that were performed electively at least 30 days prior to a diagnosis of gynaecological cancer. Four procedure groups were formed: (i) hysterectomy only (including hysterectomy plus unilateral salpingo-oophorectomy (USO)); (ii) BSO only (including two separate USOs); (iii) both hysterectomy and BSO; and (iv) neither (including single USO only). Procedures were conservatively classified as "hysterectomy only" in situations where it was unclear whether a hysterectomy also involved a USO or BSO (see Table 1).

Some women with breast cancer did not have a matching hospital treatment record. The reasons for this are unclear, but may include those who received treatment either interstate or overseas. As we could not be sure that these cases did not undergo any prophylactic gynaecological surgery, they were excluded from the study to ensure that they were not incorrectly included in the group who did not have surgery.

Statistical analyses

Survival time was calculated as the number of days between diagnosis and either death or 31st December 2009, whichever came first.. The follow-up period for each patient was divided between the four prophylactic gynaecological surgical procedure groups, depending on what type and timing of procedures. For instance, if a patient who survived for eight years had a prophylactic hysterectomy without BSO two years after her breast cancer diagnosis, then the first two years of her follow up were assigned to the group with no surgery, while the remaining six years were assigned to the group of "hysterectomy only".

Flexible parametric survival models (also known as Royston-Parmar models) were used for this analysis[30, 31]. The baseline survival distribution is represented as a restricted cubic spline function in Royston-Parmar models. This leads to several advantages over the traditional Cox proportional hazard models, particularly the ease with which non-proportional effects can be handled.

Royston-Parmar models may be fitted using various scales for the restricted cubic spline function, including hazards (Weibull models), odds (loglogistic models) and normal (probit models). A differing number of internal "knot points" (where the pieces of the spline function join) can also be defined. The aim is to choose the scale and number of knot points which result in the best proportionality assumption for the covariates, and is determined by the combination that minimizes the Bayes information criterion statistic. Significant covariates are selected via backward elimination using a multivariable fractional polynomial approach[31].

We conducted modelling for all-cause survival, breast-cancer specific survival and survival due to causes other than breast cancer. The analysis of breast-cancer specific survival was further stratified for "pre-menopausal" and "post-menopausal" women (20-49 years and 50-79 years). For the all-cause and breast-cancer specific survival models, the normal scale with 3 degrees of freedom (2 internal knot points) provided the best fit, while for non-breast cancer survival the optimum model was on the odds scale also with 3 degrees of freedom.

The main variable of interest was prophylactic gynaecological procedure group. Delayed entry survival models were utilised to account for the fact that the prophylactic gynaecological procedure group for an individual could alter during their time at risk. Other covariates that were considered included age group at diagnosis of first primary breast cancer, Indigenous status, area-based socioeconomic status, locality of residence, morphology, tumour size, lymph node ratio, laterality, type of breast cancer surgery, hospital type, diagnosis of second primary cancer (breast, gynaecological, and other), and the comorbidities listed above. In addition, significant covariates ($p <= 0.20$), including prophylactic gynaecological procedure group, were tested for time dependency within each model, by fitting interactions between the covariates and time using additional spline functions.

Unadjusted and adjusted estimates of 10-year survival with 95% confidence intervals were calculated. Differences in survival by prophylactic gynaecological procedure group were determined using the model coefficients (β), with the reference group being "neither hysterectomy nor BSO". The significance of the overall effect for prophylactic gynaecological surgery group was also assessed using the Wald test and expressed in terms of a chi-square statistic. Individual estimates were only considered significant if p <= 0.05 for the overall effect. Adjusted survival curves were produced by averaging the predicted survival curve for each subject in a particular stratum.

Propensity score analysis was retrospectively applied to breast cancer specific survival among younger women, in an attempt to minimise selection bias that could have explained survival differences by prophylactic gynaecological procedure group [32, 33]. The propensity score is defined as the probability of treatment assignment conditional on observed baseline covariates. Covariates recorded at the time of breast cancer diagnosis and known to influence survival were age, tumour size and positive lymph node ratio expressed as continuous variables along with categorical groupings for Indigenous status, locality of residence and cell type/morphology (as shown in Table 2). Observations were randomly sorted prior to matching. Propensity scores for treatment ranged from 0.056 to 0.319 for breast cancer patients aged 20-49 years. Those who had some form of prophylactic gynaecological surgery were matched with three others who did not have surgery using nearest neighbour matching without replacement, with a maximum absolute difference of 0.01 allowed in the propensity score for each matched pair (one woman was excluded as there were only 2 suitable matches). Paired t-tests were used to ensure that there were no biases in the distribution of the matching variables between the treated and untreated subjects.

The survival analysis described above was then repeated for the matched cohort. The optimum Royston-Parmar model was on the the normal scale with 2 degrees of freedom. Variables used in the matching process were not included as covariates; rather, Austin [ref] suggests that survival models should be stratified on the matched groups to account for the matched nature of the cohort. As it is not possible to stratified a parametric model when the numbers in each strata are so small (n=4), instead we divided the matched groups into deciles based on the propensity score of the treated case, and the model was then stratified by these deciles (n~340 in each strata).

All data analyses were performed using Stata/SE version 12.1 for Windows. Human Research and Ethics approval for this study was obtained from the Human Research Ethics Committee at the Royal Brisbane and Women's Hospital (HREC/10/QRBW/425).

Results

Of the 25,536 patients diagnosed with primary female breast cancer in QLD between 1997 and 2008, 21,067 (82%) were eligible. The remaining 4,467 women were excluded due to not having a matching hospital record (2,736 cases, 11%), being younger than 20 years or older than 79 years at the time of diagnosis (1,726 cases, 7%), or where the basis of diagnosis was either autopsy or death certificate only (7 cases, 0.03%). Those who were eligible amassed a total of 119,340 years at risk (median follow-up of 4.6 years; interquartile range 3.0 to 8.6 years). Overall, 3,165 (15%) women died during follow-up, including 2,195 (10%) from breast cancer. Key demographic, clinical and treatment characteristics of the study cohort are summarised in Table 2.

Overall, 1,426 women (7%) underwent prophylactic gynaecological surgery (Table 2). However, this varied by age, with 13% of breast cancer patients in the 20-39 age group having prophylactic gynaecological surgery compared to only 3% who were aged 70-79 years old at diagnosis. Apart from younger age, women were more likely to have prophylactic gynaecological surgery if they were non-Indigenous, diagnosed with infiltrating ductal and lobular carcinoma, if they had positive axillary lymph nodes and attended both a public and private hospital for breast cancer treatment. Women who lived in a major city, or who had cerebrovascular disease, diabetes mellitus or heart disease were less likely to undergo prophylactic gynaecological surgery.

A total of 171 women developed gynaecological cancer subsequent to breast cancer, all in women who did not have prophylactic gynaecological surgery ($p = 0.006$, Table 2). Of those, 23 cancers developed in premenopausal women (including 8 ovarian cancers), and 148 in postmenopausal women, respectively. In addition, 1,006 women developed new primary breast cancers and 868 were diagnosed with at least one

other cancer following their initial breast cancer. There were no significant differences in the distribution of subsequent new breast cancers (p = 0.094) or other cancers (p = 0.123) by final prophylactic surgery status.

After adjustment for the covariates listed in Table 3, breast cancer patients who had both a hysterectomy and BSO had a significantly higher survival rate 10 years after diagnosis for all causes of mortality (85%) compared to those who did not have any prophylactic gynaecological surgery (79%, p = 0.002; Table 4 and Figure 1). The differential was similar for breast cancer specific mortality (adjusted 10 year survival of 89% and 85% respectively, p = 0.005). However, for both all cause and breast cancer specific mortality, there was no statistically significant evidence of a survival benefit among women who had either a prophylactic hysterectomy only or BSO only compared to the non-surgery group. There was also no disparity in survival by prophylactic gynaecological surgery group due to causes other than breast cancer, including other types of cancer (Table 4 and Figure 1), or for non-cancer deaths only (data not shown).

Further analysis by age at diagnosis for breast cancer specific survival indicated that the improvement in prognosis among those who had both a hysterectomy and BSO was only significant among younger women (Table 5, Figure 2). Premenopausal women (20-49 age group) had significantly better survival after 10 years (93%) compared to women of the same age who had neither procedure (83%, p = 0.001). In contrast, there were no significant differences in breast cancer specific survival by type of prophylactic gynaecological surgery for women 50-79 years.

When we repeated the breast cancer specific survival analysis for women aged 20-49 using the matched sample, results were similar (Supplementary Table). Again, a significant survival advantage was only seen for women who had hysterectomy plus BSO compared to those who did not have any prophylactic gynaecological surgery (p=0.002).

Discussion

In premenopausal women diagnosed with primary breast cancer, prophylactic hysterectomy and BSO increased breast cancer-specific survival from 83% to 93% after 10 years. This effect remained after

matching for some characteristics that are known to influence prognosis. In contrast, no significant survival benefit of prophylactic gynaecologic surgery was observed for postmenopausal women.

It is generally accepted that estrogen can stimulate breast cancer growth [7]. Endocrine treatments suppressing circulating estrogens via action on the hypothalamic-pituitary-ovarian axis improve survival outcomes in premenopausal hormone receptor-positive breast cancer patients [28]. Ovarian ablation either by radiation treatment or through surgical removal of the ovaries has been advocated in the past but has become less commonly used due to the availability of a modern array of non-invasive endocrine treatment options [34]. These modern treatments are widely thought to be at least as effective as surgical removal of the ovaries [35].

Our findings may provide a challenge to this belief. The main effect of hysterectomy and BSO on breast cancer-specific survival limited to premenopausal women suggests that hysterectomy plus BSO provides advantage by combined hormone ablation [28]. In Australia, endocrine treatment is well accepted and established in hormone receptor-positive breast cancer patients. Before the introduction of anti-estrogenic medication in the late 1970s, ovarian ablation was performed through surgical removal of the ovaries, radiation treatment, GnrH analogues and chemotherapy. Silencing of the ovaries using radiation treatment resulted in a 25% benefit compared to patients who had no adjuvant treatment [34]. As has been highlighted elsewhere [34], we can also assume that BSO had a smaller impact in terms of hormonal ablation on breast cancer patients who were given chemotherapy. However, chemotherapy is variable in its effectiveness of silencing the ovaries with reported rates ranging between 10-98% [36, 37] and BSO may thus have an effect in addition to either chemotherapy or hormonal treatment. While the current study does not answer this important question, a three-arm randomised controlled clinical trial (SOFT) that assigned patients to receive either oral tamoxifen (control) or tamoxifen plus ovarian function suppression through triptorelin, surgical oophorectomy, or ovarian irradiation is in progress [38]. It remains to be researched further as to why only patients who had a BSO plus hysterectomy benefitted from improved survival but patients who had a BSO or hysterectomy alone did not.

We did not find any difference in survival after 10 years from causes other than breast cancer by prophylactic gynaecological surgery status. Our results therefore indirectly suggest that the effect of

combined prophylactic surgery on menopause-related risk factors such as cardiovascular health was minimal and appear to have been heavily outweighed by the survival advantages due to a decrease in breast cancer-specific mortality. However, a significantly higher proportion of women in the "no surgery" group were identified as having cerebrovascular and/or heart disease comorbidities, and this may be part of the reason why they were not offered prophylactic surgery; only women with low risk of cardiovascular disease may have elected for prophylaxis.

While population-based studies reflect "real" world scenarios, they do not provide definitive proof of mechanism of action leading to the observed outcomes. Overall, within the 10-year observation period of our study, 171 women who did not have prophylactic surgery developed gynaecological cancer. Of those only 23 patients were premenopausal (14 developed uterine cancer, eight ovarian cancers). In contrast, none of the women who had prophylactic gynaecological surgery developed gynaecological cancer. The small number of prevented cancers in premenopausal women indicates that it is unlikely that the significant survival advantage among premenopausal women is mainly a result of surgical prophylaxis of these potential gynaecological cancers. Our data did not provide details of women's BRCA1/2 status and family history. Given that only eight premenopausal breast cancer patients who did not have prophylactic surgery developed a new primary ovarian cancer during the observation period, it is also unlikely that the results were largely driven by patients at high risk due to genetic mutations. However, the possibility remains that the majority of those who were BRCA1/2 positive may have been offered risk-reducing prophylactic gynaecological surgery.

As noted in the introduction, for women from the general population, the effect of hysterectomy plus BSO on overall survival is controversial. The prospective Nurses' Health Study cohort study included 29,380 women who had a hysterectomy for benign disease (mean age at surgery = 45 years; 28 years follow-up) [21-23, 39]. Women who additionally had a BSO had significant reductions in ovarian cancer incidence and mortality and reduced risk of breast cancer incidence for premenopausal women following hysterectomy and BSO. However, BSO at the time of hysterectomy was associated with increased overall mortality in women younger than 50 years who never used estrogen therapy, and at no time was BSO associated with increased overall survival [39, 40].

The prospective Women's Health Initiative Observational Study included 25,448 women who had a hysterectomy for a benign condition (average age 49 years; follow-up eight years) [20]. Women in this study were initially invited to participate in the Women's Health Initiative randomized trial that evaluated postmenopausal hormone therapy, but were either found ineligible or declined participation in the trial. Women who had a BSO during hysterectomy had significant reductions in ovarian cancer incidence and mortality compared with women who conserved their ovaries. In contrast to the Nurses' Health Study, breast cancer incidence was not reduced for women who had a BSO, nor was there an increased risk in all cause mortality among pre- or postmenopausal women who had a BSO at the time of hysterectomy.

The retrospective population-based Mayo Clinic Cohort Study of Oophorectomy and Aging enrolled 2365 women who underwent USO or BSO for benign disease in conjunction with hysterectomy [26]. Every member of the cohort was matched by age to a referent woman in the same population who had not undergone oophorectomy. The median age at time of surgery was 44 years among premenopausal women who had a BSO and 62 years among postmenopausal women (average follow-up 25 years). Overall mortality was significantly higher in women who had received prophylactic BSO before the age of 45 years compared to referent women, while having a BSO made no difference to all-cause mortality in postmenopausal women.

The differences in outcomes of these studies compared to the results presented here are likely explained by the different groups of women enrolled. In particular, the three studies outlined above enrolled women from the general population who required a hysterectomy for benign conditions, whereas our study enrolled only patients diagnosed with primary breast cancer. The latter population clearly has a significantly increased risk of death, as well as a significantly increased risk of developing gynaecological cancers [9].

While this population-based study uses innovative new statistical models, which better handle non-proportional effects, the design employed within the present study inherits limitations that need to be acknowledged. First, the follow-up duration available to us was limited to a maximum of 10 years, due to the fact that health administrative data became available in Queensland only in 1997. Secondly, we were unable to determine whether pre-existing comorbidities were present at the time of breast cancer diagnosis; in most cases these could only be subsequently ascertained if they were recorded in the hospital chart during

treatment. On that basis we were unable to take comorbidities into account in the propensity score matching, which leaves open the possibility of some bias remaining in the matched cohort analysis. There was also some potential for misclassification of women regarding the prophylactic gynaecological surgery groups due to procedures that may have been performed prior to matched records being available. Further, reasons for surgery were not recorded in the information provided by Queensland Health. Information on postoperative, adjuvant treatment as well as hormonal replacement therapy (HRT) could not be obtained because these treatments do not require a hospital admission. Finally, data on hormone receptor status were not available, which would have been valuable to examine if prophylactic gynaecological surgery was effective in hormone-receptor positive patients only, or if the effect also extended to hormone-receptor negative breast cancer patients. Similarly we were not able to obtain patients' BRCA status.

In summary, the results indicate that premenopausal women with breast cancer may benefit from hysterectomy plus BSO in addition to the ovarian ablation provided by the adjuvant treatment they commonly receive. While the results of the present study are promising and important, the decision to undergo prophylactic gynaecological surgery obviously has major ramifications for younger women. Therefore, our findings need to be replicated in at least one other independent dataset before current treatment recommendations for premenopausal women diagnosed with breast cancer are reconsidered.

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