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Association between pelvic inflammatory disease, infertility, ectopic pregnancy and the development of ovarian serous borderline tumor, mucinous borderline tumor and low-grade serous carcinoma

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ABSTRACT

Objective. Risk factors for ovarian borderline tumors and low-grade serous carcinoma (LGSC) are poorly understood. The aim of this study was to examine the association between infertility, pelvic inflammatory disease (PID), endometriosis, ectopic pregnancy, hysterectomy, tubal ligation and parity and the risk of serous borderline tumor (SBT), mucinous borderline tumor (MBT) and LGSC.

Methods. This was a population-based cohort study using linked administrative and hospital data. Participants were 441,382 women born between 1945 and 1975 who had been admitted to hospital in Western Australia between 1 January 1980 and 30 June 2014. We used Cox regression to estimate hazard ratios (HRs).

Results. We observed an increased rate of SBT associated with infertility, PID and ectopic pregnancy (HRs and 95% CIs were, respectively, 1.98 (1.20-3.26); 1.95 (1.22-3.10) and 2.44 (1.20-4.96)). We did not detect an association between any of the factors under study and the rate of MBT. A diagnosis of PID was associated with an increased rate of LGSC (HR 2.90, 95% CI 1.21-6.94).

Conclusions. The association with PID supports the hypothesis that inflammatory processes within the upper gynaecological tract and/or peritoneum may predispose to the development of SBT and LGSC.

INTRODUCTION

Epithelial ovarian tumors are diverse in their origins, risk factors, pathology, molecular biology, invasiveness and prognosis [1-5]. There are five major histotypes: high-grade serous, endometrioid, clear cell, mucinous and low-grade serous. They can occur as invasive carcinomas or as borderline tumors (tumors of low malignant potential).

Given the acknowledged diversity in tumor types, it is important that risk factors be investigated separately for each subtype. For example, pelvic high-grade serous carcinoma has been shown to be associated with BRCA mutations [6] and likely originates in the fimbrial end of the fallopian tube [7], involving the ovary only secondarily, whereas endometrioid and clear cell carcinomas have been associated with endometriosis [8].

Historically, a number of hypotheses have been proposed to explain the observed epidemiological associations with ovarian neoplasia. The most prominent among these include the incessant ovulation hypothesis [9], the gonadotrophin hypothesis [10] and the inflammation hypothesis [11]. The inflammation hypothesis posits that chronic inflammation results in increased cell division, the production of reactive oxygen and nitrogen species, the release of prostaglandins and pro-inflammatory cytokines, all leading to the potential for epigenetic alterations, errors in DNA replication, and possible tumorigenesis. Inflammatory conditions that have been associated with an increased risk of ovarian cancer include endometriosis, talc and asbestos exposure [12, 13] and pelvic inflammatory disease (PID).

PID occurs when pathogens ascend from the vagina or cervix to the upper female reproductive tract. Chronic inflammation from repeated, untreated or unresolved infections can lead to tubal damage, ectopic pregnancy and infertility. PID has been associated in some studies with ovarian carcinoma [14], serous ovarian carcinoma [15], high-grade serous ovarian carcinoma [16] and serous borderline tumors (SBT) [17]. We have previously

reported on the association between reproductive factors and the risk of high-grade serous

ovarian carcinoma [16]. The aim of the present study was to extend this work and examine

the association between low-grade serous ovarian carcinoma (LGSC), SBT and mucinous

borderline ovarian tumors (MBT), and potential risk factors including PID, infertility,

endometriosis, ectopic pregnancy, hysterectomy, tubal ligation and parity.

METHODS

The study population

We conducted a population-based cohort study using linked administrative and hospital data.

The study was set in Western Australia (WA), Australia's largest state by geographic area

and fourth largest by population (estimated resident population 2.6 million). Most of WA's

residents live in the south-west corner of the state; the remainder is sparsely populated.

Participants were selected from WA's Hospital Morbidity Data Collection (HMDC) [18], and

comprised all women, born between 1945 and 1975 inclusive, who had been admitted to a

WA hospital at any time between 1 January 1980 and 30 June 2014. We excluded non-

residents as previously described [16].

Data linkage

Data for this study were sourced from the WA Data Linkage System, a collection of over 35

different datasets maintained by the Data Linkage Branch of the WA Department of Health

[18]. Datasets are linked using probabilistic matching with clerical review and ongoing

surveillance to maximise linkage quality. We used data from the HMDC, the Midwives

Notification System, Birth Registrations, the WA Cancer Registry, Death Registrations and

the WA Electoral Roll.

Exposure variables

We identified diagnoses of infertility, PID, endometriosis, ectopic pregnancy and parity and surgical procedures including hysterectomy (without oophorectomy or salpingectomy) and tubal ligation. Medical diagnoses and surgical procedures were recorded in the HMDC, with information available from 1 January 1970 onward, and coded according to contemporaneous International Classification of Diseases (ICD) codes. Codes used to classify all the above diagnoses and procedures, with the exception of ectopic pregnancy, have been previously published [16]. Women were classified as having a tubal ectopic pregnancy if their HMDC records contained a diagnosis of 633.1 or 633.9 (ICD 9) or O00.1 or O00.9 (ICD10). Information on parity was derived from the Midwives Notification System for births from 1980 and from the WA Births Register for births 1970-1980.

Outcome variables

We considered three separate outcomes: diagnoses of SBT, MBT and LGCS. These were recorded in the WA Cancer Registry with data available from 1982. We conducted a detailed pathology review of all identified ovarian tumors, revising and reclassifying where appropriate to ensure the correct classification of ovarian tumor histotypes identified in our cohort [19].

Bias

The participants in this study were part of a dynamic population that could move in or out of the state. This can lead to exposure misclassification in women who migrate into the state, and loss to follow-up in women who migrate out. To minimise loss to follow-up we excluded women who were overseas visitors, women who resided out of WA, women whose WA Electoral Roll records showed that they had migrated out of the state, and women for whom we did not have an electoral roll record showing residence in WA. Registration on the

6

126   Electoral Roll is compulsory for Australian citizens aged 18 years and older. We also

127   excluded women who had ovarian cancer diagnosed interstate. A flow chart of this selection

128   strategy has been previously published [16].

129   Women who migrated into the state could have given birth prior to moving into WA. We

130   were able to correctly classify parity in women who gave birth interstate or overseas and

131   subsequently gave birth in WA since the Midwives Notification System includes information

132   on previous births. However, women who had completed their family before migrating into

133   WA would have been misclassified as nulliparous since we had no record of births for these

134   women. After extensive data checking and sensitivity analyses, we found the best way to

135   address this issue was to classify parity into two categories: low parity (0-2 births) and high

136   parity (3 or more births).

137   Women were classified as having PID, endometriosis or infertility only if this was included

138   in their HMDC records. However, these conditions can be clinically occult or may be

139   diagnosed without necessarily involving hospital admission. The comparison in this study

140   therefore was not between women with and without endometriosis, for example, but rather,

141   between women with and without a hospital diagnosis of endometriosis.

142   **Data analysis**

143   We used multivariable Cox proportional hazards regression to estimate hazard ratios (HRs)

144   and 95% confidence intervals (CIs). We used age as the time scale. Follow-up was censored

145   at any ovarian tumor diagnosis, bilateral oophorectomy, oophorectomy which was not

146   specified as bilateral or unilateral, death or the censor date of 14 June 2014; whichever came

147   first. All exposure variables were included as time-varying binary variables such that each

148   individual contributed follow-up time to the unexposed category until the date of exposure

149   and thereafter contributed follow-up time to the exposed category. We examined interactions

150 between study variables and tested the proportional hazards assumption using Schoenfeld

151 residuals. We only found evidence for a violation of the assumption with PID. For this

152 reason, we also derived HRs for PID from flexible non-parametric hazard models. Statistical

153 analyses were performed using SPSS version 24 (IBM) and STATA version 14 (StataCorp,

154 College Station, Texas).

155 **Ethics**

156 The study received ethics approval from WA Department of Health Data Custodians, the WA

157 Department of Health Ethics Committee, Curtin University Human Research Ethics

158 Committee and The University of Notre Dame Human Research Ethics Committee.

159

160 **RESULTS**

161 A total of 583,488 women were admitted to hospital during the period 1980-2014 and were

162 eligible for inclusion in the study population. Following exclusion of cases as detailed in the

163 Methods, the final cohort of 441,382 women contributed 23,206,070 person-years of follow-

164 up. The median age at the end of follow-up was 52 years (interquartile range [IQR] 45-60

165 years).

166 During follow-up, 205 women were diagnosed with SBT, 138 with MBT and 41 with LGSC.

167 The median age at diagnosis of SBT was 45 years (IQR 36-52 years); MBT, 43 years (IQR

168 34-50 years) and LGSC, 49 years (IQR 40-54 years). Infertility was diagnosed in 7% of

169 women; PID in 8%, endometriosis in 8%, and 2% of women experienced an ectopic

170 pregnancy (Table 1).

171 **Serous borderline tumor (SBT)**

In parity-adjusted analysis, using age as the time scale, we found an increased rate of SBT associated with infertility, PID and ectopic pregnancy (Table 2) for women of all ages. The association with PID varied according to infertility status and so we considered four possible combinations: no diagnosis of infertility and no diagnosis of PID (referent); infertility without PID; PID without infertility and both PID and infertility. We found that the association between PID and SBT did not satisfy the proportional hazards assumption, so we investigated the association at different ages (Fig 1 and Table 3). A diagnosis of both PID and infertility in women aged 35 was associated with an 8-fold increase in the rate of SBT compared to women aged 35 without PID or infertility. A diagnosis of PID alone was associated with a 2-fold increase in the rate of SBT while a diagnosis of infertility alone was associated with a 1.6-fold increase. The difference in rates between women with and without PID and infertility declined with increasing age (Fig 1 and Table 3); by age 50, only a diagnosis of both PID and infertility was associated with an increased rate of SBT, compared to women of the same age without these conditions, although this did not reach statistical significance. There was no detectable increase in the rate associated with only PID or only infertility at this age (Table 3).

We observed a two-fold increase in the rate of SBT associated with ectopic pregnancy (HR 2.44; 95% CI 1.20-4.96) (Table 2). In subgroup analysis, we investigated the hypothesis that the increased rate of SBT associated with ectopic pregnancy was related to prior PID. Among the subset of women without a PID diagnosis, ectopic pregnancy was associated with a 2.6-fold increase in the rate of SBT (HR 2.58; 95% CI 1.14-5.83). Among a smaller subset with neither PID nor infertility, the HR associated with ectopic pregnancy was 2.13 (95% CI 0.94-4.81).

Mucinous borderline tumor (MBT)

196   We did not detect any associations between the risk factors under study and MBT: confidence

197   intervals were wide and none of the estimates reached statistical significance. (Table 2).

198   **Low grade serous carcinoma (LGSC)**

199   We observed a three-fold increase in the rate of LGSC associated with PID. With only 41

200   cases of LGSC in the cohort, risk estimates were imprecise with wide confidence intervals.

201   Endometriosis and infertility were associated with increased hazards of LGSC, while tubal

202   ligation and high parity were inversely associated, however, none of these estimates reached

203   statistical significance (Table 2).

204

205   **DISCUSSION**

206   In this study we observed an increased risk of SBT associated with a hospital diagnosis of

207   PID. This finding is in line with previous studies, including a pooled analysis of case control

208   studies [20] and a registry-based cohort study [17]. Both of these studies identified an

209   apparent dose-response relationship, such that women with more than two episodes of PID

210   had a greater increase in risk of SBT than women with only one. Along with PID, we also

211   found an increased risk of SBT associated with hospital-diagnosed infertility and a marked

212   elevation in risk where both diagnoses were present, particularly in younger women. This

213   finding could imply a dose response effect, given that infertility as a sequela to PID is more

214   likely to occur in women with chronic or repeated infections rather than a single, promptly

215   treated infection. The heightened risk in younger women could suggest that the development

216   of SBT after PID may occur over a relatively short period of time. Alternatively, the observed

217   increased risk in younger women may be due to detection bias. Women with PID and

218   infertility may be more likely to have diagnostic imaging or laparoscopy and as a result have

219   relatively indolent tumours diagnosed, which may otherwise have escaped detection.

220 Our novel finding of an increased risk of SBT associated with ectopic pregnancy warrants

221 further investigation. PID is a known risk factor for ectopic pregnancy and it is possible that

222 the observed association with ectopic pregnancy was simply due to confounding by PID.

223 However, we also found an association between ectopic pregnancy and SBT in the absence of

224 a hospital admission for PID. The inflammatory response to an ectopic pregnancy is likely to

225 be acute and short-lived rather than chronic. If the inflammation hypothesis is correct, it is

226 unlikely that ectopic pregnancy on its own would lead to the development of SBT. Therefore,

227 we hypothesise that the observed association between ectopic pregnancy and SBT could be

228 due to PID, because many women have clinically silent infections that would not be recorded

229 as a hospital diagnosis.

230 PID leading to functional damage to the fallopian tubes and consequent ectopic pregnancy

231 may lend further support to the hypothesis of a tubal origin for serous ovarian tumors [21],

232 although currently the tubal hypothesis largely refers to high grade serous ovarian carcinoma;

233 data supporting a tubal origin of ovarian SBT and LGSC are not universally accepted.

234 We also observed an increased risk of LGSC associated with PID, a not unexpected finding

235 given that some authors have proposed that LGSC develops in a stepwise fashion from SBT

236 [22], although others have suggested this may not be true for all cases of LGSC [2].

237 Our study has a number of strengths and limitations. A particular strength of our study was

238 prior pathology review of all ovarian tumor cases, ensuring that histotypes were correctly

239 classified according to the latest criteria [19]. Other strengths include the large population-

240 based cohort and long-term follow-up, accurate recording of diagnoses and procedures in

241 hospital records thereby avoiding the possibility of recall error common in self-reported data.

242 A major limitation of our study, in common with many registry-based studies, is the

243 possibility of exposure misclassification. This can occur if a particular health condition was

244 diagnosed prior to hospital admission and not recorded in a woman's hospital records, for

245 example, if she moved into the catchment area after diagnosis, or if the condition was

246 diagnosed and treated in a primary practice rather than a hospital. This type of

247 misclassification is likely to be non-differential with respect to the outcome under study and

248 could potentially lead to an underestimation of any association.

249 In conclusion, we have found that PID appears to be associated with an increased risk of

250 developing ovarian SBT and LGSC. In a previous study we demonstrated an association

251 between PID and high grade serous ovarian carcinoma [16]. Together these results suggest

252 that chronic inflammation may play a role in the development of pelvic serous tumors.

253 Routine screening for sexually transmitted infections in young and/or high-risk populations,

254 educating women about the often-silent nature of pelvic inflammation and encouraging

255 health-care seeking behavior and early treatment, may have the potential to reduce the

256 incidence of these tumors in the future.

257

267

268 **AUTHOR CONTRIBUTIONS**

269 All authors contributed to this research: to the interpretation of data, the revision of the draft

270 manuscript and approval of the final version to be published. LMS and CS contributed to the

271 conception and design and acquisition of data. LMS and KS contributed to the analysis of

272 data. LMS drafted the article.

273

278

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Table 1: Characteristics of the study population.

Characteristic	Study population (N=441,382) N (%)	SBT (N=205) N (%)	MBT (N=138) N (%)	LGSC (N=41) N (%)
Infertility				
No	412,523 (93.5)	188 (91.7)	132 (95.7)	>36 (>87.8)
Yes	28,859 (6.5)	17 (8.3)	6 (4.3)	<5[2] (<12.2)
PID				
No	408,047 (92.4)	185 (90.2)	130 (94.2)	35 (85.4)
Yes	33,335 (7.6)	20 (9.8)	8 (5.8)	6 (14.6)
Endometriosis				
No	406,830 (92.2)	195 (95.1)	132 (95.7)	36 (87.8)
Yes	34,552 (7.8)	10 (4.9)	6 (4.3)	5 (12.2)
Ectopic pregnancy				
No	432,442 (98.0)	197 (96.1)	>133 (>96.4)	41 (100)
Yes	8,940 (2.0)	8 (3.9)	<5 (<3.6)	0 (0)
Hysterectomy [1]				
No	393,435 (89.1)	185 (90.2)	130 (94.2)	>36 (>87.8)
Yes	47,947 (10.9)	20 (9.8)	8 (5.8)	<5 (<12.2)
Tubal ligation				
No	362,743 (82.2)	174 (84.9)	119 (86.2)	36 (87.8)
Yes	78,639 (17.8)	31 (15.1)	19 (13.8)	5 (12.2)
Parity				
Low (0-2 births)	317,605 (72.0)	162 (79.0)	111 (80.4)	35 (85.4)
High (3 or more births)	123,777 (28.0)	43 (21.0)	27 (19.6)	6 (14.6)

Abbreviations: PID, pelvic inflammatory disease; SBT, serous borderline tumor; MBT, mucinous borderline tumor; LGSC, low grade serous carcinoma

[1] Hysterectomy without salpingectomy or oophorectomy

[2] Subgroups numbering less than 5 are not documented to maintain participants' confidentiality.

Table 2: Hazard ratios and 95% confidence intervals from multivariable Cox models for the association between reproductive factors and the risk of serous borderline tumor (SBT) mucinous borderline tumor (MBT) and low-grade serous carcinoma (LGSC).

Characteristic	SBT		MBT		LGSC	
	HR[2]	95% CI	HR	95%CI	HR	95%CI
Infertility						
No	1.00	Referent	1.00	Referent	1.00	Referent
Yes	1.98	1.20-3.26	0.98	0.43-2.23	1.68	0.52-5.47
PID						
No	1.00	Referent	1.00	Referent	1.00	Referent
Yes	1.95[3]	1.22-3.10	1.16	0.57-2.38	2.90	1.21-6.94
Endometriosis						
No	1.00	Referent	1.00	Referent	1.00	Referent
Yes	0.95	0.50-1.80	0.91	0.41-2.08	2.26	0.88-5.81
Ectopic pregnancy						
No	1.00	Referent	1.00	Referent	1.00	Referent
Yes	2.44	1.20-4.96	0.44	0.06-3.18	-	-
Hysterectomy [1]						
No	1.00	Referent	1.00	Referent	1.00	Referent
Yes	1.10	0.69-1.78	0.73	0.35-1.52	0.90	0.31-2.58
Tubal ligation						
No	1.00	Referent	1.00	Referent	1.00	Referent
Yes	0.90	0.61-1.34	0.89	0.54-1.47	0.66	0.26-1.72
Parity						
Low (0-2 births)	1.00	Referent	1.00	Referent	1.00	Referent
High (3 or more births)	0.80	0.57-1.13	0.77	0.50-1.17	0.49	0.21-1.17

Abbreviations: SBT, serous borderline tumor; MBT, mucinous borderline tumor; LGSC, low grade serous carcinoma; HR, hazard ratio; CI, confidence interval; PID, pelvic inflammatory disease.

[1]Hysterectomy without salpingectomy or oophorectomy

[2]All HR estimates adjusted for age (age was used as the time scale) and parity.

[3] The proportional hazard assumption was not satisfied for the association between PID and SBT and therefore we explored this association at different ages (Table 3 and Fig 1).

Table 3: The association between pelvic inflammatory disease (PID) and infertility and the risk of serous borderline tumor (SBT). Age-specific hazard ratios and 95% confidence intervals for the hazard of SBT associated with a diagnosis of PID and/or infertility in women of low parity.

Age	Sub-group	HR[1]	95%CI
30	No infertility, no PID	1.00	Referent
	Infertility without PID[2]	1.99	0.95-4.19
	PID without infertility[3]	3.60	1.70-7.60
	Both PID and infertility[4]	17.23	5.72-51.89
35	No infertility, no PID	1.00	Referent
	Infertility without PID	1.62	0.79-3.32
	PID without infertility	2.34	1.20-4.55
	Both PID and infertility	8.42	3.58-19.79
40	No infertility, no PID	1.00	Referent
	Infertility without PID	1.36	0.66-2.77
	PID without infertility	1.59	0.83-3.07
	Both PID and infertility	4.13	1.58-10.78
45	No infertility, no PID	1.00	Referent
	Infertility without PID	1.19	0.58-2.43
	PID without infertility	1.21	0.64-2.31
	Both PID and infertility	2.56	0.89-7.36
50	No infertility, no PID	1.00	Referent
	Infertility without PID	1.09	0.53-2.23
	PID without infertility	1.03	0.54-1.96
	Both PID and infertility	2.17	0.71-6.58
55	No infertility, no PID	1.00	Referent
	Infertility without PID	1.02	0.49-2.10
	PID without infertility	0.91	0.46-1.81
	Both PID and infertility	1.93	0.51-7.30
60	No infertility, no PID	1.00	Referent
	Infertility without PID	0.95	0.46-1.99
	PID without infertility	0.81	0.38-1.71
	Both PID and infertility	1.68	0.37-7.76

Abbreviations: HR, hazard ratio; CI, confidence interval; PID, pelvic inflammatory disease.

[1]HR estimates derived from a flexible non-parametric proportional hazards model with time-varying covariates, adjusted for parity and using age as the time scale.

[2] Women with a diagnosis of infertility in one or more of their hospital records, but no mention of PID.

[3] Women with a diagnosis of PID in one or more of their hospital records, but no mention of infertility.

[4] Women with diagnoses of both PID and infertility in one or more of their hospital records.

Figure 1: Predicted age-specific incidence rates of SBT by pelvic inflammatory disease (PID) and infertility from a flexible non-parametric proportional hazards model with time-varying covariates, adjusted for parity and using age as the time scale.