2018

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

Louise Stewart
The University of Notre Dame Australia, louise.stewart@nd.edu.au

Katrina Spilsbury
The University of Notre Dame Australia, katrina.spilsbury@nd.edu.au

Susan Jordan

Colin Stewart

C. D'Arcy J. Holman

See next page for additional authors

This article was originally published as:
Stewart, L., Spilsbury, K., Jordan, S., Stewart, C., Holman, C. J., Powell, A., Reekie, J., & Cohen, P. (2018). Risk of high-grade serous ovarian cancer associated with pelvic inflammatory disease, parity and breast cancer. *Cancer Epidemiology, 55*, 110-116.

Original article available here:
https://doi.org/10.1016/j.canep.2018.05.011

This is the author's post-print copy of the article published as:

Stewart, L.M., Spilsbury, K., Jordan, S., Stewart, C., Holman, C.D.J., Powell, A., Reekie, J., and Cohen, P. (2018) Risk of high-grade serous ovarian cancer associated with pelvic inflammatory disease, parity and breast cancer. *Cancer Epidemiology, 55,* 110-116. doi: 10.1016/j.canep.2018.05.011

This article has been published in final form at https://doi.org/10.1016/j.canep.2018.05.011

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

Louise M Stewart [a,b], Katrina Spilsbury [a,b], Susan Jordan [c,d], Colin Stewart [e,f], C D'Arcy J Holman [g], Aime Powell [a], Joanne Reekie [h] and Paul Cohen [f,i,j]

[a]Institute for Health Research, The University of Notre Dame Australia, Fremantle, Western Australia, Australia

[b]Health Research and Data Analytics Hub and PHRN Centre for Data Linkage, Curtin University, Bentley, Western Australia, Australia

[c]QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia

[d]The School of Public Health, The University of Queensland, Australia

[e]Department of Pathology, King Edward Memorial Hospital for Women, Subiaco, Western Australia, Australia

[f]School of Women's and Infant's Health, The University of Western Australia, Crawley, Western Australia, Australia

[g]The University of Western Australia, Crawley, Western Australia, Australia

[h]The Kirby Institute, UNSW Australia, Sydney, Australia

[i]Department of Gynaecological Oncology, King Edward Memorial Hospital for Women, Subiaco, Western Australia, Australia

[j]Department of Gynaecological Oncology, St John of God Hospital Bendat Family Comprehensive Cancer Centre, Subiaco, Western Australia, Australia

Corresponding author

Louise M Stewart, PhD, Institute for Health Research, The University of Notre Dame Australia, 19 Mouat Street (PO Box 1225) Fremantle, Western Australia 6959. Telephone +61 8 9433 0285, Facsimile +61 8 9433 0210 email louise.stewart@nd.edu.au

Declaration of interest

LMS reports grants from Ovarian Cancer Research Foundation, during the conduct of the study.

KS, SJ, CS, CDJH, AP, JR and PC report no declaration of interest.

Word count

Abstract - 233

Manuscript – 4,024

Highlights

Point 1 – 85 characters including spaces

Point 2 – 66 characters including spaces

Point 3 – 68 characters including spaces

Point 4 – 72 characters including spaces

Keywords

Pelvic inflammatory disease, parity, endometriosis, infertility, hysterectomy, tubal ligation, ovarian neoplasms, breast neoplasms, cohort studies, risk

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 Rassmussen 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].

Acknowledgements

The authors wish to thank the staff at the Western Australian Data Linkage Branch and staff and custodians of the Hospital Morbidity Data Collection, the WA Cancer Registry, the Midwives Notification System, Birth Registrations, Deaths Registrations and the WA Electoral Roll.

Funding

This work was supported by a grant from the Ovarian Cancer Research Foundation (OCRF).

Susan Jordan is supported by a fellowship from the National Health and Medical Research Council of Australia.

The funding source had no role to play in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

REFERENCES

1. Kossai M, Leary A, Scoazec JY, Genestie C. Ovarian Cancer: A Heterogeneous Disease. Pathobiology. 2017. doi: 10.1159/000479006.
2. McCluggage WG. Morphological subtypes of ovarian carcinoma: a review with emphasis on new developments and pathogenesis. Pathology. 2011;43(5):420-32. doi: 10.1097/PAT.0b013e328348a6e7.
3. Prat J. Ovarian carcinomas: five distinct diseases with different origins, genetic alterations, and clinicopathological features. Virchows Arch. 2012;460(3):237-49. doi: 10.1007/s00428-012-1203-5.
4. Webb PM, Jordan SJ. Epidemiology of epithelial ovarian cancer. Best Pract Res Clin Obstet Gynaecol. 2017;41:3-14. doi: 10.1016/j.bpobgyn.2016.08.006.
5. Hunn J, Rodriguez GC. Ovarian cancer: etiology, risk factors, and epidemiology. Clin Obstet Gynecol. 2012;55(1):3-23. doi: 10.1097/GRF.0b013e31824b4611.
6. Permuth-Wey J, Sellers TA. Epidemiology of ovarian cancer. Methods Mol Biol. 2009;472:413-37. doi: 10.1007/978-1-60327-492-0_20.
7. Riman T, Nilsson S, Persson IR. Review of epidemiological evidence for reproductive and hormonal factors in relation to the risk of epithelial ovarian malignancies. Acta Obstet Gynecol Scand. 2004;83(9):783-95. doi: 10.1111/j.0001-6349.2004.00550.x.
8. Albrektsen G, Heuch I, Kvale G. Reproductive factors and incidence of epithelial ovarian cancer: a Norwegian prospective study. Cancer Causes Control. 1996;7(4):421-7.
9. Chiaffarino F, Parazzini F, Bosetti C, Franceschi S, Talamini R, Canzonieri V, et al. Risk factors for ovarian cancer histotypes. Eur J Cancer. 2007;43(7):1208-13. doi: 10.1016/j.ejca.2007.01.035.

10. Cibula D, Widschwendter M, Majek O, Dusek L. Tubal ligation and the risk of ovarian cancer: review and meta-analysis. Hum Reprod Update. 2011;17(1):55-67. doi: 10.1093/humupd/dmq030.
11. Fortner RT, Ose J, Merritt MA, Schock H, Tjonneland A, Hansen L, et al. Reproductive and hormone-related risk factors for epithelial ovarian cancer by histologic pathways, invasiveness and histologic subtypes: Results from the EPIC cohort. Int J Cancer. 2015;137(5):1196-208. doi: 10.1002/ijc.29471.
12. Gaitskell K, Green J, Pirie K, Barnes I, Hermon C, Reeves GK, et al. Histological subtypes of ovarian cancer associated with parity and breastfeeding in the prospective Million Women Study. Int J Cancer. 2018;142(2):281-9. doi: 10.1002/ijc.31063.
13. Gaitskell K, Green J, Pirie K, Reeves G, Beral V, Million Women Study C. Tubal ligation and ovarian cancer risk in a large cohort: Substantial variation by histological type. Int J Cancer. 2016;138(5):1076-84. doi: 10.1002/ijc.29856.
14. Gates MA, Rosner BA, Hecht JL, Tworoger SS. Risk factors for epithelial ovarian cancer by histologic subtype. Am J Epidemiol. 2010;171(1):45-53. doi: 10.1093/aje/kwp314.
15. Jensen A, Sharif H, Olsen JH, Kjaer SK. Risk of breast cancer and gynecologic cancers in a large population of nearly 50,000 infertile Danish women. Am J Epidemiol. 2008;168(1):49-57. doi: 10.1093/aje/kwn094.
16. Kurian AW, Balise RR, McGuire V, Whittemore AS. Histologic types of epithelial ovarian cancer: have they different risk factors? Gynecol Oncol. 2005;96(2):520-30. doi: 10.1016/j.ygyno.2004.10.037.
17. Kvale G, Heuch I, Nilssen S, Beral V. Reproductive factors and risk of ovarian cancer: a prospective study. Int J Cancer. 1988;42(2):246-51.
18. Madsen C, Baandrup L, Dehlendorff C, Kjaer SK. Tubal ligation and salpingectomy and the risk of epithelial ovarian cancer and borderline ovarian tumors: a nationwide case-control study. Acta Obstet Gynecol Scand. 2015;94(1):86-94. doi: 10.1111/aogs.12516.
19. Merritt MA, De Pari M, Vitonis AF, Titus LJ, Cramer DW, Terry KL. Reproductive characteristics in relation to ovarian cancer risk by histologic pathways. Hum Reprod. 2013;28(5):1406-17. doi: 10.1093/humrep/des466.
20. Merritt MA, Green AC, Nagle CM, Webb PM, Australian Cancer S, Australian Ovarian Cancer Study G. Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. Int J Cancer. 2008;122(1):170-6. doi: 10.1002/ijc.23017.
21. Modugno F, Ness RB, Wheeler JE. Reproductive risk factors for epithelial ovarian cancer according to histologic type and invasiveness. Ann Epidemiol. 2001;11(8):568-74.
22. Pearce CL, Templeman C, Rossing MA, Lee A, Near AM, Webb PM, et al. Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies. Lancet Oncol. 2012;13(4):385-94. doi: 10.1016/S1470-2045(11)70404-1.
23. Rasmussen CB, Jensen A, Albieri V, Andersen KK, Kjaer SK. Is Pelvic Inflammatory Disease a Risk Factor for Ovarian Cancer? Cancer Epidemiol Biomarkers Prev. 2017;26(1):104-9. doi: 10.1158/1055-9965.EPI-16-0459.
24. Rice MS, Murphy MA, Tworoger SS. Tubal ligation, hysterectomy and ovarian cancer: A meta-analysis. J Ovarian Res. 2012;5(1):13. doi: 10.1186/1757-2215-5-13.
25. Rice MS, Hankinson SE, Tworoger SS. Tubal ligation, hysterectomy, unilateral oophorectomy, and risk of ovarian cancer in the Nurses' Health Studies. Fertil Steril. 2014;102(1):192-8 e3. doi: 10.1016/j.fertnstert.2014.03.041.

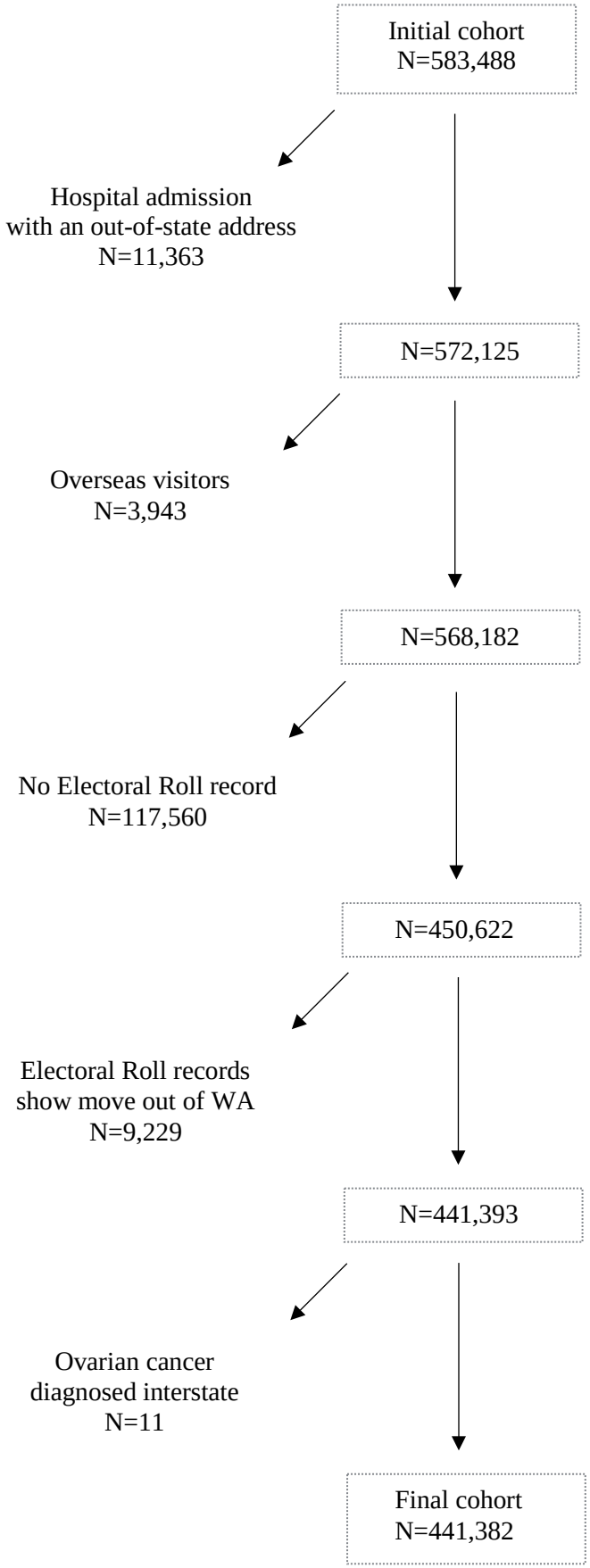
26. Risch HA, Marrett LD, Jain M, Howe GR. Differences in risk factors for epithelial ovarian cancer by histologic type. Results of a case-control study. Am J Epidemiol. 1996;144(4):363-72.
27. Rosenblatt KA, Thomas DB. Reduced risk of ovarian cancer in women with a tubal ligation or hysterectomy. The World Health Organization Collaborative Study of Neoplasia and Steroid Contraceptives. Cancer Epidemiol Biomarkers Prev. 1996;5(11):933-5.
28. Tung KH, Goodman MT, Wu AH, McDuffie K, Wilkens LR, Kolonel LN, et al. Reproductive factors and epithelial ovarian cancer risk by histologic type: a multiethnic case-control study. Am J Epidemiol. 2003;158(7):629-38.
29. Weiss NS, Young JL, Jr., Roth GJ. Marital status and incidence of ovarian cancer: the U.S. Third National Cancer Survey, 1969--71. J Natl Cancer Inst. 1977;58(4):913-5.
30. Wentzensen N, Poole EM, Trabert B, White E, Arslan AA, Patel AV, et al. Ovarian Cancer Risk Factors by Histologic Subtype: An Analysis From the Ovarian Cancer Cohort Consortium. J Clin Oncol. 2016;34(24):2888-98. doi: 10.1200/JCO.2016.66.8178.
31. Yang HP, Trabert B, Murphy MA, Sherman ME, Sampson JN, Brinton LA, et al. Ovarian cancer risk factors by histologic subtypes in the NIH-AARP Diet and Health Study. Int J Cancer. 2012;131(4):938-48. doi: 10.1002/ijc.26469.
32. Albrektsen G, Heuch I, Thoresen S, Kvale G. Twin births, sex of children and maternal risk of ovarian cancer: a cohort study in Norway. Br J Cancer. 2007;96(9):1433-5. doi: 10.1038/sj.bjc.6603687.
33. Ji J, Forsti A, Sundquist J, Hemminki K. Risks of breast, endometrial, and ovarian cancers after twin births. Endocr Relat Cancer. 2007;14(3):703-11. doi: 10.1677/ERC-07-0088.
34. Jordan SJ, Green AC, Nagle CM, Olsen CM, Whiteman DC, Webb PM, et al. Beyond parity: association of ovarian cancer with length of gestation and offspring characteristics. Am J Epidemiol. 2009;170(5):607-14. doi: 10.1093/aje/kwp185.
35. Lambe M, Wuu J, Rossing MA, Hsieh CC. Twinning and maternal risk of ovarian cancer. Lancet. 1999;353(9168):1941. doi: 10.1016/S0140-6736(99)02000-0.
36. Neale RE, Darlington S, Murphy MF, Silcocks PB, Purdie DM, Talback M. The effects of twins, parity and age at first birth on cancer risk in Swedish women. Twin Res Hum Genet. 2005;8(2):156-62. doi: 10.1375/1832427053738809.
37. Neale RE, Purdie DM, Murphy MF, Mineau GP, Bishop T, Whiteman DC. Twinning and the incidence of breast and gynecological cancers (United States). Cancer Causes Control. 2004;15(8):829-35. doi: 10.1023/B:CACO.0000043433.09264.58.
38. Titus-Ernstoff L, Perez K, Cramer DW, Harlow BL, Baron JA, Greenberg ER. Menstrual and reproductive factors in relation to ovarian cancer risk. Br J Cancer. 2001;84(5):714-21. doi: 10.1054/bjoc.2000.1596.
39. Whiteman DC, Murphy MF, Cook LS, Cramer DW, Hartge P, Marchbanks PA, et al. Multiple births and risk of epithelial ovarian cancer. J Natl Cancer Inst. 2000;92(14):1172-7.
40. Ness RB, Cottreau C. Possible role of ovarian epithelial inflammation in ovarian cancer. J Natl Cancer Inst. 1999;91(17):1459-67.
41. Ness RB, Grisso JA, Cottreau C, Klapper J, Vergona R, Wheeler JE, et al. Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. Epidemiology. 2000;11(2):111-7.
42. Rasmussen CB, Kjaer SK, Albieri V, Bandera EV, Doherty JA, Hogdall E, et al. Pelvic Inflammatory Disease and the Risk of Ovarian Cancer and Borderline Ovarian Tumors: A Pooled Analysis of 13 Case-Control Studies. Am J Epidemiol. 2017;185(1):8-20. doi: 10.1093/aje/kww161.

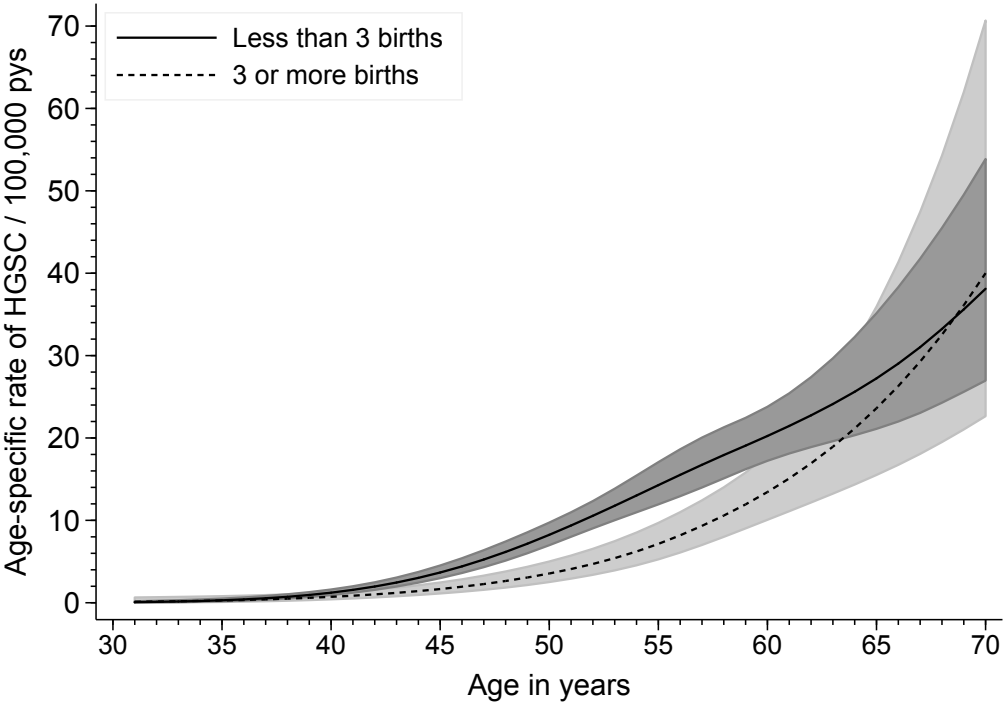
43. Data Linkage Western Australia. Enabling health and medical research in Western Australia. http://www.datalinkage-wa.org/ [updated 24 August 2016; cited 25 April 2018].
44. Holman CD, Bass AJ, Rosman DL, Smith MB, Semmens JB, Glasson EJ, et al. A decade of data linkage in Western Australia: strategic design, applications and benefits of the WA data linkage system. Aust Health Rev. 2008;32(4):766-77.
45. Hill L. Compulsory Voting in Australia: A Basis for a Best Practice Regime. Fed L Rev. 2004;32:479-98.
46. Stewart CJR, Stewart LM, Holman CDJ, Jordan S, Semmens J, Spilsbury K, et al. Value of Pathology Review in a Population-based Series of Ovarian Tumors. Int J Gynecol Pathol. 2017;36(4):377-85. doi: 10.1097/PGP.0000000000000342.
47. Royston P, Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Stat Med. 2002;21(15):2175-97. doi: 10.1002/sim.1203.
48. Ferlay J, Héry C, Autier P, Sankaranarayanan R. Global Burden of Breast Cancer. In: Li C, editor. Breast Cancer Epidemiology. New York, NY: Springer New York; 2010. p. 1-19.
49. McPherson K, Steel CM, Dixon JM. ABC of breast diseases. Breast cancer-epidemiology, risk factors, and genetics. BMJ. 2000;321(7261):624-8.
50. Grossman DC, Curry SJ, Owens DK, Barry MJ, Davidson KW, Doubeni CA, et al. Screening for Ovarian Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2018;319(6):588-94. doi: 10.1001/jama.2017.21926.
51. Henderson JT, Webber EM, Sawaya GF. Screening for Ovarian Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2018;319(6):595-606. doi: 10.1001/jama.2017.21421.
52. McGuire V, Hartge P, Liao LM, Sinha R, Bernstein L, Canchola AJ, et al. Parity and Oral Contraceptive Use in Relation to Ovarian Cancer Risk in Older Women. Cancer Epidemiol Biomarkers Prev. 2016;25(7):1059-63. doi: 10.1158/1055-9965.EPI-16-0011.
53. Whiteman DC, Siskind V, Purdie DM, Green AC. Timing of pregnancy and the risk of epithelial ovarian cancer. Cancer Epidemiol Biomarkers Prev. 2003;12(1):42-6.
54. Wu AH, Pearce CL, Lee AW, Tseng C, Jotwani A, Patel P, et al. Timing of births and oral contraceptive use influences ovarian cancer risk. Int J Cancer. 2017;141(12):2392-9. doi: 10.1002/ijc.30910.
55. Friebel TM, Domchek SM, Rebbeck TR. Modifiers of cancer risk in BRCA1 and BRCA2 mutation carriers: systematic review and meta-analysis. J Natl Cancer Inst. 2014;106(6):dju091. doi: 10.1093/jnci/dju091.
56. Kotsopoulos J, Lubinski J, Gronwald J, Cybulski C, Demsky R, Neuhausen SL, et al. Factors influencing ovulation and the risk of ovarian cancer in BRCA1 and BRCA2 mutation carriers. Int J Cancer. 2015;137(5):1136-46. doi: 10.1002/ijc.29386.
57. Modan B, Hartge P, Hirsh-Yechezkel G, Chetrit A, Lubin F, Beller U, et al. Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a BRCA1 or BRCA2 mutation. N Engl J Med. 2001;345(4):235-40. doi: 10.1056/NEJM200107263450401.
58. Stewart LM, Holman CD, Aboagye-Sarfo P, Finn JC, Preen DB, Hart R. In vitro fertilization, endometriosis, nulliparity and ovarian cancer risk. Gynecol Oncol. 2013;128(2):260-4. doi: 10.1016/j.ygyno.2012.10.023.
59. Jareid M, Licaj I, Standahl Olsen K, Lund E, Bovelstad HM. Does an epidemiological comparison support a common cellular lineage for similar subtypes of postmenopausal uterine and ovarian carcinoma? The Norwegian Women and Cancer Study. Int J Cancer. 2017;141(6):1181-9. doi: 10.1002/ijc.30826.

60. Reid BM, Permuth JB, Sellers TA. Epidemiology of ovarian cancer: a review. Cancer Biol Med. 2017;14(1):9-32. doi: 10.20892/j.issn.2095-3941.2016.0084.
61. Goswami B, Rajappa M, Sharma M, Sharma A. Inflammation: its role and interplay in the development of cancer, with special focus on gynecological malignancies. Int J Gynecol Cancer. 2008;18(4):591-9. doi: 10.1111/j.1525-1438.2007.01089.x.

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.


Initial cohort
N=583,488
Hospital admission
with an out-of-state address
N=11,363
N=572,125
Overseas visitors
N=3,943
N=568,182
No Electoral Roll record
N=117,560
N=450,622
Electoral Roll records
show move out of WA
N=9,229
N=441,393
Ovarian cancer
diagnosed interstate
N=11
Final cohort
N=441,382


Less than 3 births
3 or more births
Age-specific rate of HGSC / 100,000 pys
0
10
20
30
40
50
60
70
30
35
40
45
50
55
60
65
70
Age in years

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

Diagnosis or procedure	**ICD-8** (01/01/1970-31/12/1978)	**ICD-9**[1] (01/01/1979-30/06/1999)	**ICD-10-AM** (01/07/1999-present)	**Code of Surgical Operations** (01/01/1970-31/12/1978)	**International Classification of Procedures in Medicine** (01/01/1979-31/12/1987)	**ICD-9** (01/01/1988-30/06/1999)	**Australian Classification of Health Interventions** (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 [2]	-	-	-	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 [3]							35638-09, 35638-11, 35713-11

[1]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)

[2]Women who had a hysterectomy with an oophorectomy or salpingectomy in the same or any other admission were not included in this category.

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