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## **Risk of high-grade serous ovarian cancer associated with pelvic inflammatory disease, parity and breast cancer**

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## **Abbreviations**

BO Bilateral oophorectomy

BSO Bilateral salpingo-oophorectomy

CI Confidence Interval

HGSC High-grade serous ovarian carcinoma

HR Hazard ratio

ICD International classification of diseases

PID Pelvic inflammatory disease

USO Unilateral salpingectomy, oophorectomy or salpingo-oophorectomy

WA Western Australia

## **Abstract**

### **Background**

Ovarian carcinoma is not a single disease, but rather a collection of subtypes with differing molecular properties and risk profiles. The most common of these, and the subject of this work, is high-grade serous ovarian carcinoma (HGSC).

### **Methods**

In this population-based study we identified a cohort of 441,382 women resident in Western Australia who had ever been admitted to hospital in the State. Of these, 454 were diagnosed with HGSC. We used Cox regression to derive hazard ratios (HRs) comparing the risk of disease in women who had each of a range of medical diagnoses and surgical procedures with women who did not.

### **Results**

We found an increased risk of HGSC associated with a diagnosis of pelvic inflammatory disease (PID) (HR 1.47, 95% CI 1.04-2.07) but not with a diagnosis of infertility or endometriosis with HRs of 1.12 (95% CI 0.73-1.71) and 0.82 (95% CI 0.55-1.22) respectively. A personal history of breast cancer was associated with a three-fold increase in the rate of HGSC. Increased parity was associated with a reduced risk of HGSC in women without a personal history of breast cancer (HR 0.57; 95% CI 0.44-0.73), but not in women with a personal history of breast cancer (HR 1.48; 95% CI 0.74-2.95).

### **Conclusions**

Our finding of an increased risk of HGSC associated with PID lends support to the hypothesis that inflammatory processes may be involved in the etiology of HGSC.

## 1. Introduction

Epithelial carcinomas account for 90% of all ovarian cancers and have been classified into five major histological subtypes: high-grade serous, low grade serous, endometrioid, clear cell and mucinous. These subtypes are different diseases with differing molecular, histopathological and clinical characteristics [1-3] and risk factors [4]. For this reason, it is important that associations between risk factors and disease are established separately for each subtype. Of all the histological subtypes, high-grade serous tumours (including ovarian, fallopian tube and primary peritoneal carcinomas) (HGSC) are the most common, representing around 70% of all carcinomas [3].

Numerous studies have evaluated the association between established risk factors and ovarian cancer overall (reviewed in [5-7]). Many have also examined these associations separately for each subtype [8-31]. Those that have done so have generally grouped high- and low-grade serous subtypes together into a single category: serous ovarian cancer. It is now recognised that high- and low-grade serous carcinoma are two different tumour types [2]. Few studies have examined the associations with HGSC. Among six such studies, two identified ovarian, fallopian tube and peritoneal cancers and classified tumours according to histological pathways; one [11] grouped together invasive ovarian, fallopian tube and peritoneal serous cancers with high-grade endometrioid and undifferentiated tumours into the Type 2 category [11, 19], whilst another [19] created three categories and grouped high-grade serous together with undifferentiated tumours. A third classified serous ovarian and peritoneal cancers into three grades: well, moderately and poorly differentiated [30]. Three others considered high-grade serous tumours of the ovary but did not mention fallopian tube or peritoneal tumours [12, 13, 22].

It is generally established that increasing parity is associated with a reduced risk of ovarian cancer, although this association differs across subtypes with the greatest reduction in risk for endometrioid and clear cell, the least reduction for serous and some heterogeneity across studies of mucinous subtypes [8, 9, 11, 12, 14, 16, 17, 19, 21, 26, 28-31]. It is possible that the different hormonal milieu seen in women carrying multiple pregnancies may lead to a modification in ovarian cancer risk, although most studies have not found an association between ovarian cancer overall and twin pregnancies [32-39].

Endometriosis appears to be associated with an increased risk of endometrioid and clear cell subtypes [19, 20]; possibly associated with an increased risk of low grade serous but perhaps not high-grade serous tumours [22, 30].

Findings with regard to tubal ligation are contradictory: some find a reduced risk of serous ovarian cancer [10, 16, 21, 24, 26] whilst others do not [14, 18, 25, 27, 30]. An early study by Risch [26] examining the association between hysterectomy and serous ovarian cancer found a reduced risk, though later studies have generally not found an association [11, 14, 19, 21, 25, 30].

It has been speculated that chronic inflammation resulting from pelvic inflammatory disease (PID) may play a role in ovarian carcinogenesis [40]. This association has been investigated by a number of authors, with contradictory findings. Risch et al [26] found that self-reported recurrent PID was associated with an increased risk of ovarian cancer overall, whereas Ness et al [41] found only a weak association between the two. A pooled analysis of individual level data did not find an association between self-reported PID and either serous or high-grade serous ovarian cancer [42]. A subsequent record linkage study [23] found an association between hospital-diagnosed PID and serous ovarian cancer.

A family history of breast or ovarian cancer, usually in the mother or sister, has often been included in multivariable analyses of risk factors for serous [9, 16, 21, 30], and high-grade serous [30] ovarian cancer. Identifying cancers in only first degree relatives may underestimate risk as it does not take into account inheritance of cancer susceptibility genes from the paternal line. A personal history of breast cancer has generally not been investigated.

The aim of the present study was to examine the association between HGSC and a number of ovarian cancer risk factors, including parity, plurality (the delivery of twins and higher order multiples), endometriosis, infertility, PID, hysterectomy, unilateral salpingo-oophorectomy, tubal ligation and a personal history of breast cancer.

## **2. Methods**

### **2.1. The study population**

This study was conducted in Western Australia (WA), the largest state in Australia with a geographic area of 2,529,875 square kilometres and a population of 2.59 million (11% of the total Australian population). The majority of the population resides in the south west corner of the state.

This was a population-based cohort study. The study population included all women, born between 1945 and 1975 inclusive, residing in WA, who had been admitted to hospital in WA at any time between 1 January 1980 and 30 June 2014. Hospital records for these women extended back to 1 January 1970. We used WA's Hospital Morbidity Data Collection [43] to identify the study population and also to define many of the exposure variables. The remaining exposure variables and the outcome variable were identified through linkage to other state-wide demographic and health databases using WA's data linkage system [44]. Linkage to the WA Deaths Register enabled the identification of deaths to allow for censoring in survival analysis. Linkage to the WA Midwives Notification System allowed the identification of births and parity-related variables from 1980; the WA Births Register was used to identify births in the period 1970-1980. The WA Electoral Roll, with



information available from 1988 onward, was used to identify women who were not registered to vote or who had moved interstate. Ovarian cancer and breast cancer cases were identified from the WA Cancer Registry.

The state of WA, although geographically isolated, has a dynamic population, experiencing both inward and outward migration. This has the potential to lead to bias due to misclassification of early exposures in women who migrate into the state, and loss to follow-up in women who migrate out. For this reason, we excluded women whose hospital records showed they were overseas visitors or resided out of the state, and women whose cancer records showed that ovarian cancer was diagnosed out of the state. We also excluded women for whom we did not have WA Electoral Roll records, and women whose Electoral Roll records showed they had moved out of the state (Fig 1). With only a few exceptions, all Australian citizens are required to register on the Electoral Roll and to update their residential address soon after moving [45]. We also conducted comparative and sensitivity analyses to assess the impact of inward and outward migration on our risk estimates, comparing the final cohort of women which included only those known to be resident in WA with a larger preliminary cohort that also included women who were not known to be WA residents.

## 2.2. Exposure variables

We examined the association between HGSC and diagnoses of infertility, endometriosis and PID; parity and plurality (the delivery of twins and higher order multiples); tubal ligation; hysterectomy without salpingectomy or oophorectomy; unilateral salpingectomy, oophorectomy or salpingo-oophorectomy (USO) without hysterectomy and a personal history of breast cancer. We did not examine the association with hysterectomy plus USO.

Diagnoses and procedures were recorded in the Hospital Morbidity Data Collection and coded according to contemporaneous International Classification of Diseases (ICD) codes, including ICD-8, ICD-9 and ICD-10-AM diagnostic codes and COSO (Code of Surgical Operations), ICPM (International Classification of Procedures in Medicine), ICD-9 and ACHI (Australian Classification of Health Interventions) procedure codes. Diagnostic and procedure codes used to identify each study variable are listed in Supplementary Table 1. We included any mention of the diagnosis or procedure – whether it was recorded as a principal or additional diagnosis or a principal or additional procedure. Exposure variables were reported as categorical time-varying binary variables, with exposure changing from 0 to 1 (unexposed to exposed) at the date of the relevant diagnosis or procedure or birth of third child. We compared women whose hospital records mentioned the diagnosis or procedure, with women whose hospital records had no mention of the diagnosis or procedure.

We used a binary classification for parity, comparing women who delivered 3 or more children with women who delivered 0, 1 or 2. The reason for this was because of the possibility of misclassification of parity in women who only gave birth before 1970 or out of

WA. Women who gave birth either prior to 1970 or out of WA and did not have any subsequent deliveries in WA were classified as nulliparous because we did not have any information on deliveries in these women. Women who gave birth out of WA or prior to 1970 and had subsequent deliveries in WA were correctly classified. We reasoned that this misclassification was much less likely in women who delivered three or more children than in women who delivered one or two. Preliminary investigation and sensitivity analyses supported this assumption.

Plurality was included as a binary variable, with women who delivered twins, triplets and higher order multiples grouped together.

We also considered a personal history of breast cancer. Cases were identified from the WA Cancer Registry (from 1982), with earlier cases (between 1970 and 1982) identified from the Hospital Morbidity Data Collection.

### 2.3. Outcome variable

The outcome of interest was a diagnosis of HGSC. Data were obtained from the WA Cancer registry and classification of ovarian cancer subtypes was reviewed and revised where appropriate [46]. Consequently, HGSC included correctly classified ovarian, tubal and peritoneal high-grade serous carcinomas.

### 2.4. Data analysis

Data were analysed using Cox regression with time-varying covariates. We used age as the time-scale. Women were followed from birth until the censor date of 30 June 2014, or a diagnosis of HGSC or any type of ovarian cancer, or death, whichever came first. Follow-up was also censored at the time of bilateral salpingo-oophorectomy (BSO) or bilateral oophorectomy (BO); unilateral oophorectomy after a previous unilateral oophorectomy; hysterectomy with BSO or BO, or hysterectomy where salpingo-oophorectomy was not specified as bilateral or unilateral. All exposure variables were time-varying, that is, the value of the binary exposure variables changed from 0 to 1 at the time of exposure.

Data were analyzed first in unadjusted models and then in multivariable models. Because age was used as the time scale, all models were effectively age-adjusted. All variables included in the multivariable model are listed in Table 2. We checked for interactions between all the study variables. We tested the proportional hazards assumption by examining Schoenfeld residuals in the initial univariate and final multivariable models and did not find any evidence for an overall violation of the assumption.

Because age was used as the time-scale, hazard rates could be interpreted as age-specific incidence rates of HGSC. However, the semi-parametric Cox model produces only relative hazard rates (hazard rate ratios) rather than hazard rates. To visualise age-specific incidence

rates of HGSC by parity in this cohort, flexible parametric proportional hazards (Royston-Parmar) models were employed [47]. Spline functions with one internal knot were used to model the baseline hazards, while parity was included as a time-dependent spline function with one internal knot. This allowed us to investigate subtle changes in the proportionality of hazards with age which we have represented graphically.

Data were analysed using SPSS version 24 (IBM) and Stata version 14 (StataCorp, College Station, Texas).

## 2.5. Ethics

This study was approved by Department of Health Custodians, the WA Department of Health Ethics Committee and Curtin University and The University of Notre Dame Human Research Ethics Committees.

## 3. Results

### 3.1. The cohort

A total of 583,488 women, born between 1 January 1945 and 31 December 1975 had a hospital admission in WA between 1 January 1980 and 30 June 2014. We excluded women not known to be resident in WA, as described in Fig 1, and derived a final cohort numbering 441,382.

A total of 454 women were diagnosed with HGSC. The average age at diagnosis was 54.4 years (Table 1); (median 55.4 years).

Endometriosis was the most common gynecological diagnosis, identified in 7.8% of women in our cohort. PID was diagnosed in 7.6% of women and infertility in 6.5%. The most common gynaecological surgery was tubal ligation, in 17.8% of the women. Breast cancer was identified in 2.8% of women (Table 1).

### 3.2. Association between risk factors and HGSC

We first examined the association between exposure variables and the rate of HGSC in unadjusted analysis, and then included all exposure variables in the final multivariable model (see Table 2).

Neither infertility nor endometriosis appeared to be associated with an increased risk of HGSC in either unadjusted or adjusted analyses. Women in our cohort diagnosed with PID had a 47% increased rate of HGSC compared to women with no such diagnosis (Table 2).

There did not appear to be an association between hysterectomy and HGSC. Tubal ligation was associated with a 17% reduction in risk but confidence intervals included one (Table 2).

The delivery of twins and higher order multiples was associated with a 59% increased rate of HGSC with confidence intervals that also included one (Table 2).

Increased parity (3 or more births, compared with 0, 1 or 2 births) was associated with a reduced risk of HGSC whereas a personal history of breast cancer was associated with an increased risk. A total of 12,168 women had a personal history of breast cancer; of these, 37 had a later diagnosis of HGSC (Table 1). We observed a significant interaction between parity and breast cancer, and for this reason, present results for each category separately.

Among women without breast cancer, higher parity was associated with a 43% reduced rate of HGSC (Table 2). This was not the case in women with a history of breast cancer where the HR associated with higher parity was 1.48, (95% CI 0.74-2.95) (data not shown, but this can be estimated by dividing 4.14 by 2.79 (see Table 2)).

A personal history of breast cancer was associated with an almost 3-fold increase in the rate of HGSC in women of low parity (women with 0, 1 or 2 births) and a 4-fold increase in the rate of HGSC in women of high parity (women with 3 or more births) (Table 2).

Among women of high parity, a personal history of breast cancer was associated with a 7.30 times increased rate of HGSC (95% CI 3.96-13.46) (this can be estimated by dividing 4.14 by 0.57 (see Table 2)).

Spline functions were used to graph the association between a woman's age and the rate of HGSC. We compared women of low and high parity (women with 0, 1 or 2 births compared with women with 3 or more births). Age-specific rates of HGSC were lower in women of higher parity throughout their middle years. The difference between parity groups diminished as women approached their mid-60s (Fig 2).

### 3.3. Comparative and sensitivity analyses

To estimate the impact of potential misclassification due to inward and outward migration, we conducted comparative and sensitivity analyses comparing findings from a cohort which included both WA residents and non-residents (n=583,488) with our final cohort which included only women known to be WA residents (n=441,382). Our overall conclusions were the same irrespective of which cohort we chose and HR estimates for all variables were similar. The estimate for higher parity (comparing women with 3 or more births with women with 0, 1 or 2 births) was slightly closer to the null in the larger cohort, which included women known to have migrated into or out of the state (the HR estimate was 0.67 in the preliminary cohort (95% CI 0.52-0.85), compared with 0.57 in the final cohort (95% CI 0.44-

0.73)) suggesting there may have been some misclassification of parity in the larger cohort which we were able to reduce by restricting the cohort to known WA residents.

We also compared the results in figure 2 with those from a restricted cohort which excluded, firstly, nulliparous women, secondly, women born prior to 1950 and thirdly, women born prior to 1955. Our conclusions remained the same, suggesting that the findings could not be explained by parity misclassification.

#### **4. Discussion**

In this study we examined the association between high-grade serous ovarian carcinoma and a range of risk factors.

One of the factors we considered was a personal history of breast cancer. Breast cancer is a relatively common cancer [48], usually sporadic in nature [49]. In our study, the rate of HGSC in women with a personal history of breast cancer was around three times that of women without a breast cancer diagnosis. It is likely that at least some of these affected women carried a *BRCA* mutation, which is associated with an increased risk of both breast and ovarian cancer, particularly HGSC. There is currently no reliable screening test for the early detection of ovarian cancer [50, 51]. As the cost of genetic testing becomes more affordable, it may be worthwhile expanding the criteria for women in whom genetic testing is appropriate. It may become cost effective to offer this simple saliva or blood test to more women treated for breast cancer.

We also examined the association between parity and risk of HGSC and found a reduced risk of HGSC in women of higher parity (i.e. women with 3 or more births, compared with women with 0, 1 or 2 births), consistent with most studies of serous [8, 9, 11, 12, 16, 17, 19, 21, 26, 28-31] and high-grade serous [19, 30] ovarian carcinoma, but not all. Some studies did not find an association with serous [14, 28] or high-grade serous [14] carcinoma. Our analysis of age specific rates suggested that this parity-associated risk reduction attenuates over time, so that as women approach their mid-60s, the reduced risk associated with higher parity diminishes. This observation finds support from studies of McGuire et al [52] and might help to explain why some studies have found that older age at delivery is associated with a reduced ovarian cancer risk [53, 54] with a later delivery extending parity-related protection further into middle age.

Among women with a personal history of breast cancer, there did not appear to be a reduced risk of HGSC associated with high parity. Instead, we found a 48% increase in the risk of HGSC in women of increased parity, although the statistical evidence was weak. Many studies have examined ovarian cancer risk in *BRCA* mutation carriers [55-57]. Some of these found a reduced risk of ovarian cancer associated with increasing parity in *BRCA1* carriers, but not in *BRCA2* carriers [55, 56]. It is possible that the long-held association between

parity and ovarian cancer and in particular, HGSC, may not hold for all subgroups of the population, in particular, for older women and women with a personal history of breast cancer.

We did not find any evidence for an association between HGSC and hysterectomy without salpingo-oophorectomy. This is consistent with most studies examining the association with serous ovarian cancer [11, 14, 21, 25, 30]. Few papers report the association specifically with HGSC, but where they do, they generally find a weaker association between hysterectomy and HGSC than between hysterectomy and other ovarian cancer subtypes [30].

We found a small, 17% reduction in risk of HGSC associated with tubal ligation, though with confidence intervals that included one. Findings from other groups are mixed; for example Gaitskell et al [13] found a significant 23% reduction in risk of HGSC associated with tubal ligation whereas Wentzensen [30] found a non-significant 9% reduction in the risk of serous ovarian cancer associated with tubal ligation. With regard to high-grade serous ovarian cancer, Gaitskell et al [13] found a reduced risk associated with tubal ligation whereas Merritt et al [19] did not.

We found a reduced risk of HGSC associated with USO without hysterectomy, although this finding was based on only a few HGSC cases in the exposed. This was consistent with results from Rice et al [25] but contrasts with our earlier findings of the relationship with ovarian cancer overall in a cohort of women undergoing investigation and treatment for infertility [58].

We did not detect an association between infertility and HGSC. In other studies, Merritt et al [19] did not find an association between infertility and high-grade serous carcinomas whereas Jensen et al [15], but not Tung et al [28] found an association between infertility and serous carcinomas. Our findings with regard to the relationship between HGSC and endometriosis are consistent with others [19, 22, 30].

We found that a diagnosis of PID was associated with an increased risk of HGSC. This finding was consistent with a recent record linkage cohort study by Rasmussen et al [23] which found an increased risk of serous ovarian cancer associated with PID, but not with an earlier meta-analysis of case control studies, which did not find an association between PID and either serous ovarian cancer or high-grade serous ovarian cancer [42]. These discrepancies may be due to the fact that PID may be underreported in studies that rely on self-report due to its sensitive nature, whilst only more severe or recurring episodes of PID may be captured in hospital records.

We found a 59% increased risk of HGSC in women who delivered twins and higher order multiples compared with women who did not, with confidence intervals that included one. Other authors have generally not found an association between ovarian cancer overall and the

delivery of twins [33, 37, 39], although Albrektsen [32] found an increased risk of serous tumours in women who delivered twin girls. These different findings may be related to the fact that individual studies may not have sufficient power to adequately explore this association and because the association may differ according to ovarian cancer subtype.

Our study has several strengths and limitations. A major strength was the implementation of a detailed pathology review of all ovarian tumours recorded in our cohort using up-to-date methodology and currently recognized classification schemes [46]. This review led to the re-classification of a number of cases, particularly those previously classified as “not otherwise specified” and those of uncertain grade and mixed type. These unspecified (other) categories can make up as much as 30% of all ovarian cancer cases [13, 31, 52], and are predominantly high-grade serous [46]. Other authors have emphasized the importance of histopathological review [2] and noted that without histopathological review, estimates of risk may be less precise [59]. Strengths include the size of the study population; accurate recording of diagnoses and procedures in administrative databases rather than relying on personal report which could be subject to error and recall bias. Nevertheless, medical record linkage studies are not without flaws. Conditions under study had to have been diagnosed in hospital. Women who were not admitted to hospital for infertility, PID or endometriosis were classified as unexposed, even though some of these women would be suffering from these conditions.

The major limitation of this study was our inability to include information on oral contraceptive use. Use of oral contraceptives is associated with a significant reduction in ovarian cancer risk [60]. If women taking oral contraceptives were more, or less likely to be exposed to the factors under study, then confounding may have resulted, and our risk estimates would be inaccurate. For example, if women diagnosed with PID were more likely to have taken oral contraceptives, then we may have underestimated the association between PID and HGSC. Another limitation of our study was the need to classify parity into two categories, with women who delivered zero, one or two children compared with women who delivered three or more. We classified parity in this way to reduce misclassification of women who migrated into the state and only gave birth outside WA and women who only delivered children prior to 1970 as being nulliparous. A further limitation was the age of the study population. Because we wanted to capture information on exposures that occurred early in a woman’s life, including births and tubal ligation, we needed to choose a relatively young study population. The average age at the end of follow-up was 53 years, with the oldest women in the cohort aged 69 years.

#### 4.1. Conclusions

Our finding that PID was associated with an increased risk of HGSC lends support to the hypothesis that inflammatory processes may play a role in the development of HGSC [40, 61].

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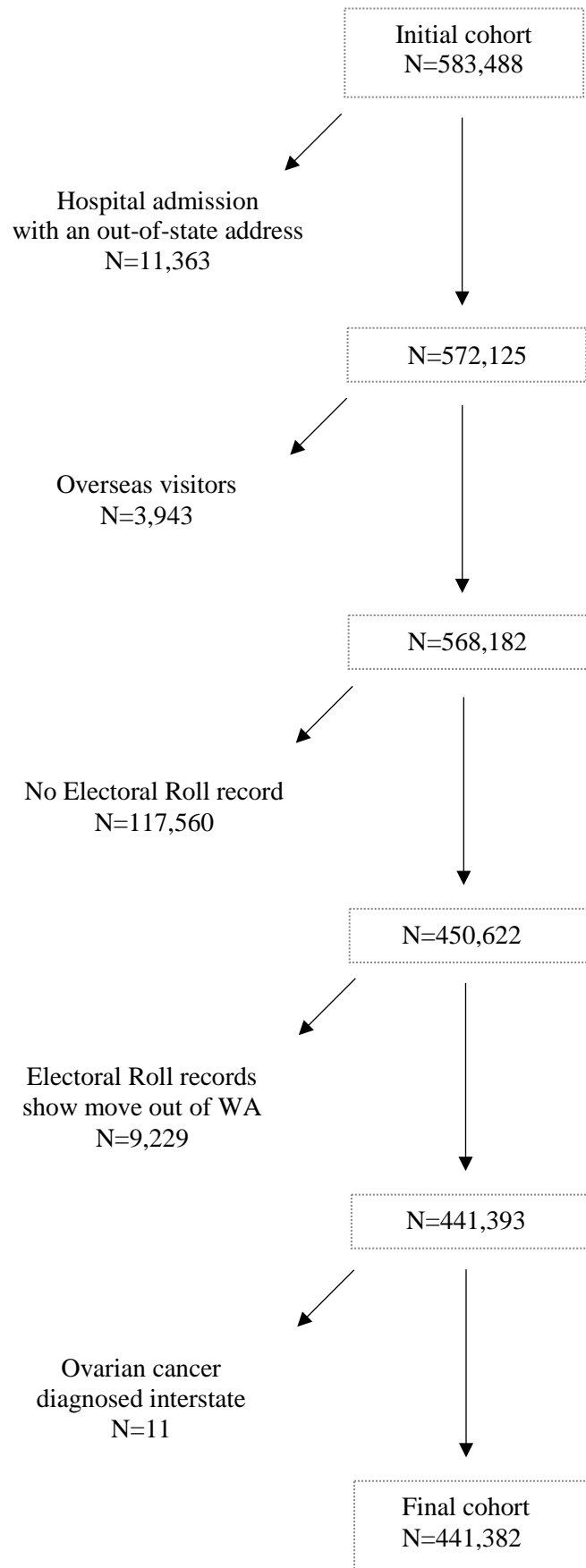
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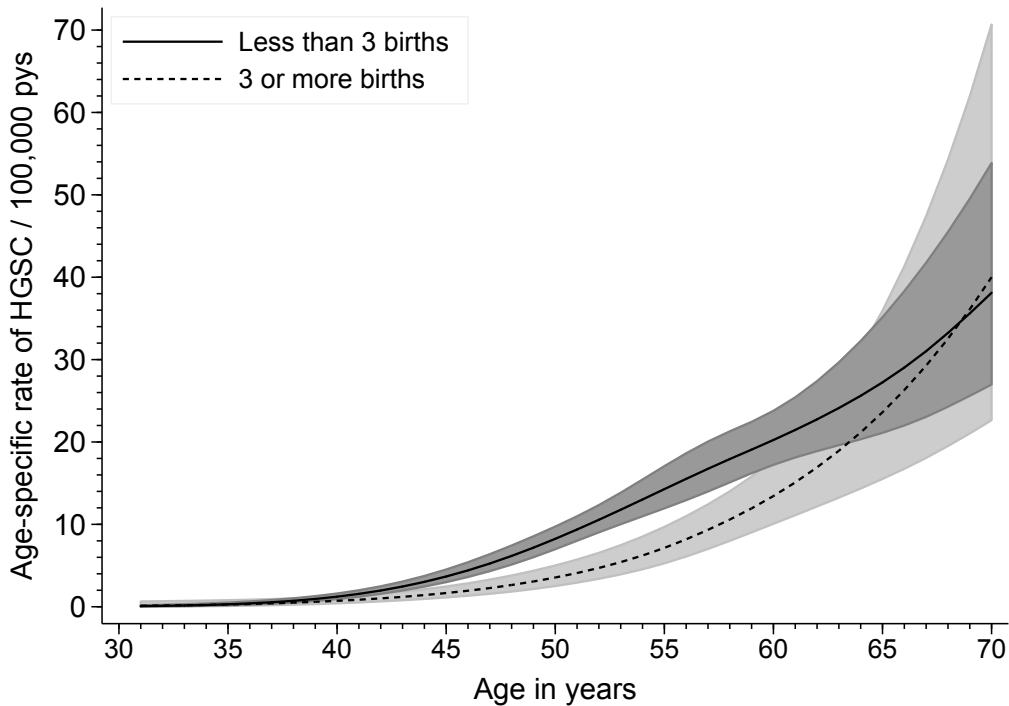
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**Figure 1.** Flow chart showing cohort selection with eligible and ineligible study participants

**Figure 2.** Predicted age-specific rates of HGSC in women without a history of breast cancer stratified by periods of time having had less than three births and periods of time having had three or more births. Predictions adjusted for infertility, endometriosis, PID, hysterectomy, USO, sterilisation, plurality, parity and breast cancer and the interaction between parity and breast cancer. All the above variables set at 0 for the predicted parity rates. Shading represents 95%CI.





**Supplementary Table 1.** Diagnostic and procedure codes used to identify study variables

<b>Diagnosis or procedure</b>	<b>ICD-8</b> (01/01/1970-31/12/1978)	<b>ICD-9<sup>1</sup></b> (01/01/1979-30/06/1999)	<b>ICD-10-AM</b> (01/07/1999-present)	<b>Code of Surgical Operations</b> (01/01/1970-31/12/1978)	<b>International Classification of Procedures in Medicine</b> (01/01/1979-31/12/1987)	<b>ICD-9</b> (01/01/1988-30/06/1999)	<b>Australian Classification of Health Interventions</b> (01/07/1999-present)
Infertility diagnosis, investigation or treatment	628	628.0 to 628.9 V26.1 to V26.9	N97.0 to N97.9 and Z31.1 to Z31.9	-	-	-	-
Endometriosis	625.3	617.0 to 617.9	N80.0 to N80.9	-	-	-	-
Pelvic Inflammatory Disease	612, 613, 614, 616.0, 616.1	614.0 to 615.9	N70.0 to N71.9, N73.0 to N73.9 and N74.1 to N74.8	-	-	-	-
Tubal ligation	-	V25.2	Z30.2	684	5-663, 5-664, 5-980	66.2 to 66.39	35688-00 to 35688-04
Hysterectomy without oophorectomy or salpingectomy <sup>2</sup>	-	-	-	692 to 694 and 696	5-682 to 5-686	68.3 to 68.7 and 68.9	35653-00, 35653-01, 35657-00, 35750-00, 35756-00 90448-00, 90448-01
Unilateral salpingo-oophorectomy (USO), unilateral	-	-	-	-	5-652 5-653, 5-661	65.3, 65.4, 66.4	35638-02, 35713-07, 35713-09,



salpingectomy (US) and unilateral oophorectomy (UO) without hysterectomy <sup>3</sup>							35638-09, 35638-11, 35713-11
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<sup>1</sup>Four versions of ICD-9 were used in Western Australia:

ICD-9 (01/01/1979 – 31/12/1987)

ICD-9-CM (01/01/1988 – 30/06/1995)

ICD-9-CM Australian Version 1 (01/07/1995 – 30/06/1996)

ICD-9-CM Australian Version 2 (01/07/1996 – 30/06/1999)

<sup>2</sup>Women who had a hysterectomy with an oophorectomy or salpingectomy in the same or any other admission were not included in this category.

<sup>3</sup>Women who had a USO, UO or US and a hysterectomy in the same or any other admission were not included in this category.