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Do breast cancer survivors benefit from prophylactic removal of uterus and ovaries? A population-based data linkage replication study

Running title: breast cancer prophylactic surgery

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Abstract:

Aim: Our previous population-based research found that prophylactic surgery (hysterectomy and bilateral salpingo-oophorectomy (BSO) halved the mortality risk for premenopausal breast cancer patients. Here we aim to replicate findings in a Western Australia (WA) dataset.

Method: Data from the WA Cancer Registry of 15,395 women 20-79 years diagnosed with primary breast cancer (1997-2011) was categorised into four groups: neither hysterectomy nor BSO; hysterectomy only; BSO only or; hysterectomy + BSO. 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.

Results: 12,630 (82.0%) patients had no surgery, 1,799 (11.7%) had a hysterectomy only, 337 (2.2%) had BSO only and, 629 (4.1%) had both a hysterectomy and BSO. For all-causes mortality, unadjusted 10-year survival was highest for women who had either a hysterectomy + BSO (84.7%) or a hysterectomy only (84.2%). After adjusting for covariates, the survival advantage compared to women without any surgery remained significant for the hysterectomy only group (HR=0.89, 95% CI=0.81-0.98; p=0.02). A similar pattern emerged in breast cancer-specific survival with significantly improved survival for women who had a hysterectomy only (HR=0.83, 95% CI=0.74-0.94; p=0.003). However for non-breast cancer related survival, having a BSO alone increased risk of death (HR=1.83, 95% CI=1.14-2.93; p=0.01).

Conclusion: We observed significantly improved overall and breast cancer-specific survival among women who had a hysterectomy only, but increased non-breast cancer related risk after BSO only. Breast cancer patients must weigh up pros and cons of prophylactic surgery.

Introduction:

Breast cancer is the most common cancer for females worldwide, with an estimated 1.67 million new cases diagnosed in 2012 [1]. Genetic factors are implicated in a small proportion of women at very high risk. Women with such germline mutations (BRCA 1, BRCA 2 genes) often consider prophylactic surgery to reduce their risk of contralateral breast, ovarian and/or uterine cancers [2,3].

Among healthy women without known germline mutations, some studies have indicated that prophylactic removal of the uterus and/or ovaries (and therefore reduction of exposure to endogenous estrogen) may also reduce risk of developing and dying from breast cancer [4,5]. Few women may choose this option however, as this requires surgery and may be associated with health effects such as increased risk of osteoporosis and heart disease, especially for women who are premenopausal at the time of prophylactic surgery [6-8].

Given that one in eight women in Australia [9] will develop breast cancer, and a large majority of these breast cancers arise in women without BRCA germline mutation, we recently raised the question whether prophylactic surgery (hysterectomy ± bilateral salpingoophorectomy (BSO)) should be considered by women who have been diagnosed with breast cancer [10]. Currently, women are often prescribed anti-estrogenic medication after breast cancer, but studies have shown that many women do not take these medications consistently as prescribed and many women stop the treatment altogether ahead of the recommended treatment period [11,12]. This is likely due to the common side effects of these treatments including hot flushes, musculoskeletal problems, depression, and other symptoms. For example, the Suppression of Ovarian Function Trial (SOFT) [13] which assigned women to five years of either tamoxifen, tamoxifen plus ovarian suppression, or exemestane plus ovarian suppression, and 80%, 69% and 49% of premenopausal women in the tamoxifen arm reported hot flushes, musculoskeletal symptoms and depression, respectively. The incidence of these side effects was even higher among the women in the other two treatment arms[13]. While the trial did not find a significant difference in treatment effect between the trial arms overall, ovarian suppression (monthly injections of triptorelin, surgical removal of the ovaries or radiation) was of survival benefit to women at higher risk of recurrence, including those who required chemotherapy and were premenopausal.

Before the advent of anti-estrogenic medication, surgical removal of the ovaries was a relatively common procedure in breast cancer treatment pathways, but has been rarely performed in recent years, in part due to many women receiving chemotherapy and/or hormone therapy, and the observation of improved survival in women with chemotherapy-induced amenorrhea [14,15]. However, some women may choose to undergo prophylactic surgery as part of their treatment or for other, unrelated reasons, such as treatment of benign gynecological conditions.

Given the above mentioned considerations with regards to adherence to long-term medication, we previously explored the impact of prophylactic hysterectomy ± BSO on the disease-free and overall survival of women after breast cancer treatment. Among a large population-based dataset of 21,067 women with breast cancer in Queensland (QLD), Australia, with 10 years of follow-up available, we found that 1,426 women (7%) underwent risk-reducing surgery (13% of premenopausal and 3% of postmenopausal women, respectively). The benefit of risk-reducing surgery (hysterectomy plus BSO) on overall survival was largely confined to women younger than 50 years (adjusted hazard ratio = 0.69; P =0.005), and appeared to be mainly due to a reduction in breast cancer-specific mortality within this age group[10].

Due to the potential implications of these results for women with breast cancer and their choice of adjuvant treatment options it is essential that they are verified elsewhere. Here we aim to replicate our findings in a new and independent dataset from the jurisdiction of Western Australia (WA).

Methods:

Data

After appropriate approvals were obtained from the WA Department of Health, de-identified data was extracted by the WA Data Linkage System custodians. The WA Data Linkage System was established to connect all available health and related information for the WA population. For consistency with our earlier study, all cases of invasive breast cancer (ICD-O-3 code C50) diagnosed among women 20-79 years in WA between 1997 and 2011 were selected from the WA Cancer Registry, with follow-up on mortality status available to 31 Dec 2012. Cases based on autopsy or death certificate only or where the patient died on the same day as diagnosis were excluded from the analysis. Other data items regarding demographic and tumour details available from the WA Cancer Registry included Indigenous status (self-identified), breast cancer cell type (morphology), laterality, size of the tumour, number of lymph nodes surgically excised and number of positive lymph nodes.

The WA Data Linkage System also holds a record of the admissions to every public and private hospital within WA for each cancer patient. Data for all admissions on or after the date of diagnosis of breast cancer as well as any gynaecological surgery that occurred between 1979 and 2012 was requested. In particular, we obtained details of breast-cancer related surgical treatment (breast conserving surgery or mastectomy) as well as any gynaecological surgery (bilateral oophorectomy (BSO) +/-hysterectomy). Based on this information, all eligible breast cancer patients were categorised into one of the following four clinically relevant groups: *Group 1 (neither hysterectomy nor BSO group):* includes those who did not undergo any prophylactic gynaecological procedures or who only underwent removal of one ovary and fallopian tube; *Group 2 (hysterectomy only group):* includes those who underwent hysterectomy alone or hysterectomy + unilateral removal of one ovary and fallopian tube (cases where it was unclear whether a hysterectomy also involved a USO or BSO were conservatively classified as "hysterectomy only"); *Group 3 (BSO only group)*: includes those who underwent removal of both fallopian tubes and ovaries but not hysterectomy; *Group 4 (hysterectomy + BSO group):* includes those who underwent removal of the uterus (hysterectomy) and both fallopian tubes and ovaries. Data on selected comorbidities (other cancers, atherosclerosis, cerebrovascular disease, hypercholesterolemia, dementia, deep vein thrombosis, diabetes, heart disease, osteoporosis/bone fractures or pulmonary embolism) documented during admission were also obtained (refer to Table 1 for coding definitions).

Statistical analyses

Survival time was calculated as the number of days between diagnosis and either death or censoring date (31 Dec 2012), whichever came first. Cause of death was ascertained through routine matching with the Australian National Death Index. Unadjusted estimates of 10-year survival were obtained using the Kaplan-Meier method.

Flexible parametric survival models were then applied to the data [16,17]. The method was detailed in our previous analysis conducted in QLD [10]. Briefly, the baseline survival distribution is represented as a restricted cubic spline function in flexible parametric survival models, in contrast to the simpler linear function employed in traditional Cox proportional hazard models. This approach makes it easier to model non-proportional effects in the underlying hazard function. The optimum scale and number of internal knot points for the cubic spline function in each model were determined based on the Bayes information criterion statistic.

Significant covariates ($p <= 0.20$) were selected via backward elimination using a multivariable fractional polynomial approach [17]. The models were extended to allow for time dependencies of the covariates by fitting interactions between the covariates and time using additional spline functions where appropriate.

Follow-up time for each patient was divided between the four prophylactic gynaecological surgical procedure groups, depending on the type and timing of any relevant procedures that were performed. For example, if a breast cancer patient survived for a total of four years but had a prophylactic hysterectomy without removal of the ovaries one year after her breast cancer diagnosis, then the first year of her follow up would be classified as belonging to the "neither hysterectomy nor BSO" group, while the remaining three years of survival would be assigned to the group of "hysterectomy only".

We conducted modelling for both all-cause survival and breast-cancer specific survival by prophylactic gynaecological procedure group. The analysis was further stratified into "pre-menopausal" and "post-menopausal" women (defined as 20-49 years and 50-79 years, respectively, for the purpose of this study). Delayed entry models were fitted to allow for the possibility that an individual could switch prophylactic gynaecological procedure groups during follow-up. Differences in survival were assessed in terms of adjusted hazard ratios (HRs), which were presented along with the corresponding 95% confidence intervals (95% CI). For each model, the reference group used was "neither hysterectomy nor BSO". Individual estimates were only considered significant if $p <= 0.05$ for the overall effect of prophylactic gynaecological procedure group.

Finally, a propensity score analysis was conducted in order to assess the possibility that selection bias could explain any survival differences by the type of treatment received[18,19]. The propensity score is defined as the probability of treatment assignment conditional on observed baseline covariates. Factors recorded at the time of breast cancer diagnosis that are known to influence survival were age, Indigenous status, locality of residence, cell type/morphology, tumour size and lymph node status. Breast cancer survivors who had prophylactic gynaecological surgery were matched using these covariates with three patients who did not have any surgery. Chi-squared tests were used to check for equality in the distribution of the covariates used in the matching process. The analysis described above was then repeated for breast cancer-specific survival using the matched cohort.

All data analyses were performed using Stata/SE version 13.1 for Windows.

Results:

Out of a total of 17,517 women who were diagnosed with a first primary breast cancer in WA between 1997 and 2011, 15,395 (87.9%) were eligible to be included in the analysis based on the criteria described. The reasons for exclusion were age at diagnosis younger than 20 years or older than 79 years (n=1,779, 10.2%), where the basis of diagnosis was autopsy or death certificate only (n=21, 0.1%) or not having a matching hospital record (n=322, 1.8%). Women with missing hospital data had a slightly younger median age compared to the eligible cohort (54 versus 57 years, respectively), and also tended to be more likely to have missing details for Indigenous status, morphology, tumour size, lymph node status and laterality. Of the remaining cohort, 12,630 (82.0%) had no record of a hysterectomy or a BSO, while 1,799 (11.7%) had a hysterectomy only, 337 (2.2%) had a BSO only and 629 (4.1%) had both a hysterectomy and BSO recorded.

The distribution of prophylactic surgery differed significantly between most of the subgroups listed in Table 2, for example by women's age, Indigenous status, tumour size and lymph node status. Overall in the observation period, 778 patients were diagnosed with second primary breast cancers and 112 second primary gynaecological cancers were detected, including cancers of the uterus (n= 62; 55.4%), ovary (n = 27; 24.1%), cervix (n = 7; 6.3%) and other gynaecological organs (n = 16; 14.3%). None of the women in the hysterectomy and BSO group developed gynaecological cancers. There were also 174 additional other cancers diagnosed with colorectal, skin and lung cancers the most commonly observed.

For all-cause mortality, unadjusted 10-year survival was highest for women who had either a hysterectomy and BSO (84.7%) or a hysterectomy only (84.2%, Table 3). After adjusting for the covariates indicated in Table 4, the survival advantage compared to women without any prophylactic gynaecological surgery remained significant for the hysterectomy only group (HR=0.89, 95% CI=0.81-0.98; p=0.02). A similar pattern emerged in breast cancer specific survival (Table 3 and Figure 1) with significantly improved survival for women who had a hysterectomy only (HR=0.83, 95% CI=0.74-0.94; p=0.003). For non-breast cancer related survival however, women who had a BSO only were at increased risk to die within 10 years of diagnosis relative to women who did not have any prophylactic gynaecological surgery (HR=1.83, 95% CI=1.14-2.93; p=0.01).

Table 5 and Figure 2 show breast cancer specific survival estimates for women stratified by age group. In younger women, unadjusted 10-year survival was highest (91.0%) for those who had both a hysterectomy and BSO, but the overall effect of prophylactic gynaecological procedure group was not statistically significant after adjustment (p=0.14). For women 50 years or older, there was a significant association (p=0.02) in the fully adjusted model, with hysterectomy only again resulting in a significant benefit in breast cancer specific survival compared to having no prophylactic surgery (HR=0.77, 95% CI=0.65-0.92; p=0.004), while there was no significant difference for either BSO only or hysterectomy and BSO.

Results for the breast cancer-specific survival using the matched sample from the propensity score analysis are contained in Supplementary Table 1. As observed in the main analysis, the only statistically significant difference between the surgery groups was that women who had a hysterectomy only had significantly better adjusted survival at 10 years from the time of diagnosis compared to women who did not have any prophylactic surgery (HR=0.81, 95% CI=0.71-0.92; p=0.002).

Discussion:

The main aim of this study was to use an independent cohort to replicate our previous finding of significantly improved survival among breast cancer patients with unknown mutation status who underwent prophylactic surgery, in particular through the combined procedures of hysterectomy and BSO. Similar to the original analyses from QLD, none of the women from WA in the hysterectomy and BSO prophylactic surgery group developed gynaecological cancer[10], and overall survival was optimised among women when they had a hysterectomy. While the results between the two cohorts were broadly consistent, there were some apparent variations. In QLD, a combination of hysterectomy and BSO was found to lead to a survival advantage, particularly for breast cancer-specific survival among premenopausal women. For the WA data we observed significantly improved overall and breast cancer-specific survival among women who had a hysterectomy only. When stratified by age, this effect remained significant for women who were aged 50-79 years old at diagnosis. Women in WA who had a BSO but no hysterectomy were also found to have lower survival for causes of death other than breast cancer, a finding not observed in the QLD cohort.

It is not clear what may have caused these differences between the data from WA and QLD. The smaller sample size in WA may have been insufficient to demonstrate statistical significance for some outcomes. For example, for women with breast cancer aged 20-49, the point estimate for the adjusted HR for those who had a hysterectomy and a BSO was 30% lower than for the non-surgery reference group, but this potential survival advantage failed to reach statistical significance. Further, the hospital records in WA went back much earlier than in QLD (1979 and 1995, respectively). Consequently, 18% of breast cancer patients in WA were reported to have had a prophylactic gynaecological procedure, compared to only 6% in QLD. It is therefore possible that patients in QLD may have been less likely to be allocated to the correct procedure group. Unobserved differences in the surgical approach, for example whether or not the fallopian tubes were also removed during BSO, the adjuvant treatment that women received, characteristics of the sample, lack of information about some key confounders in the WA data set (hospital type, area-based socioeconomic status and locality of residence) or other unmeasured confounders may have also contributed to these somewhat divergent findings.

Prophylactic surgery is increasingly used by women who are BRCA 1/2 or Lynch syndrome mutation carriers to reduce the risk of gynaecological cancers[20-22]. The impact of such surgery on hot flashes and other vasomotor symptoms, as well as sexual wellbeing, has been described as significant from before to after surgery among premenopausal women, although physical and psychosocial wellbeing were not significantly affected [23-25]. Most of these side effects remained even if women took hormone replacement therapy. One study included a small number of women with breast cancer (n=200) before prophylactic surgery, and these women already had significantly greater vasomotor symptoms already before surgery (most likely a consequence of their adjuvant breast cancer treatment) compared to other premenopausal women in the series [24].

Considering the results of our QLD and WA analyses in conjunction, which included more than 42,000 Australian women with breast cancer, patients may consider prophylactic gynaecological surgery after a breast cancer diagnosis even if they are not known to carry a germline mutation. In addition to the benefit of a reduced risk of second gynaecological malignancies, the two large samples also provide some evidence that risk-reducing prophylactic surgery may have an advantageous effect on the progression of the breast cancer as a lower risk of breast cancer specific mortality was observed. The pathway and mechanism of this effect are unclear and it is also unknown whether it is limited to certain breast cancer subgroups, or is independent of hormone-receptor status and other breast cancer features.

The recently published SOFT trial reported a survival benefit in premenopausal high risk breast cancer patients (those that required chemotherapy) assigned to ovarian suppression in addition to tamoxifen [13]. These results and the result from our observational cohorts indicate that medical ovarian ablation with chemotherapy or hormone therapy alone without ovarian suppression are insufficient to completely reduce the hormonal drivers of breast cancer, at least in premenopausal patients. Neither cohort showed a negative impact of prophylactic surgery on survival from causes other than breast cancer except for women in WA who had a BSO only, indicating that the risk of alternative causes of death such as heart disease or atherosclerosis was not unduly increased when hysterectomy ± oophorectomy is performed.

Both of our QLD and WA studies share the inherent limitations of using a hospital-derived administrative dataset. This includes absence of data about BRCA1/2 mutation status, as well as hormone receptor status of the breast cancer, potential for misclassification of women regarding the prophylactic gynaecological surgery groups due to procedures that may have been performed in other jurisdictions or prior to matched records being available (less so in WA), coding errors, as well as a lack of information about the reasons for the gynaecological surgery.

The WA dataset had some further distinctive limitations. In particular, for about 10% of the WA patients the tumour size was unavailable, compared to only 4% of the QLD cohort. Furthermore, the WA dataset did not include information on the locality of residence, area-based socioeconomic status or whether treatment was conducted in a public or private hospital. Consequently, although the models used for the two cohorts were similar, the WA analyses could not be adjusted for these potential confounding variables. A small proportion of women did not have matching hospital records and therefore had to be excluded from the study as their prophylactic surgery status was unknown, which may have introduced some bias into the results. Other biological features of the tumour that are known to be related to prognosis, such as hormone receptor status, were not available for inclusion in the analysis. Finally, data on second primary cancers were derived from the same data set as the comorbidities that were recorded during hospital admissions rather than being obtained directly from the WA cancer registry, and therefore are unlikely to represent all subsequent cancers.

In summary, data from two large administrative cohorts in Australia jointly indicate the potential for a survival benefit from prophylactic gynaecological surgery for breast cancer patients. However, it remains unclear whether hysterectomy alone or combined with BSO should be considered. There is also some ambiguity as to exactly what subgroups of patients might or might not benefit from the intervention. These results are generally in agreement with the recently reported outcomes from the SOFT trial of a benefit for breast cancer survival through medical ovarian suppression, which also highlighted the significant side effects of such treatment[23,24]. We therefore put forward the question of whether a randomised trial of prophylactic gynaecological surgery (hysterectomy plus BSO) compared to the best arm from the SOFT trial (exemestane–ovarian suppression) among women with breast cancer should be designed. Besides the potential advantages detailed in this and our previous report [10], women must consider potential harms from such surgery compared to medication before enrolling. While such a trial could help to more clearly ascertain whether prophylactic surgery definitely improves survival for breast cancer patients, the exact protocol in particular the exact surgical procedure, the age group and the best pharmacological comparator would need to be considered carefully. Large prospective cohort studies such as the Million Women Study may also be a suitable data source to further investigate the prophylactic surgery and survival association[25].

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