European Journal of Obstetrics & Gynecology and Reproductive Biology 205 (2016) 170–173

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Epithelial ovarian cancer and type of peritoneal insult: a case–control study

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ARTICLE INFO

Article history:
Received 22 February 2016
Received in revised form 5 June 2016
Accepted 26 July 2016

Keywords:
Type 1 and 2 epithelial ovarian cancer
Peritoneal insults
General population

ABSTRACT

Objective: To evaluate the association between different types of peritoneal insults and the development of sporadic epithelial ovarian cancer (EOC) subtypes in the general population.
Study design: Hospital based case control study comparing sporadic cases of EOC with age matched control group between 2003 and 2008. Medical, surgical, and gynecological histories were compared between 208 women with histological diagnosis of EOC and 224 women in the control group matched for age at presentation for well woman examination.
Results: 18% patients in the study population and 5% patients in the control group had history of diverticulosis (OR 7.3, 95% CI 2.8–19.1). 10% patients in the study populations and 39% patients in the control group had history of diabetes mellitus (OR 0.41, 95% CI 0.23–0.75). Sub classification of EOC into type 1 and type 2 further revealed 12% patients (OR 0.44, 95% CI 0.22–0.87) in type 1 group, 35% patients (OR 0.43, 95% CI 0.27–0.69) in type 2 group, and 71% patients in the control group had no prior surgical history. Furthermore, 3% patients (OR 0.27; 95% CI 0.08–0.9) in the type 1 group, 48% patients (OR 2.0, CI 95% 1.24–3.24) in the type 2 group, and 41% patients in the control group had history of bilateral tubal ligation (BTL).
Conclusion: A significant association was found between diverticulosis, hysterectomy and endometriosis increasing the likelihood of type 1 EOC; while diverticulosis, exploratory laparotomy and hysterectomy increased the likelihood of type 2 EOC. BTL was significantly associated with decreasing the likelihood of type 1 EOC, but increasing the likelihood of type 2 EOC. Diabetes mellitus and no prior surgical history were found to significantly decrease the likelihood of all EOC.

Introduction

Epithelial ovarian cancers (EOC) represent 90% of all ovarian malignancies [1]. It has traditionally been proposed that all EOC are the result of metaplasia that occurs after repetitive epithelial trauma and repair due to ovulation. However, new histopathological and molecular studies have recently explained the existence of two broad categories based on their pathogenesis, clinical presentation and histology. Type 1 tumors usually progress from Mullerian metaplasia, they are often confined to the ovary at the time of diagnosis, have a stable genome and they appear to have a slower and more indolent progression. Type 1 tumors represent 25% of all EOC and include the histologic types endometrioid, clear cell, transitional cell, borderline and mucinous tumors. Type 2 tumors may arise *de novo* and not necessarily from metaplasia, they tend to be more aggressive, are found at advanced stage, and are genetically highly unstable, sometimes with mutations of breast cancer gene (BRCA) 1/2 [2–5]. Type 2 tumors represent 75% of all EOC and include high grade serous carcinomas, undifferentiated carcinomas and carcinosarcomas.

Direct epithelial trauma of the ovary caused by repetitive ovulation might not be the only mechanism responsible for the development of all EOC. Both the ovaries and the fallopian tubes move freely and are in close contact with the different pelvic and abdominal peritoneal surfaces. The fact that type 2 EOC may originate from the fimbrial portion of the fallopian tube, supports the idea of other peritoneal insults besides ovulation playing a role in the pathogenesis of this type of cancer [6–9]. Peritoneal insults

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http://dx.doi.org/10.1016/j.ejogrb.2016.07.494
0301-2115/

that may influence the risk of EOC include surgical (bilateral tubal ligation, hysterectomy, cesarean section, unilateral salpingo-oophorectomy or cystectomy, appendectomy, cholecystectomy and exploratory laparotomy) and non-surgical (sexually transmitted infections, pelvic inflammatory disease, endometriosis, diverticulosis) insults.

The association between surgical sterilization and EOC is related to the specific type of procedure. Bilateral tubal ligation has been associated with a reduced risk of type 1 EOC while bilateral salpingectomy has been associated with a risk reduction of both type 1 and 2 EOC [10,11]. It is for that reason that the American College of Obstetrics and Gynecology recommends prophylactic salpingectomy at the time of Gynecologic surgery for the prevention of ovarian cancer [12,13].

The purpose of our study is to evaluate the association between different types of surgical and non-surgical peritoneal insults with the development of both type 1 and 2 EOC. We will be focusing our analysis on sporadic cases since they are by far more common than familial cases (90% vs 10%) and they are more difficult to predict [14]. To the best of our knowledge, no prior study has specifically evaluated associations with type 1 versus type 2 EOC in average risk patients. Knowing more specific associations between these two types of EOC and specific data from the patient's past surgical and medical history, might help guide our counseling regarding the need for salpingectomy and or oophorectomy at the time of pelvic surgery for other indications.

Materials and methods

This is a case control study of patients with confirmed primary EOC first diagnosed between 2003 and 2008 at St Luke's Hospital of Kansas City. 240 patients were diagnosed with EOC, which were then one to one age-related matched with patients who presented for well woman exam visit at the same institution over the same time period. After patients with personal history of cancer, first-degree relatives with gynecological, breast, or colon cancer, or insufficient information per chart documentation were excluded, 208 patients represented the case group and 224 patients represented the control group.

Surgical and non-surgical insults that could potentially result in peritoneal inflammatory response were recorded. Surgical insults included bilateral tubal ligation (BTL), hysterectomy, cesarean section, unilateral salpingo-oophorectomy or cystectomy (USOC), appendectomy, cholecystectomy and exploratory laparotomy. Non-surgical insults included sexually transmitted infections (STI) or pelvic inflammatory disease (PID), endometriosis and diverticulosis.

Comorbidities were collected for both control and case groups that were present at time of diagnosis. Laterality of disease was found in the pathology report from the first surgical intervention; this was carefully inspected for histological diagnosis and side of onset. If only one ovary or one fallopian tube was diseased, while the other side was not found to have evidence of malignancy, then the side with disease involvement was considered side of onset. If both sides were involved, then "unknown" was designated.

Patient health information was protected as no identifiers were recorded. This study met IRB exemption criteria. Data analysis was performed via IBM SPSS statistical analysis software. After comparing the EOC versus control group, sub classification of EOC into type 1 and 2 allowed comparison with the control group and to each other using Chi-square statistic. Comparisons were considered statistically significant if the two-sided p-value was less than 0.05. Odds ratio was calculated using logistic regression analysis.

Results

We analyzed a total of 208 cases of EOC from which 25.4% ($N = 53$) were type 1 and 74.6% ($N = 155$) were type 2. Both groups were matched for age and there was no difference between the groups regarding other risk factors for ovarian cancer including age at menarche, age at menopause, gravidity, parity, OCP use, or tobacco use (Table 1).

We found a significant association between the following surgical insults and the development of both types of EOC: hysterectomy (OR = 3.6, 95% CI 2.1–6.2), unilateral salpingo-oophorectomy (OR = 3.7, 95% CI 1.7–8) and exploratory laparotomy (OR = 2.7, 95% CI 1.2–6). Among non-surgical insults diverticulosis was the only one that showed a significant association (OR = 7.3, 95% 2.8–19.1). The rest of surgical and non-surgical insults studied did not show any significant association with both types of EOC (Table 2). Diabetes mellitus (OR = 0.41, 95% CI 0.23–0.75) was the only comorbidity associated with decreased risk of EOC. No prior abdominopelvic surgical history (OR = 0.47, 95% CI 0.32–0.71), patients who have never had an intra abdominal surgery, were also associated with a decreased risk of EOC.

When both types of EOC were analyzed separately, we found that endometriosis was only associated with type 1 (OR = 5.04, 95% CI 2.06–12.46) but not with type 2 (OR = 1.34, 95% CI 0.55–3.23). Bilateral tubal ligation was found to be protective for type 1 (OR = 0.27, 95% CI 0.08–0.9) but a risk factor for type 2 (OR = 2, 95% CI 1.24–3.24) (Tables 3–5).

Although type 1 EOC did not have a difference in laterality of disease onset, among the 155 patients with type 2 EOC, 51% had left and 12% had right side onset of disease.

Table 1
Patient characteristics.

Characteristic	EOC ($n = 240$)	Control ($n = 240$)	p value
Mean age (years)	62 ± 13	53 ± 16	NS
Mean menarche (age)	13	12.9	NS
Mean menopause (age)	48.5	50.4	NS
Gravidity	3.2	3.5	NS
Parity	2.8	2.3	NS
OCP use	183	190	NS
Tobacco use	108	100	NS

NS (not significant, $p > 0.05$); OCP (oral contraceptive pills).

Table 2
Insults and comorbidities associated with EOC versus control groups.

	EOC ($n = 208$)	Control ($n = 224$)	OR	CI	p value
Diverticulosis	18	5	7.3	2.8–19.1	0.001
Exploratory laparotomy	16	9	2.7	1.2–6.0	0.016
Appendectomy	26	38	NS	NS	NS
Cholecystectomy	21	27	NS	NS	NS
Diagnostic laparoscopy	12	21	NS	NS	NS
No prior surgery	30	71	0.47	0.32–0.71	0.001
Hysterectomy	37	21	3.6	2.1–6.2	0.001
Endometriosis	10	11	NS	NS	NS
BTL	36	41	NS	NS	NS
STI/PID	14	26	NS	NS	NS
USOC	16	9	3.7	1.7–8.0	0.001
Cesarean section	26	45	NS	NS	NS
Diabetes mellitus	10	39	0.41	0.23–0.75	0.004
Hypertension	50	47	NS	NS	NS
Hypothyroidism	65	61	NS	NS	NS

Data shown as frequency (presented as percentage, rounded to whole number). EOC (epithelial ovarian cancer); BTL (bilateral tubal ligation); STI/PID (sexually transmitted infection/pelvic inflammatory disease); USOC (unilateral salpingo-oophorectomy or cystectomy); NS (not statistically significant).