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Differences in risk for type 1 and type 2 ovarian cancer in a large cancer screening trial

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ABSTRACT

Objective: To investigate the role of previous gynecologic surgery, hormone use, and use of non-steroidal anti-inflammatory drugs on the risk of type 1 and type 2 ovarian cancer.
Methods: We utilized data collected for the Prostate, Lung, Colorectal, and Ovarian cancer screening trial. All diagnosed ovarian cancers were divided into three groups: type 1, endometrioid, clear cell, mucinous, low grade serous, and low grade adenocarcinoma/not otherwise specified (NOS); type 2, high grade serous, undifferentiated, carcinosarcoma, and high grade adenocarcinoma/NOS; and other: adenocarcinoma with grade or histology not specified, borderline tumors, granulosa cell tumors. The odds ratios for type 1, type 2, and other ovarian cancers were assessed with regard to historical information for specific risk factors.
Results: Ibuprofen use was associated with a decrease in risk for type 1 ovarian cancer. Tubal ligation and oral contraceptive use were associated with a decrease in risk for type 2 ovarian cancer. A history of ectopic pregnancy was associated with a decreased risk for all ovarian cancers by almost 70%.
Conclusion: These findings support the hypothesis that carcinogenic pathways for type 1 and type 2 ovarian cancer are different and distinct. The marked reduction in all ovarian cancer risk noted with a history of ectopic pregnancy and salpingectomy implies that the fallopian tube plays a key role in carcinogenesis for both type 1 and type 2 ovarian cancer.

Keywords: Ovarian Neoplasms; Carcinogenesis; Risk Factors

INTRODUCTION

It has become increasingly clear over the past decade, that epithelial ovarian cancer is a heterogenous disease. Clinical observations and genetic studies have divided ovarian cancer into two major subtypes [1]. Type 1 cancers are composed of low grade serous cancers, endometrioid and clear cell cancers, and mucinous cancers. This group tends to grow locally, metastasize late, and behave in a more indolent fashion. Type 2 cancers are composed of high grade serous cancers, carcinosarcomas, and undifferentiated carcinomas. These are

highly aggressive malignancies that generally present at an advanced stage. In addition to clinical differences, there are also notable genetic differences. Type 1 cancers are associated with mutations in KRAS, ARID1A, PIK3CA, PTEN, and BRAF; whereas the majority of type 2 cancers are associated with mutations in TP53 [2].

Most ovarian cancer is probably not ovarian in origin. Recent observations suggest that the majority of type 2 cancers originate as high grade intraepithelial lesions at the distal end of the fallopian tube [3]. After undergoing malignant transformation, these cells seed the ovary and rapidly spread throughout the peritoneal cavity. In contrast, endometrioid and clear cell cancers of the ovary appear to arise in association with endometriosis, suggesting that the endometrial lining, via retrograde menstruation, is the source for many type 1 cancers. Given this theory of pathogenesis, preceding gynecologic surgery can be anticipated to affect the subsequent appearance of ovarian cancer differently, depending on the type of surgery and the type of cancer. Previous reports have also found an increased or decreased risk for ovarian cancer associated with oral contraceptives [4], menopausal hormone therapy (MHT) [5], aspirin use, and ibuprofen use [6]. It remains unclear, however, whether the risk of type 1 and type 2 cancers are affected equally by these commonly used medications. The current study, therefore, was undertaken to differentiate the type 1 and type 2 cancer risk associated with previous gynecologic surgery, hormone use, and nonsteroidal anti-inflammatory drug (NSAID) use.

MATERIALS AND METHODS

Enrollment for the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial occurred between November 1993 and July 2001. Women eligible for participation were ages 55 to 74 with no previous diagnosis of lung, colorectal, or ovarian cancer. Signed informed consent was required for all participants; the Institutional Review Board for each screening center approved all consent forms and procedures. A total of 78,216 participants were enrolled, and randomized to either a screening arm or a usual medical care arm. All participants completed a detailed baseline questionnaire, which included information on personal medical and surgical history. In the screening arm, participants underwent a baseline pelvic ultrasound and serum cancer antigen 125 (CA-125), with subsequent annual pelvic ultrasound for an additional 3 years, and annual CA-125 for 5 years. The usual care group did not undergo cancer specific screening. The current study included all patients diagnosed with ovarian cancer, both from the screening group, and the usual care group.

Participants and physicians were notified of abnormal screening results; diagnostic and therapeutic interventions were at the discretion of the primary physician. Participants were followed for a minimum of ten years. Detailed information regarding the PLCO methodology has been published in previous publications from the PLCO group [7-13]. Recorded ovarian cancer information was utilized to identify three groups of patients: (1) type 1, patients with endometrioid, mucinous, clear cell, low grade serous, and low grade adenocarcinoma/not otherwise specified (NOS); (2) type 2, high grade serous, undifferentiated, carcinosarcoma, and high grade adenocarcinoma/NOS; and (3) all others were classified as 'other' (granulosa cell tumors, borderline tumors, tumors with grade or histology not available). Each group was then compared to unaffected participants to assess the odds ratio (OR) associated with each of the following reported historical events: hysterectomy, tubal ligation, ectopic pregnancy, birth control use, hormone replacement therapy, aspirin use, ibuprofen use.

Table 1. Study participants with type 1, type 2, and other cancer

Variable	Type 1	Type 2	Others	No cancer	p-value*
Hysterectomy					0.240
Yes	15 (25.0)	98 (35.0)	47 (36.2)	27,417 (36.3)	
No	45 (75.0)	182 (65.0)	83 (63.8)	48,043 (63.7)	
Tubal ligation					0.004
Yes	15 (25.4)	40 (14.2)[†]	21 (16.3)	16,190 (21.5)	
No	44 (74.6)	241 (85.8)	108 (83.7)	59,022 (78.5)	
Ectopic pregnancy					0.033
Yes	0	2 (0.7)	1 (0.8)	1,564 (2.1)	
No	60 (100)	277 (99.3)	127 (99.2)	73,764 (97.9)	
Birth control pills					<0.001
Yes	35 (58.3)	130 (46.3)[†]	56 (43.1)[†]	40,975 (54.3)	
No	25 (41.7)	151 (53.7)	74 (56.9)	34,540 (45.7)	
Aspirin					0.830
Yes	27 (45.0)	116 (41.1)	58 (44.3)	31,849 (42.2)	
No	33 (55.0)	166 (58.9)	73 (55.7)	43,535 (57.8)	
Ibuprofen					0.460
Yes	12 (20.0)[†]	90 (32.3)	41 (31.3)	24,439 (32.5)	
No	48 (80.0)	189 (67.7)	90 (68.7)	50,699 (67.5)	
Hormone replacement					0.520
Yes	42 (70.0)	196 (70.0)	83 (63.8)	49,927 (66.4)	
No	18 (30.0)	84 (30.0)	47 (36.2)	25,291 (33.6)	

Values are presented as number (%).
*Comparison of all cancer (type 1+type 2+others) with no cancer. [†]p<0.05 single group compared to no cancer group (control).

Patient characteristics were summarized by descriptive statistics for each group and compared using chi-square tests or Fisher exact tests (for categorical variables), and analysis of variance, or non-parametric Kruskal-Wallis tests if the normality assumption was not satisfied (for continuous variables). The OR with 95% CI were estimated for each group by comparison to the non-affected patients and illustrated with forest plots. All data analyses were performed in SAS ver. 9.3 (SAS Institute Inc., Cary, NC, USA). A two-tailed p-value of less than 0.05 was regarded as statistically significant.

RESULTS

In the PLCO trial there were 64 patients identified with type 1 ovarian cancer, 289 with type 2 cancer, and 133 with other cancer. A significantly greater proportion of patients with type 1 cancer were diagnosed at stage I and II, than type 2 patients (57.8% vs. 15.2%, p<0.001). There were 65,280 patients that reported having at least one child; 12,934 patients were nulliparous. Parity versus non-parity did not affect the risk for type 1 or type 2 ovarian cancer. **Table 1** summarizes the number of type 1, type 2, and other cancers with regard to each historical question (patients that answered "I don't know" to any question were excluded from that analysis). **Fig. 1** summarizes the OR for each type of cancer.

Hysterectomy did not appear to reduce cancer risk for any of the groups. Tubal ligation (OR 0.60; 95% CI, 0.43 to 0.84), and birth control pills (OR, 0.72; 95% CI, 0.57 to 0.91), significantly reduced the risk for type 2 ovarian cancer. Birth control pills also reduced the risk for other cancers (OR, 0.63; 95% CI, 0.45 to 0.90). Ibuprofen reduced the risk for type 1 ovarian cancer (OR, 0.51; 95% CI, 0.27 to 0.97). MHT and aspirin did not significantly alter
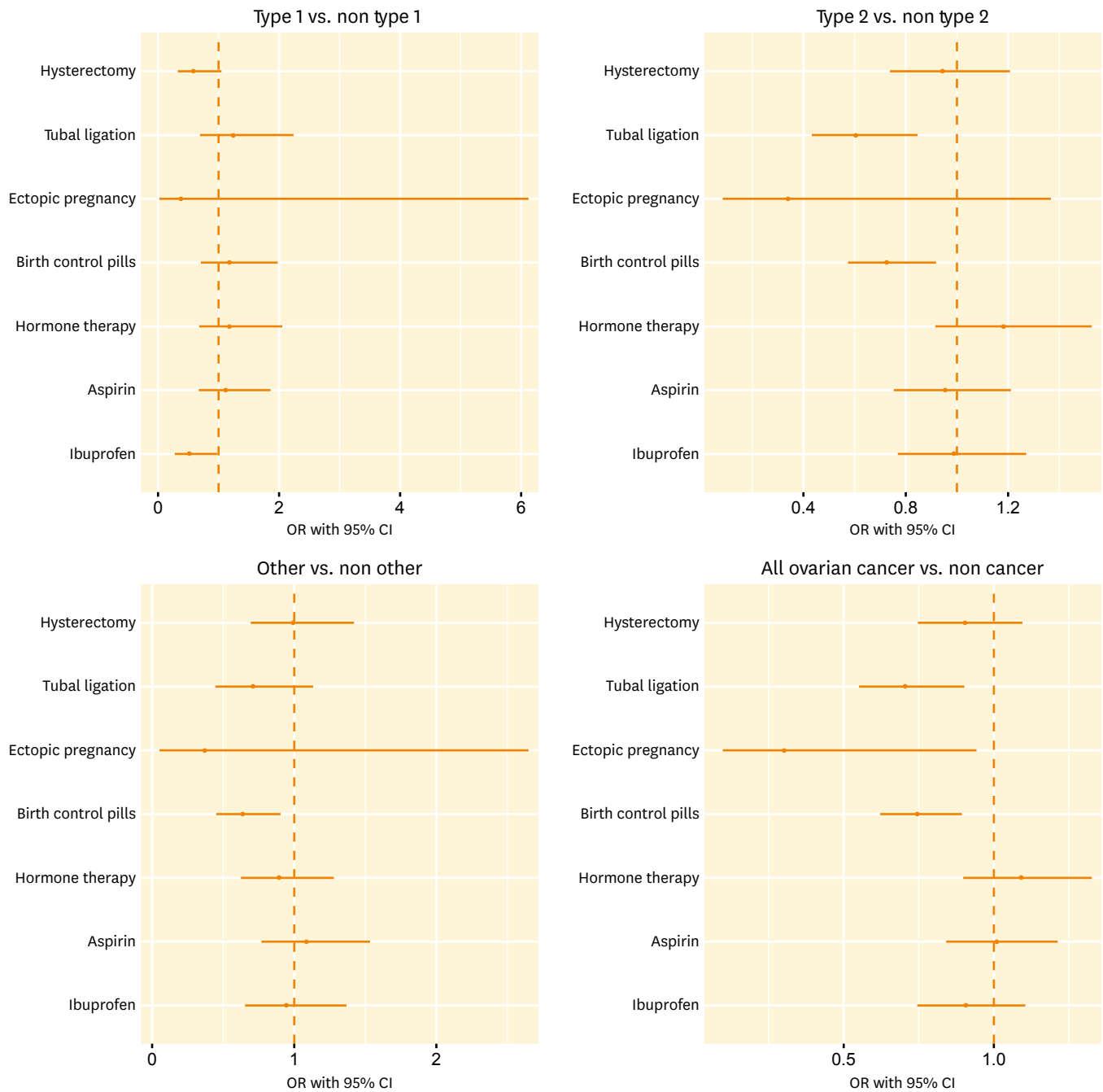
Fig. 1. Plots of odds ratio (OR) and 95% CI for type 1, type 2, other, and all ovarian cancer.

risk for any of the groups. For all patients with ovarian cancer, compared to patients without ovarian cancer, a separate analysis examined the risk for birth control pills when stratified by MHT use. Participants that used birth control pills and not MHT had a significantly lower risk of ovarian cancer (OR, 0.60; 95% CI, 0.43 to 0.82). However, for participants that reported both birth control pill and MHT use, the risk reduction was not statistically significant (OR, 0.83; 95% CI, 0.67 to 1.03). Use of MHT, therefore, appeared to negate the beneficial effect of birth control pills.

There were 1,567 patients that reported a history of ectopic pregnancy; 1,469 reported a history of one ectopic pregnancy, 98 reported two or more ectopic pregnancies. The ORs for type 1 and type 2 cancer with a history of ectopic pregnancy were not significant; however, for the combined group of all cancers, the reduction in risk was significant (OR, 0.30; 95% CI, 0.09 to 0.94). Tubal ligation (OR, 0.70; 95% CI, 0.55 to 0.90) and birth control pills (OR, 0.74; 95% CI, 0.62 to 0.89) also appeared to reduce the risk for all cancers.

DISCUSSION

Previous epidemiologic studies have identified multiple risk factors that affect the risk for ovarian cancer. Factors shown to attenuate risk include hysterectomy [14], tubal ligation [15], birth control pills [4], and NSAID use [6]. Conversely, menopausal hormone replacement therapy "MHT" has been associated with an increased risk of ovarian cancer [5]. The current study utilized data collected for the PLCO trial to differentiate the impact of these risk factors for type 1 versus type 2 ovarian cancer. In addition, the current study also examined the role of previous ectopic pregnancy on subsequent risk of ovarian cancer.

It is now recognized that the fimbriated end of the fallopian tube is the source for most, if not all, high grade serous cancers. A distinct precursor lesion, serous tubal intraepithelial carcinoma, has been described as a recognizable step in early carcinogenesis [16]. This has led some authors to advocate salpingectomy in all patients undergoing tubal sterilization [17]. Definitive evidence demonstrating that salpingectomy is associated with a decreased risk of ovarian cancer, however, has been lacking. The PLCO trial began in 1993, and enrolled women age 55 to 75 years old. Therefore women who reported a history of ectopic pregnancy were treated between the mid 1940's to mid 1980's. Standard treatment in this era was laparotomy and salpingectomy. The current study demonstrates an almost 70% reduction in the incidence of all ovarian cancers associated with the removal of at least one fallopian tube. In the absence of prospective trials examining the role of risk reducing salpingectomy, the current study provides support for performing salpingectomy in women undergoing hysterectomy or sterilization.

Previous reports have recognized that both tubal ligation, and birth control pills, decrease the risk of ovarian cancer [15,18]. Investigators propose that carcinogenic mutations in the fimbriated portion of the fallopian tube are facilitated by inflammatory cytokines, resulting from exposure to incessant ovulation and retrograde menstruation [19]. A pooled analysis of 13 case control studies by the Ovarian Cancer Association Consortium analyzed risk reduction of tubal ligation for various histologic subtypes [15]. A significant reduction was noted in the risk for serous, endometrioid, clear cell, and mucinous cancers. Also, a collaborative reanalysis of 45 epidemiologic studies on the role of oral contraceptives and the risk of ovarian cancer reported a significant reduction in serous and endometrioid cancers associated with birth control pills [18]. Although these analyses do not specifically address type 1 versus type 2 risk; the findings are consistent with observations of the current study.

There is accumulating evidence that anti-inflammatory drugs reduce the risk for various malignancies. Results of studies investigating the role of NSAIDs in ovarian cancer have shown mixed results; some studies indicate a protective effect, and some do not [20,21]. Trabert et al. [6] conducted a meta-analysis of pooled data from 12 population-based case

control studies, and found a significant reduction in ovarian cancer risk associated with aspirin use. The current study, in contrast, did not find any risk reduction associated with aspirin use. Ibuprofen use, however, was associated with a significant reduction in type 1 cancers. This apparent contradiction may be due to underlying confounding variables, or a lack of sufficient statistical power. Further investigation is necessary to delineate the role of NSAIDs in type 1 and type 2 ovarian cancer risk.

The recently published meta-analysis on MHT from the Collaborative Group on Epidemiological Studies of Ovarian Cancer demonstrated a significant increase in ovarian cancer risk associated with MHT [22]. Overall relative risk was 1.14 (range, 1.10 to 1.19); risk was not stratified by type 1 versus type 2. The current study found a modest, nonstatistically significant increase in risk for both type 1 and type 2 ovarian cancer. However, despite the nonsignificant increase in risk, MHT appeared to negate the beneficial risk reduction observed with oral contraceptive use. The major drawback to the current study is the low number of cases, particularly type 1 cases; this precludes analysis of multiple variables.

In conclusion, surgery, hormone use, and NSAID use appear to have different effects on the risk of type 1 and type 2 ovarian cancer. Ibuprofen reduces the risk for type 1 ovarian cancer; this implies that inflammation may be involved in the pathogenesis of type 1 cancer. Tubal ligation and birth control pills reduce the risk for type 2 ovarian cancer; this suggests that an intact tube and incessant ovulation are involved in the pathogenesis of type 2 cancer. These observations support the hypothesis that these cancers arise through different pathways and represent distinct clinical entities. The reduction in all ovarian cancer risk associated with ectopic pregnancy implies that the fallopian tube plays a key role in carcinogenesis for both type 1 and type 2 ovarian cancer.

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