Long-term outcomes of bilateral salpingo-oophorectomy in women with personal history of breast cancer

Hend Hassan1,2; Tameera Rahman3; Andrew Bacon2; Craig Knott3; Isaac Allen1,2; Catherine Huntley2,4; Lucy Loong2,4; Yvonne Walburga1,2; Eva Morris5; Steven Hardy2; Bethany Torr4; Diana M Eccles6; Clare Turnbull4; Marc Tischkowitz7; Paul Pharoah8; Antonis C. Antoniou1

1: Centre for Cancer Genetic Epidemiology, University of Cambridge, 2: NHS England, National Disease Registration Service, 3: Health Data Insight, CIC, 4: Institute of Cancer Research, Division of Genetics and Epidemiology, 5: University of Oxford, Big data institute, 6: University of Southampton, school of Cancer Research, 7: Department of Medical Genetics, University of Cambridge, 8: Cedars Sinai Medical Centre, Los Angeles

Corresponding author:

Hend Hassan
hmamh2@cam.ac.uk

# Abstract

**Objectives:** To investigate the association between bilateral salpingo-oophorectomy and long-term health outcomes, compared to receiving standard treatment after a breast cancer diagnosis.

**Methods and analysis:** We used data on women diagnosed with invasive breast cancer between 1995 and 2019 from the National cancer Registration Dataset (NCRD) in England. The data were linked to the Hospital Episode Statistics- Admitted Patient Care (HES-APC) dataset to identify BSO delivery. Long-term health outcomes were selected from both datasets. Multivariable Cox-regression was used to examine the associations, with BSO modelled as a time-dependent covariate. The associations were investigated separately by the age at BSO.

**Results:** We identified 568,883 women, 23,401 of whom had BSO after the breast cancer diagnosis. There was an increased risk of total cardiovascular diseases with a HR of 1.10 (95%CI:1.04-1.16) in women who had BSO <55y and 1.07 (95%CI:1.01-1.13) for women who had BSO ≥55y. There was increased risk of Ischaemic heart disease, but there was no association with cerebrovascular diseases. BSO at any age was associated with increased risk of depression (HR:1.20, 95%CI:1.12-1.28) and increased risk of second non-breast cancer in older women (HR:1.21, 95%CI:1.08-1.35). BSO in older women was associated with reduced risk of all-cause mortality (HR:0.92, 95%CI:0.87-096), but not in women who had BSO <55y.

**Conclusion:** In women with personal history of breast cancer, BSO before and after the age of 55y is associated with increased risk of long-term outcomes. BSO after 55y is associated with reduced all-cause mortality. Family history or genetic predisposition may confound these associations.

## What is already known on this topic:

Prior research has showed that bilateral salpingo-oophorectomy (BSO) is associated with reduction in ovarian cancer risk but an increase in the risk of adverse long-term health outcomes. Though, there is a gap in examining the long-term outcomes of BSO in women with personal history of breast cancer.

## What this study adds:

Our findings indicate an increased risk of total cardiovascular diseases and depression in women who underwent BSO. However, there is a reduction in all-cause mortality in women who had BSO after the age of 55 years.

## How this study might affect research, practice or policy:

We hope that our study will aid in creating personalized counselling and enhancing decision-making for women with personal history of breast cancer who opt for BSO.

# Introduction

Women with personal history of breast cancer are at increased risk of developing second cancers including ovarian cancer[1]. The cumulative 20-year risk of developing ovarian cancer after a breast cancer diagnosis has been estimated to be 1.4% for women diagnosed with breast cancer before the age of 50 and 1.9% for those diagnosed at age of 50 or older[2]. There is no effective modality for screening for ovarian cancer. The only recommended method for prevention in women at elevated risk for ovarian cancer is bilateral salpingo-oophorectomy (BSO). BSO is associated with more than 90% reduction in the risk of ovarian cancer[3, 4]. However, the benefit of ovarian cancer risk reduction should be balanced against the health sequalae caused by the pre-mature loss of estrogen. In women with no history of cancer BSO with hysterectomy for benign indications has been found to be associated with reduced risk of ovarian cancer and breast cancer and increased risk of cardiovascular diseases, depression, dementia, cancer and all-cause mortality[5].

BSO is also performed to supress ovarian function in women with estrogen receptor positive breast cancer. Ovarian function suppression could be achieved by surgical removal of both ovaries or radiation-induced ablation both of which are permanent, or by using Gonadotropin releasing hormone agonists (GnRHa) which results in temporary suppression of ovarian function. Estrogen cessation might lower the risk of recurrence, contralateral breast cancer and mortality[6]. The present study focuses on other long-term outcomes of BSO after breast cancer diagnosis, including cardiovascular diseases (CVD), neuropsychiatric outcomes and second cancer occurrence. This has not been studied before at a population scale using electronic health records. Evidence is limited and focuses only on mortality outcomes[7, 8] or on women who had the BSO prior to the diagnosis of breast cancer[9]. Also, evidence derived from the general population is often used to counsel high-risk women who are opting for BSO.

Using general population data to counsel women with personal history of breast cancer present challenges, as these women may exhibit different benefit-risk profile e.g. reproductive history, family history of cancer, weight and alcohol consumption[10]. These in turn may influence their baseline risk of developing long-term health sequalae. Tumour characteristics and treatment choices could confound the association between BSO and the long-term outcomes[11, 12]. Moreover, in general population, BSO is often performed at the time of hysterectomy which means that the evidence could be confounded by the indication for the hysterectomy or by the potential long-term outcomes of hysterectomy alone in the comparison groups used[13]. Hence, there is a need for guidance to be based on studies specifically conducted on these women. Women should be able to make decisions based on accurate knowledge of the of the risks and benefits of the BSO. This information is particularly relevant in women with personal history of breast cancer who may have additional concerns about using hormonal replacement therapy.

This study aims to investigate the association between BSO and long-term health outcomes, compared to receiving standard treatment after a breast cancer diagnosis. This is the largest study to date to examine these associations, using population scale linked data from the National Cancer Registration Dataset (NCRD) and Hospital Episode Statistics- Admitted Patient Care (HES-APC) in England.

# Methods

## Data sources

### National Cancer Registration Dataset (NCRD)

The National cancer Registration dataset (NCRD) is collected and manged by the National Cancer Registration and Analysis Service (NCRAS), population-based cancer registry for England with national coverage since 1971[14]. NCRAS collects data from multiple sources including multidisciplinary team meetings, pathology reports, molecular testing results, treatment records and hospital activity records. The NCRD contains demographic data including the age at diagnosis, gender, deprivation index, tumour characteristics data including the cancer stage using the TNM staging system, grade, hormonal receptor status, tumour morphology, tumour size, number of nodes excised and treatment data on the receipt of radiotherapy, chemotherapy, immunotherapy, and surgery. The Office for National Statistics provides NCRAS with data on the date and cause of death. Section 254 of the health and social care act 2012 allows NCRAS to collect individual-level data on cancer patients without consent.

### Hospital Episode Statistics- Admitted Patient Care (HES-APC)

HES- APC collects data on all NHS hospital admissions in England. HES-APC also collects data on admissions to independent providers funded by the NHS[15]. The NHS funds more than 98% of the hospital activity in England[15]. HES-APC includes all hospital care episodes since financial year 1989/90. Data fields include diagnoses, procedures, patient demographics and admission and discharge dates. Diagnoses are coded using the International Classification of Diseases version 10 (ICD-10). Each admission could have up to 20 diagnoses. We considered any of the first three diagnosis fields as the primary diagnosis/es and the other diagnosis fields as comorbidities. Procedures are coded using OPCS4 codes (Office of Population, Census and Surveys Classification of interventions and Procedures, 4th Revision). Pseudonymized patient identifiers allows linkage of HES APC to NCRD.

## Inclusion and exclusion criteria

We included women diagnosed with invasive breast cancer between 1995 and 2019, diagnosed between the ages 20 and 75 and who had no history of previous cancer diagnosis. We excluded women with history of hysterectomy or oophorectomy before the date of breast cancer diagnosis. The number of women excluded for different reasons are summarised in Figure 1. For each outcome investigated, women diagnosed with the specific outcome (in any of the 20 HES diagnosis fields) before or within the first year of the breast cancer diagnosis were excluded from the analysis. For the association with contralateral breast cancer, women with bilateral tumours or unknown laterality of the first tumour were excluded from the analysis.

## Identifying BSO procedures

BSO procedures were identified using the OPCS4 Q221 and Q223 codes in HES-APC. Hysterectomy procedures were identified using the codes Q073, Q074, Q075, Q078, Q079, Q081, Q082, Q083, Q088, Q089. BSO was considered to be for a malignant indication if the patient was diagnosed with a gynaecological malignancy 1 year before or 1 year after the procedure date.

## Identifying long-term outcomes

Outcomes of interest were all-cause mortality, total cardiovascular diseases, ischaemic heart diseases, cerebrovascular diseases, dementia, depression and parkinsonism (extrapyramidal movement disorders), breast cancer mortality, non-breast cancer mortality, contralateral breast cancer (CBC) and second non-breast cancer (excluding non-melanoma skin cancer). Cancer outcomes and mortality data were identified from the NCRD. Breast cancer specific mortality was defined as death where breast cancer was listed as a cause on part I of the death certificate. Non-cancer outcomes were identified from HES admissions using the first three diagnosis fields (primary diagnosis) or from part Ia of the death certificate. The ICD 10 codes used are summarised in Table 1S. The associations with the severity of CVD outcomes (fatal/non-fatal) were assessed separately. Fatal outcomes were outcomes identified either from the cause of death or from HES admissions followed by fatality within the first 48 hours after the admission. Non-fatal were outcomes identified from HES admissions which were not followed by death within the first 48 hours.

## Follow up and Censoring

Follow up started one year after the date of breast cancer diagnosis to avoid misclassifying bilateral breast cancers as second primary cancers and to allow time for exclusion of cases with any comorbidities identified after the breast cancer diagnosis. Follow up ended at the first of the following: the outcome of interest, censoring or end of data collection. Data collection ended on 30th December 2020 for cancer outcomes and 1st May 2022 for mortality and non-cancer outcomes. Follow up time was censored at the time of unilateral oophorectomy, pelvic clearance, or bilateral oophorectomy for malignant indications (except for ovarian cancer and second non-breast cancers analyses). In addition, for the CBC analysis women were censored one year after a breast surgery on the opposite side or a breast surgery with unknown laterality occurring more than one year after the breast cancer diagnosis. In each separate analysis for an outcome of interest, women who developed any of the other outcomes studied here were still followed for the outcomes of interest. Follow up for BSO started one year after the surgery date, to allow time for biological plausibility (allow time for the cessation of estrogen to cause a pathological effect) and to minimize detection bias. We performed separate analyses by the age at surgery, BSO <55y in younger women and BSO ≥ 55y in older women. The age 55 was chosen as a proxy for the age at menopause. According to the British Menopause Society it is estimated that more than 80% of women will be menopausal by the age of 54[16]. In the younger women analysis, we only included women diagnosed with breast cancer before the age of 55. Women who were diagnosed before age 55 and had BSO after age 55y were included in the non-BSO group and censored at the date of their surgery, occurrence of events, whichever occurred first.

## Multiple imputation of missing data

We used multivariate imputations by chained equations to impute the missing TNM stage, grade, ER status, HER2 status, tumour size, number of lymph nodes excised, ethnicity and Charlson-comorbidity index. Supplementary materials.

## Statistical analysis

We used Cox-regression to calculate hazard ratios for the association between BSO and the long-term outcomes, with BSO modelled as a time dependent covariate. The models were adjusted for age at breast cancer diagnosis, year of diagnosis, tumour size, number of excised lymph nodes, M-stage, grade, ER status, HER2 status, ethnicity (White, Asian, Black, Mixed and other), deprivation index (1-least deprived, 2, 3, 4, 5-most deprived) and Charlson comorbidity index. The Charlson comorbidity index is a weighted scale that predicts the risk of mortality within 1 year of hospitalisation[17]. The index was derived from HES-APC records for all the patients 6 years prior to the breast cancer diagnosis and calculated using the method described by Quan et al[18]. The association with second cancer was further adjusted for hysterectomy. A regression model was fitted using each of the imputed datasets and the log (hazard ratios) were combined using the Rubin’s rule[19]. We fitted the models for the CBC and second non-breast cancer analyses with an interaction term between BSO and M-stage (0/1). This was done to provide estimates for the association in women with M-stage 0. The Cox-regression proportional hazard assumption was assessed by plotting the Schoenfeld residuals (Supplementary materials 2: Figure 2S -17S). All analyses were carried out using R (version 4.1.0; R Foundation for Statistical Computing, Vienna, Austria).

## Sensitivity analyses

We assessed whether the findings were influenced after adjustment for hysterectomy. We also examined the associations between the long-term outcome and three types of procedures (hysterectomy alone, hysterectomy and BSO, BSO alone).

We conducted sensitivity analyses for the associations between the long-term outcomes and BSO in older women by restricting the analyses to women diagnosed with breast cancer at age 55 years or older.

To examine whether the association with breast cancer mortality is explained by CBC diagnosis, we conducted a sensitivity analysis where CBC diagnosis served as a censoring event. Given that the initial cohort analysis for assessing the association with breast cancer mortality included women with bilateral tumours or unknown literalities of the first tumour, we repeated the analysis after excluding women with unknown first tumour literalities or bilateral tumours. This was done while retaining the initial censoring methodology, and subsequently employing CBC as a censoring event to allow comparability of the results.

## Patients and Public involvement

The CanGene-CanVare programme includes a Patient Reference Panel (PRP) made up of patients, carers and member of the public who are, or have been, affected by cancer. The PRP is involved in programme governance and oversight, contributing personal perspectives and experiences as well as in the communication and dissemination of programme output.

# Results

We identified 568,883 women, 23,401 of whom had BSO after the breast cancer diagnosis, 8,243 after the age of 55 years and 15,158 before the age of 55 years. Baseline demographic, tumour and clinical characteristics of women who had BSO (< 55 and ≥ 55 years) alongside their corresponding reference groups are shown in Table 1. The median age at diagnosis for women who had BSO <55y was 43 years (IQR:38-47 years) and for women in the reference group was 48 years (IQR:43-51 years). The median age at diagnosis in women who had BSO ≥ 55y was 57 years (IQR:52-63 years) and for women in the corresponding reference group 58 years (IQR:50-66). The percentage of white women in the BSO groups was higher than in the non-BSO groups, in the “≥ 55y” BSO group 94% were white versus 86% in the reference group and in the “< 55y” BSO group 92% were white versus 84% in their reference group. Among the women who had BSO ≥ 55y 65% had hysterectomy compared to 2% in the reference group and 43% in those who had BSO <55y compared to 3% in the reference group.

Summaries of the numbers at risk, person years and number of events in the cohort and the hazard ratios (HR) for the associations between BSO and the long-term outcomes are shown in Table 2.

## Associations with cardiovascular outcomes

There was an increased risk of total CVD with a HR of 1.10 (95%CI:1.04-1.16) in women who had BSO <55y and a HR of 1.07 (95%CI:1.01-1.13) for women who had BSO ≥55y. There was increased risk of Ischaemic heart disease (IHD) for both younger and older women with HRs of 1.20 (95%CI:1.06-1.37) and 1.15 (95%CI:1.05-1.27), respectively. Further exploration of associations with IHD subtypes, BSO was significantly associated only with angina (unstratified HR:1.27, 95%CI:1.13-1.42), but not with myocardial infarction (unstratified HR:1.03, 95%CI:0.89-1.18) or chronic ischaemic heart disease (unstratified HR:1.08, 95%CI:0.99-1.19).

There was no association between BSO and cerebrovascular diseases, haemorrhagic stroke, or ischaemic stroke with unstratified HR estimates 1.00 (95%CI:0.91-1.11), 0.97(95%CI:0.80-1.19) and 1.04(95%CI:0.90-1.19), respectively. Investigating the associations by the severity of the CVD outcomes yielded significant associations only with the non-fatal total CVD and non-fatal IHD outcomes.

## Association with neuropsychiatric outcomes

BSO was associated with increased risk of depression both in women who had BSO <55y (HR:1.18, 95%CI:1.09-1.28) and ≥55y (HR:1.18, 95%CI:1.05-1.33). BSO was not associated with parkinsonism in women who had BSO <55y (HR:0.98, 95%CI:0.67-1.44), but was associated with a reduced risk of parkinsonism in those who had BSO ≥55y (HR:0.67, 95%CI:0.48-0.94).

## Association with cancer outcomes

BSO was associated with increased risk of second primary non-breast cancers in women having BSO ≥55y (HR:1.21, 95%CI:1.08-1.35), but there was no association in women who underwent BSO before age 55y (HR:1.03, 95%CI:0.91-1.17). BSO at any age was not associated with contralateral breast cancer (HR:1.04, 95%CI:0.95-1.15)

## Association with mortality outcomes

Having BSO at or after the age of 55 years was associated with reduced risk of all-cause mortality with a hazard ratio of 0.92 (95%CI:0.87-0.96), but not in younger women (HR:1.03, 95%CI:0.98-1.08). BSO <55y was associated with increased risk of breast cancer mortality 1.09 (1.04-1.15), but no association was observed in women who had BSO after the age of 55y (HR:0.96, 95%CI:0.89-1.05). Finally, BSO was associated with reduction in the risk of non-breast cancer mortality for both women who had BSO <55y (HR:0.86, 95%CI:0.78-0.96) and BSO ≥55y (HR:0.93, 95%CI:0.88-0.99).

## Sensitivity analyses

Sensitivity analysis for the associations in women who underwent the BSO ≥55y and restricted on women diagnosed with breast cancer at or after age 55y yielded similar results (Supplementary materials 2: Table 6S).

Sensitivity analysis revealed that adjusting for hysterectomy primarily influenced the association between BSO performed before age 55y and breast cancer and all-cause mortalities. Among the “BSO <55y” analysis cohort hysterectomy alone and hysterectomy and BSO were associated with reduction in the risks of all-cause mortality and breast cancer mortality. While BSO alone was associated with increased risk of breast cancer mortality (HR:1.26, 95%CI:1.19-1.34), all-cause mortality (HR:1.18, 95%CI:1.12-1.25) and reduced risk of non-breast cancer mortality (HR:0.82, 95%CI:0.71-0.96). More details in supplementary materials 2 (Figure 1S, Table 4S, Table 5S)

When censoring at the date of CBC, BSO alone was not associated with breast cancer mortality with HR estimates of 1.05 (95%CI:0.97-1.14) and 0.90 (95%CI:0.73-1.11), for women who had BSO <55y and ≥55y respectively.

*Table 1: Baseline characteristics of women who had BSO above or after the age of 55 with their respective reference groups used in the association analyses.*

| Bilateral salpingo-oophorectomy  | YesAge at BSO <55N = 15,158 | NoReference1N = 221,892 | Yes Age at BSO ≥55N = 8,243 | NoReference2N = 545,482 |
| --- | --- | --- | --- | --- |
| Diagnosis year  |  |  |  |  |
| Median (IQR) | 2,010 (2,004, 2,014) | 2,009 (2,002, 2,015) | 2,006 (2,000, 2,012) | 2,009 (2,003, 2,015) |
| Age at diagnosis |  |  |  |  |
| Median (IQR) | 43 (38, 47) | 48 (43, 51) | 57 (52, 63) | 58 (50, 66) |
| Age at BSO |  |  |  |  |
| Median (IQR) | 47 (43, 50) | 57 (56, 61) \* | 63 (58, 70) |  |
| Follow up years |  |  |  |  |
| Median (IQR) | 11 (7, 17) | 10 (6, 17) | 14 (9, 20) | 9 (5, 15) |
| Deprivation index |  |  |  |  |
| 1 - least deprived | 3,491 (23%) | 52,702 (24%) | 2,009 (24%) | 128,066 (23%) |
| 2 | 3,515 (23%) | 50,084 (23%) | 2,120 (26%) | 125,329 (23%) |
| 3 | 3,190 (21%) | 45,113 (20%) | 1,736 (21%) | 113,116 (21%) |
| 4 | 2,700 (18%) | 39,413 (18%) | 1,395 (17%) | 96,451 (18%) |
| 5 - most deprived | 2,262 (15%) | 34,580 (16%) | 983 (12%) | 82,520 (15%) |
| Ethnicity  |  |  |  |  |
| White | 13,988 (92%) | 186,939 (84%) | 7,721 (94%) | 471,331 (86%) |
| Asian | 375 (2.5%) | 8,184 (3.7%) | 125 (1.5%) | 14,913 (2.7%) |
| Black | 199 (1.3%) | 4,566 (2.1%) | 48 (0.6%) | 7,300 (1.3%) |
| Mixed | 100 (0.7%) | 1,416 (0.6%) | 25 (0.3%) | 2,240 (0.4%) |
| Other | 163 (1.1%) | 3,065 (1.4%) | 41 (0.5%) | 5,610 (1.0%) |
| Missing | 333 (2.2%) | 17,722 (8.0%) | 283 (3.4%) | 44,088 (8.1%) |
| TNM stage |  |  |  |  |
| 1 | 4,259 (28%) | 62,373 (28%) | 3,063 (37%) | 180,007 (33%) |
| 2 | 5,242 (35%) | 69,784 (31%) | 2,070 (25%) | 154,457 (28%) |
| 3 | 1,331 (8.8%) | 16,243 (7.3%) | 329 (4.0%) | 33,840 (6.2%) |
| 4 | 315 (2.1%) | 6,104 (2.8%) | 90 (1.1%) | 17,064 (3.1%) |
| Missing | 4,011 (26%) | 67,388 (30%) | 2,691 (33%) | 160,114 (29%) |
| Grade |  |  |  |  |
| 1 | 1,649 (11%) | 31,674 (14%) | 1,633 (20%) | 86,678 (16%) |
| 2 | 6,673 (44%) | 92,744 (42%) | 3,787 (46%) | 245,097 (45%) |
| 3 | 5,983 (39%) | 79,652 (36%) | 2,217 (27%) | 166,880 (31%) |
| Missing | 853 (5.6%) | 17,822 (8.0%) | 606 (7.4%) | 46,827 (8.6%) |
| ER status |  |  |  |  |
| Positive | 6,527 (43%) | 79,593 (36%) | 2,687 (33%) | 206,476 (38%) |
| Negative | 984 (6.5%) | 18,067 (8.1%) | 428 (5.2%) | 39,371 (7.2%) |
| Missing | 7,647 (50%) | 124,232 (56%) | 5,128 (62%) | 299,635 (55%) |
| HER2 status |  |  |  |  |
| Positive | 1,109 (7.3%) | 17,333 (7.8%) | 287 (3.5%) | 36,024 (6.6%) |
| Negative | 6,251 (41%) | 80,291 (36%) | 2,470 (30%) | 206,536 (38%) |
| Missing | 7,798 (51%) | 124,268 (56%) | 5,486 (67%) | 302,922 (56%) |
| Morphology |  |  |  |  |
| Invasive ductal carcinoma | 12,191 (80%) | 174,050 (78%) | 6,075 (74%) | 410,727 (75%) |
| Invasive lobular carcinoma | 1,457 (9.6%) | 20,964 (9.4%) | 1,051 (13%) | 62,170 (11%) |
| Other | 1,510 (10%) | 26,878 (12%) | 822 (14%) | 56,611 (13%) |
| Death events |  |  |  |  |
| No | 12,576 (83%) | 165,405 (75%) | 6,205 (75%) | 357,566 (66%) |
| Yes | 2,582 (17%) | 56,487 (25%) | 2,038 (25%) | 187,916 (34%) |
| Hormonal treatment |  |  |  |  |
| No | 9,761 (64%) | 149,666 (67%) | 4,890 (59%) | 339,772 (62%) |
| Yes | 5,397 (36%) | 72,226 (33%) | 3,353 (41%) | 205,710 (38%) |
| Radiotherapy treatment |  |  |  |  |
| No | 5,517 (36%) | 81,066 (37%) | 3,162 (38%) | 207,378 (38%) |
| Yes | 9,641 (64%) | 140,826 (63%) | 5,081 (62%) | 338,104 (62%) |
|  |  |  |  |  |
| Chemotherapy |  |  |  |  |
| No | 6,061 (40%) | 106,622 (48%) | 5,697 (69%) | 346,938 (64%) |
| Yes  | 9,097 (60%) | 115,270 (52%) | 2,546 (31%) | 198,544 (36%) |
| Hysterectomy |  |  |  |  |
| Yes | 6,478 (43%) | 6,439 (2.9%)  | 5,321 (65%) | 11,419 (2.1%) |
| No | 8,680 (57%) | 215,453 (97%) | 2,922 (35%) | 534,063 (98%) |

*1: Women who were diagnosed with invasive breast cancer before the age of 55 and did not have a BSO before the age of 55, 2: Women who were diagnosed with invasive breast cancer at any age and did not have a BSO. \* Reference includes women who were diagnosed before the age of 55 and had a BSO after the age of 55, these women were censored at the date of their BSO ≥55, outcome development or occurrence of a censoring event whichever occurred first.*

*IQR: Interquartile range, TNM stage: Tumour, Node, Metastasis stage, ER: Estrogen receptor, HER2: Human Epidermal Growth Factor Receptor 2*

*Table 2: Associations between BSO and long-term outcomes by age at BSO*

| Outcome | Age at BSO | N at risk  | N events | Person years | HR (95% CI)\* |
| --- | --- | --- | --- | --- | --- |
| All-cause mortality  | Unstratified | 547,246 | 158,447 | 5,108,170 | 1.01 (0.98-1.05) |
| <55 | 231,281 | 50,053 | 2,304,019 | 1.03 (0.98-1.08) |
| ≥55 | 532,118 | 156,083 | 4,947,996 | 0.92 (0.87-0.96) |
| Total CVD | Total | Unstratified | 415,485 | 104,491 | 3,570,242 | 1.09 (1.05-1.13) |
| Non-fatal | 100,279 | 3,570,245 | 1.10 (1.05-1.14) |
| Fatal | 11,546 | 4,157,063 | 0.93 (0.82-1.06) |
| Total  | <55 | 206,942 | 33,189 | 1,935,037 | 1.10 (1.04-1.16) |
| Non-fatal | 32,070 | 1,935,038 | 1.10 (1.05-1.16) |
| Fatal | 2,153 | 2,119,670 | 0.88 (0.70-1.11) |
| Total | ≥55 | 401,756 | 102,312 | 3,434,178 | 1.07 (1.01-1.13) |
| Non-fatal | 98,144 | 3,434,181 | 1.08 (1.02-1.15) |
| Fatal | 11,461 | 4,008,443 | 0.88 (0.75-1.03) |
| IHD | Total | Unstratified | 525,665 | 28,178 | 4,805,042 | 1.15 (1.06-1.24) |
| Non-fatal | 25,710 | 4,805,043 | 1.17 (1.08-1.27) |
| Fatal | 3,549 | 4,951,005 | 0.81 (0.61-1.06) |
| Total  | <55 | 229,018 | 5,871 | 2,250,590 | 1.20 (1.06-1.37) |
| Non-fatal | 5,556 | 2,250,590 | 1.21 (1.07-1.38) |
| Fatal | 428 | 2,285,240 | 0.93 (0.53-1.63) |
| Total | ≥55 | 510,653 | 27,873 | 4,647,631 | 1.15 (1.05-1.27) |
| Non-fatal | 25,418 | 4,647,632 | 1.20 (1.08-1.32) |
| Fatal | 3,534 | 4,791,818 | 0.78 (0.56-1.06) |
| Cerebrovascular diseases  | Total | Unstratified | 540,517 | 20,141 | 5,002,065 | 1.00 (0.91-1.11) |
| Non-fatal | 18,203 | 5,002,068 | 1.01 (0.91-1.12) |
| Fatal | 4,106 | 5,068,176 | 0.93 (0.73-1.18) |
| Total  | <55 | 230,308 | 3,512 | 2,282,799 | 0.92 (0.77-1.10) |
| Non-fatal | 3,207 | 2,282,800 | 0.94 (0.78-1.12) |
| Fatal | 518 | 2,296,864 | 0.94 (0.59-1.48) |
| Total | ≥55 | 525,428 | 19,980 | 4,842,903 | 0.98 (0.87-1.10) |
| Non-fatal | 18,052 | 4,842,906 | 1.00 (0.88-1.13) |
| Fatal | 4,085 | 4,908,357 | 0.83 (0.62-1.10) |
| Angina | Unstratified | 525,664 | 11,760 | 4,872,452 | 1.27 (1.13-1.42) |
| <55 | 229,017 | 2,740 | 2,265,645 | 1.28 (1.06-1.54) |
| ≥55 | 510,652 | 11,609 | 4,714,269 | 1.34 (1.16-1.54) |
| Myocardial infarction | Unstratified | 525,664 | 9,074 | 4,917,312 | 1.03 (0.89-1.18) |
| <55 | 229,017 | 1,747 | 2,277,193 | 0.84 (0.65-1.09) |
| ≥55 | 510,652 | 9,004 | 4,758,434 | 1.09 (0.92-1.29) |
| Chronic IHD | Unstratified | 525,664 | 19,686 | 4,849,348 | 1.08 (0.99-1.19) |
| <55 | 229,017 | 4,033 | 2,262,022 | 1.14 (0.98-1.34) |
| ≥55 | 510,652 | 19,488 | 4,691,219 | 1.12 (1.00-1.25) |
| Haemorrhagic stroke | Unstratified | 543,914 | 4,584 | 5,076,992 | 0.97 (0.80-1.19) |
| <55 | 230,728 | 1,101 | 2,296,233 | 0.96 (0.71-1.29) |
| ≥55 | 528,808 | 4,530 | 4,917,201 | 0.90 (0.69-1.18) |
| Ischaemic stroke | Unstratified | 543,914 | 9,971 | 5,055,430 | 1.04 (0.90-1.19) |
| <55 | 230,728 | 1,513 | 2,294,263 | 0.92 (0.70-1.20) |
| ≥55 | 528,808 | 9,902 | 4,895,713 | 1.06 (0.90-1.24) |
| Parkinsonism | Unstratified | 545,231 | 3,533 | 5,082,902 | 0.78 (0.61-1.01) |
| <55 | 230,926 | 648 | 2,298,880 | 0.98 (0.67-1.44) |
| ≥55 | 530,135 | 3,493 | 4,923,142 | 0.67 (0.48-0.94) |
|  |
| Dementia | Unstratified | 545,933 | 12,036 | 5,072,461 | 0.94 (0.81-1.08) |
| <55 | 231,212 | 625 | 2,301,234 | 0.90 (0.55-1.47) |
| ≥55 | 530,804 | 12,016 | 4,912,385 | 0.95 (0.82-1.11) |
| Depression | Unstratified | 506,423 | 21,243 | 4,784,915 | 1.20 (1.12-1.28) |
| <55 | 213,588 | 10,491 | 2,150,730 | 1.18 (1.09-1.28) |
| ≥55 | 492,741 | 20,103 | 4,640,259 | 1.18 (1.05-1.33) |
| Second non breast cancer# | Unstratified | 544,682 | 39,886 | 4,494,403 | 1.05 (0.97-1.14) |
| <55 | 230,904 | 11,049 | 2,044,405 | 1.03 (0.91-1.17) |
| ≥55 | 529,581 | 39,362 | 4,353,510 | 1.21 (1.08-1.35) |
| Contralateral breast cancer | Unstratified | 522,802 | 13948 | 4,071,952 | 1.04 (0.95-1.15) |
| <55 | 221,647 | 6819 | 1,799,643 | 1.01 (0.89-1.14) |
| ≥55 | 508,460 | 13179 | 3,967,272 | 1.13 (0.97-1.33) |
| Breast cancer mortality  | Unstratified | 547,246 | 80,795 | 5,107,400 | 1.11 (1.06-1.16) |
| <55 | 231,281 | 36,745 | 2,303,692 | 1.09 (1.04-1.15) |
| ≥55 | 532,118 | 78,865 | 4,947,241 | 0.96 (0.89-1.05) |
| Non-breast cancer mortality | Unstratified | 547,246 | 77,629 | 5,107,400 | 0.91 (0.86-0.96) |
| <55 | 231,281 | 13,300 | 2,303,692 | 0.86 (0.78-0.96) |
| ≥55 | 532,118 | 77,196 | 4,947,241 | 0.93 (0.88-0.99) |

*N: number, HR: Hazard ratio, CI: Confidence interval, CVD: Cardiovascular diseases, IHD: Ischaemic heart disease*

*\* Models adjusted for age at breast cancer diagnosis, year of diagnosis, tumour size, number of excised lymph nodes, M-stage, grade, ER status, HER2 status, ethnicity, deprivation index and Charlson comorbidity index*

*# Additionally adjusted for hysterectomy.*

# Discussion

We used population scale electronic health records to assess the association between BSO after breast cancer diagnosis and long-term health outcomes. This is the first time that HES-APC and the NCRD datasets were linked to answer this question in a cohort of breast cancer patients diagnosed over a 24-year period.

BSO after breast cancer diagnosis was associated with increased risk of CVD, IHD and depression in women who had BSO at any age and increased risk of second non-breast cancer among women who had BSO at or after age 55 years. Investigating the CVD associations by the severity of the outcome showed no association with fatal CVD outcomes. The lack of significant association between BSO and fatal CVD outcomes, coupled with the observation that the increased risk of CVD and IHD seems to be primarily driven by an elevated risk of angina, suggests the possibility of detection bias influencing these associations.

BSO before age 55 years was associated with increased risk of breast cancer mortality, but reduced risk of non-breast cancer mortality. Although BSO after age 55 years was not associated with breast cancer mortality, it was associated with a lower risk of death from other causes (non-breast cancer mortality) and lower all-cause mortality. A sensitivity analysis was conducted where CBC was considered a censoring event to assess the robustness of the finding that BSO in younger women was associated with increased breast cancer mortality. This analysis found no association between BSO in younger women and breast cancer mortality. It is therefore possible that the group of women who opted for BSO at a young age may be enriched for women who are genetically susceptible to breast cancer, who are at an increased risk for contralateral breast cancer[20]. We explored this by stratifying the analysis on indication for BSO (prophylactic/ other benign indication), the indications were derived from the ICD10 diagnosis codes recorded in HES at the date of having the BSO. The estimated hazard ratios by indication were similar (Supplementary materials 2; Table 7S).

BSO is indicated for various reasons including treatment of ovarian cancer, ovarian cancer risk reduction in high-risk women (e.g. *BRCA1* and *BRCA2* PV carriers)[21] or for ovarian function suppression in breast cancer patients with ER positive tumours[6]. In very rare instances, benign conditions can affect both ovaries and require BSO. In this cohort we censored women who had BSO for treatment of any gynaecological cancer or as a part of pelvic clearance procedure. Thus, the women in our cohort probably had the BSO for the other listed indications. It is also possible that the cohort included women who are *BRCA1* or *BRCA2* pathogenic variants (PVs) carriers given that the prevalence of both PVs among breast cancer patients is around 2-3%[22, 23].

Several studies examined the association between ovarian function suppression (OFS) and all-cause mortality, disease free survival (DFS) and other outcomes. Ovarian function suppression is recommended to be combined with tamoxifen or aromatase inhibitors in women with hormone positive breast cancer. However, OFS could be achieved temporary by GnRH agonist or permanently using radiation-induced ablation or BSO. Only BSO is recommended for ovarian cancer risk reduction. In a recent Cochrane systematic review and meta-analysis[6] medical OFS was associated with significant reduction in the risk of all-cause mortality and DFS with hazard ratios 0.80 (95%CI:0.71-0.89) and 0.81 (95%CI:0.75-0.88), respectively. While OFS by BSO was not associated with all-cause mortality (HR:0.86, 95%CI:0.57-1.28) or DFS (HR:0.96, 95%CI:0.70-1.30). It is important to note this systematic review answers a different question from our study which compares women who had BSO to women who might have had OFS through GnRH agonist or radiation-induced ablation.

Obermair et al examined the association between BSO after breast cancer diagnosis and mortality in two independent studies using the Queensland cancer registry (n=25,536)[8] and Western Australia cancer registry (n=15,395)[7]. In both studies hysterectomy and BSO was associated with reduced risk of all-cause mortality and breast cancer mortality. However, BSO alone was not associated with all-cause mortality or breast cancer mortality. These findings are in line with our sensitivity analysis in which both hysterectomy alone and hysterectomy and BSO <55y were associated with reduced risk of mortality, while BSO alone <55y was associated with increased risk of mortality.

The findings for the associations with CVD and all-cause mortality in the age stratified analyses are in line with the associations in the general population. In a recent systematic review and meta-analysis on the long-term outcomes of BSO at the time of hysterectomy[5], hysterectomy and BSO were associated with increased risk of IHD in women who had the procedure before or after the age of 50 years and increased risk of all-cause mortality in women who had BSO before the age of 50 years. However, there was no association with all-cause mortality in women who had BSO after the age of 50 years.

These findings are important for counselling women with personal history of breast cancer who are considering BSO. Guidance based on studies specifically conducted on this group would provide more informative support for decision-making than evidence derived from the general population.

The major strength of this study is the large sample size, up to date this is the largest study to examine the long-term outcomes of BSO after the diagnosis of breast cancer. The NCRD contains data on all cancer patients diagnosed in England which minimises selection bias. We modelled the BSO and hysterectomy as time-dependent covariates to avoid immortal time bias. Also, we excluded women who had history of any of the outcomes before start of the follow up.

Assessment of the association between BSO and long-term outcomes in electronic health records has several limitations. Unlike randomised controlled studies several factors (possibly confounders) influence the receipt or uptake of intervention in observational studies. To address this, we adjusted the analysis for a number of confounders including hormonal receptor status, treatment, age at diagnosis, deprivation index and Charlson comorbidity index. In addition, we censored women who had BSO for malignant indications to minimise confounding by indication of the BSO. However, there could be residual confounding resulting from the lack of information on confounders like family history of breast cancer, smoking status and body mass index. Also, detection bias could have influenced the results as women with previous history of surgery might seek more medical attention. Nevertheless, we expect that this has not substantially biased the results as the cohort consists of breast cancer patients who are likely to receive close medical monitoring. We attempted to minimise detection bias by starting the follow up for BSO or hysterectomy 1 year following the surgery to avoid adding cases to the surgery groups who were accidentally discovered at the time of the surgery (prevalent cases). Another limitation is that non-cancer long term outcomes were identified from hospital admissions in HES and from death certificates, which means we were only capable of identifying severe outcomes and this might have limited the power of the study to detect associations with certain outcomes such as dementia. This limitation may also explain the observed reduction in the risk of parkinsonism, which is not line with previous findings[24, 25]. Additionally, the association with breast cancer mortality could be affected by the inaccurate coding of the cause of death. Finally, some tumour characteristic data were missing e.g. 29% of TNM-stage and more than 50% of the ER status and HER2 status. To address this, we employed multiple imputation (MI) which has been shown to reduce bias in estimates compared to complete case analysis[26].

# Conclusion

In women with personal history of breast cancer, BSO before and after the age of 55 years is associated with increased risk of long-term outcomes including CVD, cancer and depression. However, more work is needed to elucidate the possibility of confounding by family history and genetic susceptibility. Women with BSO above age 55 years may benefit from reduction in all-cause mortality.

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