Prevention Strategies for Gynecologic Cancers

by

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Abstract

This dissertation focused on prevention strategies for ovarian and cervical cancers. Primary prevention of ovarian cancer was explored in Aim 1 using data from the Ovarian Cancer Association Consortium (OCAC; 7,743 cases; 11,882 controls) with the goal of developing a risk stratification model for ovarian cancer. This model was the most comprehensive to date and included body mass index (BMI), height, age at menarche, parity, breastfeeding, incomplete pregnancy, age at last pregnancy, tubal ligation, age at menopause, combined oral contraceptive use, depot-medroxyprogesterone acetate use, menopausal hormone therapy use, first-degree family history of ovarian cancer, endometriosis, and a 36-variant polygenic risk score. We found that associations between ovarian cancer and family history of the disease and endometriosis were modified by menopausal status, but no pairwise interactions between the 15 risk factors themselves were identified. Hence, we developed an ovarian cancer 15-factor multiplicative risk stratification model separately for pre- and post-menopausal women (based on age). Our model stratifies women into finer risk profiles than prior models thereby allowing us to identify people who are candidates for ovarian cancer precision prevention strategies.

Tertiary prevention for ovarian cancer was examined in Aim 2 by studying the associations between lifestyle and reproductive factors and residual disease after ovarian cancer primary cytoreductive surgery (PCS). We included 2,169 OCAC participants with advanced stage high-grade serous ovarian cancer who underwent PCS. We found that parous compared to nulliparous women and menopausal estrogen users compared to never users were statistically

significantly less likely to have macroscopic residual disease after PCS after adjusting for relevant clinical factors (OR=0.65, 95% CI 0.45-0.93, p=0.018 and OR=0.69, 95% CI 0.48-1.00, p=0.048, respectively). Conversely, women who had ever breastfed compared to those who had not were more likely to have residual disease (adjusted OR=1.41, 95% CI 1.03-1.92, p=0.032). If these findings are replicated, this scope of work has tremendous potential to assist with ovarian cancer precision treatment. These factors could be included in treatment decision tools to help determine whether a patient should undergo PCS or have neoadjuvant chemotherapy followed by interval debulking surgery.

Lastly, cervical cancer secondary prevention was studied in Aim 3 where a cross-sectional survey on awareness of, experience with, and attitudes toward cervical cancer screening was carried out among urban (n=202) and rural women (n=196) in Southern Vietnam. Women in both areas reported similarly low awareness of *Human papillomavirus* (HPV; 37.6% in urban and 34.2% in rural areas had ever heard of it) and low cervical cancer screening (51.8% in urban; 49.1% in rural). Urban participants were statistically significantly more willing to try HPV self-sampling for cervical cancer screening than rural participants (56.2% in urban; 42.2% in rural; OR=2.02, 95% CI 1.26-3.23) adjusting for demographic and socioeconomic factors. Rural women were more likely to have the concern of self-sampling incorrectly (73.4% in urban; 82.5% in rural; adjusted OR=0.49, 95% CI 0.28-0.88) while urban women were more likely to fear HPV testing revealing cancer (59.9% in urban; 47.1% in rural; adjusted OR=1.78, 95% CI 1.11-2.86). Improving health literacy and healthcare access and developing rural-urban tailored health education programs are warranted to reduce the cervical cancer burden in Southern Vietnam.

This dissertation has tremendous translational potential to decrease the burden of gynecologic cancers by assisting with prevention, screening, and treatment for ovarian and cervical cancers.

Chapter 1. Introduction

1.1. Overview of the dissertation

This dissertation focused on three levels of prevention for gynecologic cancers.

- Aim 1 focused on primary prevention for ovarian cancer. Primary prevention is to prevent the disease from occurring. This aim involved the development of a risk stratification model to identify women for whom further prevention strategies should be considered because of their elevated risk of ovarian cancer.
- Aim 2 focused on tertiary prevention for ovarian cancer. Tertiary prevention is to manage the disease after a diagnosis in order to prevent complications. This aim was designed to identify factors associated with having macroscopic residual disease after ovarian cancer primary cytoreductive surgery (PCS), as this information is important in treatment selection. Patients with a low likelihood of achieving no macroscopic residual disease should consider neoadjuvant chemotherapy (NACT) followed by interval debulking surgery.
- Aim 3 focused on secondary prevention for cervical cancer. Secondary prevention is screening to detect disease early. This aim was comprised of a cross-sectional survey to assess knowledge of *Human papillomavirus* (HPV) and views of cervical cancer screening in rural and urban areas in Southern Vietnam.

The dissertation includes six chapters. Chapter 1 serves as the introduction for the dissertation and the three aims. Chapter 2 provides the backgrounds of ovarian cancer and cervical cancer as well as cervical cancer in Vietnam to describe the motivation for the projects. Chapters 3-5 present manuscripts for each of the three aims. Chapter 6 is the conclusion, which synthesizes the importance of the findings for each aim, highlights the impact of this dissertation on public health, and provides the directions for future research.

1.2. Aim 1: Developing a risk stratification tool for ovarian cancer

Ovarian cancer is the deadliest gynecologic cancer. It is estimated that there will be about 20,000 new cases and 13,000 deaths by ovarian cancer in the United States (US) in 2022, comprising 17% of new gynecologic cancer cases but ~40% of deaths among all gynecologic cancers[1]. The reason for such a high death rate is that at least half of the cases are diagnosed with distant stage disease when the five-year survival rate is very low (~30%). Conversely, less than 20% of cases are diagnosed at localized stage, when five-year survival is much higher (93%)[2]. The search for an early detection method has proved elusive, with the most recent trial showing no survival benefit for screen-detected cancers[3]. However, primary prevention to reduce the burden of ovarian cancer is feasible[4,5].

Many primary prevention strategies for ovarian cancer are available. Risk-reducing salpingo-oophorectomy (RRSO) is often recommended for individuals carrying pathogenic variants for ovarian cancer (e.g. in *BRCA1/2, RAD51C, RAD51D, BRIP1)*[6] as it reduces risk by 71-96% in this population[7-12]. Bilateral salpingectomy with ovarian retention may offer significant protection against ovarian cancer in the general population[5,13]. A recent study on about 26,000 women who underwent bilateral salpingectomy with ovarian retention found not a

single case of serous ovarian cancer and five or fewer epithelial ovarian cancer cases after a median of 3.2 years of follow-up, which were significantly fewer than the expected 5.27 serous cases and 8.68 epithelial ovarian cancer cases[5]. Bilateral salpingectomy has been recommended for women undergoing hysterectomy or requesting permanent irreversible contraception[14]. Tubal ligation[15-19] and hormonal contraceptive use[19-22] are also associated to a risk reduction although they are not officially recommended for ovarian cancer prevention.

There are many additional ovarian cancer risk and protective factors. A first-degree family history of ovarian cancer[19], common but low-penetrance genetic variants of ovarian cancer[19], a personal history of endometriosis[19], menopausal estrogen therapy use[23,24], and obesity[25-28] are associated with increased risk of the disease. Conversely, parity[16,19,29-32], incomplete pregnancy[31,33-37] and breastfeeding[38-40] are all associated with substantial reductions in ovarian cancer risk.

Lifetime risk of ovarian cancer in the general population is ~1.3%, but some individuals have a much higher than average risk of developing ovarian cancer, even among those who are not known to carry a pathogenic variant of ovarian cancer or do not have a first-degree family history of the disease[41]. Various risk stratification efforts have been undertaken to identify individuals at a substantially elevated risk[41-50]. The online CanRisk tool (https://canrisk.org/) is the only model that has been approved for use by healthcare professionals within the European Economic Area[51]; to our knowledge, no other models have been approved for clinical use in other areas of the world. The CanRisk model for ovarian cancer was developed based on five rare high-penetrance mutations, a polygenic risk score of 36 common genetic variants of ovarian cancer, and eight environmental risk factors (including body mass index, height, tubal ligation,

parity, combined oral contraceptive use duration, menopausal hormone therapy use, family history of ovarian cancer, and endometriosis); age is used to estimate age-specific risk and risk to age 80[52].

A limitation to the CanRisk model is that it assumes no interactions among the risk factors or between the risk factors and menopausal status or age. Additionally, the model does not account for several well-accepted risk/protective factors (breastfeeding[38-40], incomplete pregnancy[31,33-37], age at last pregnancy[53], and use of depot-medroxyprogesterone acetate[20]). Also, menopausal hormone therapy formulation is not considered, but may be important given recent data suggesting that unopposed estrogen therapy and combined estrogen-progestin therapy have different effects on ovarian cancer risk[23,54].

Aim 1: To develop a comprehensive risk stratification model for ovarian cancer incorporating 15 well-established risk factors for ovarian cancer. The specific sub-aims included:

- *Sub-aim 1.1:* To determine whether age and/or menopausal status modify the associations between 15 risk factors (14 environmental factors and a polygenic risk score) and ovarian cancer risk.
- *Sub-aim 1.2:* To evaluate whether pairwise interactions exist between these 15 risk factors.
- *Sub-aim 1.3:* To create a risk stratification model for ovarian cancer based on these 15 factors accounting for interactions.
- *Sub-aim 1.4:* To internally validate our 15-factor risk stratification model and to compare it with the results provided by a reduced model using the nine factors used in CanRisk to

determine the impact of adding additional risk factors on our risk stratification model for ovarian cancer.

1.3. Aim 2: Risk of residual disease after ovarian cancer primary cytoreductive surgery

A fundamental question in ovarian cancer care remains whether a patient's initial treatment should be PCS followed by chemotherapy or NACT followed by interval debulking surgery and then additional chemotherapy. Based on the results of randomized clinical trials comparing PCS and NACT[55-60], current guidelines state that women who are at high risk for perioperative complications or whose surgery is unlikely to result in residual disease <1cm (and preferably no macroscopic residual disease- R0) should receive NACT[61]. Currently, the initial assessment of the feasibility of PCS involves "computed tomography scan of the abdomen and pelvis and chest imaging"[61]. "Women who have evidence of disease that has spread to the lungs or mediastinum, unresectable parenchymal liver metastasis, bulky periportal lymph nodes, mesenteric retraction, or nonresectable extra abdominal lymph nodes are best treated with initial NACT"[61]. Magnetic resonance imaging, positron emission tomography and laparoscopy have been suggested as alternative methods to assess the likelihood of achieving residual disease <1cm (and preferably R0) after PCS, but there is insufficient validation evidence for being recommended[61].

Previously, the goal of PCS was to achieve optimal cytoreduction, which was defined as residual disease <1 cm (or sometimes defined as <2 cm)[61]. However, it is now clear that complete cytoreduction (i.e., no macroscopic residual disease or R0) leads to better survival than optimal cytoreduction to 1 cm[62]. A multivariate analysis showed improved progression-free survival and overall survival for patients with R0 compared to patients with any residual disease

($p<0.0001$)[62]. Similarly, a meta-analysis of more than 13,000 patients in 18 studies found that each 10% increase in the proportion of patients with R0 was associated with a significant 2.3 month increase in cohort median survival (95% CI 0.6-4.0, $p=0.011$)[63]. Therefore, it is now recommended that the goal of PCS is to achieve R0.

Extensive efforts have been made to examine the associations between several epidemiologic factors and residual disease at the time of PCS. Patients with older age at diagnosis have been found to be less likely to have complete cytoreduction[64-68] or optimal cytoreduction[69-74]. Patients with higher body mass index are less likely to have complete cytoreduction[67,75] or optimal cytoreduction[76]. It is possible that patients with older age and higher body mass index are less likely to withstand an extensive surgery. Post-menopausal women have been found to be less likely to have complete cytoreduction[77] or optimal cytoreduction[76,78] compared to pre-menopausal women, but that could be a proxy for older age because these analyses did not adjust for age. In contrast, it has been suggested that women with a personal history of endometriosis or those with a family history of cancer are more likely to have optimal cytoreduction[73]. Individuals with these two exposures may be diagnosed at a younger age and it is their age that accounts for their better outcomes.

Moreover, it was previously reported that use of menopausal hormone therapy prior to ovarian cancer diagnosis was strongly associated with achieving R0 ($p=0.009$)[79]. In addition, one previous study suggested that tobacco smokers are less likely to have optimal cytoreduction compared to non-smokers[76]. Estrogen at high concentrations has anti-inflammatory properties[80-82] whereas smoking is a pro-inflammatory factor; these findings may suggest that an anti-inflammatory milieu might be beneficial for resection. However, women using menopausal

hormone therapy may have better healthcare access compared to non-users and smokers are more likely to have comorbidities compared to non-smokers, thus explaining these associations.

Findings from previous studies on factors associated with residual disease after PCS are difficult to interpret because there was no adjustment for potential confounders and there was heterogeneity in inclusion eligibility criteria and outcome definitions. Some studies included all epithelial ovarian cancer patients, some restricted to invasive tumors only[71,76], and others restricted to advanced stage ovarian cancer patients only[70,71]. Some studies defined the outcome as complete cytoreduction (R0: no macroscopic residual disease) versus any macroscopic residual disease[64,65,67]. Others dichotomized the surgery outcome as optimal cytoreduction (residual disease ≤1 cm) versus suboptimal cytoreduction (residual disease >1 cm)[70,73]. There is evidence that factors associated with complete cytoreduction (R0) do not mirror the factors associated with optimal cytoreduction (residual disease <1 cm)[75].

Aim 2: To comprehensively evaluate epidemiologic factors associated with achieving R0 after ovarian cancer PCS, considering health profile, lifestyle, reproductive and exogenous hormonal factors.

1.4. Aim 3: HPV and cervical cancer awareness and screening approaches in Southern Vietnam

Vietnam is a middle-income country. There were more than 35 million people in Southern Vietnam in 2019, of which 50% were female and 56% lived in rural areas[83]. It is evident that rural people have lower socioeconomic status and poorer access to healthcare compared to those in urban areas[83].

Cervical cancer is the second most common and the deadliest gynecologic cancer in Vietnam, accounting for more than 4,000 new cases and about 2,200 deaths in 2020[84]. The incidence rate of cervical cancer in urban areas in Southern Vietnam was 1.5-4 times higher than that in the Northern urban areas based on the most recent data available during 2004-2008[85,86]. However, there is limited information on the awareness of, experience with and attitudes toward cervical cancer prevention among women living in Southern Vietnam. Further, to our knowledge, no study has been conducted in Southern rural areas in Vietnam.

Human Papillomavirus (HPV) vaccine is available in Vietnam. However, very few Vietnamese women are HPV vaccinated because it is not included in the national vaccination program and the price is not affordable[87]. Another reason for low vaccination rates is the lack of awareness: the most recent population survey in Southern urban areas in 2010-2011 found that 50-60% of women aged 18-65 had never heard of HPV or the HPV vaccine, and they did not know that HPV is the primary cause of cervical cancer[88]. No survey about the awareness of HPV or cervical cancer has been conducted among Southern rural women.

Secondary prevention for cervical cancer is not common either: only ~30% of at-risk Vietnamese women had ever had cervical cancer screening based on the most recent data available in 2015[89]. One potential reason is the lack of a national cervical cancer screening program, even though it has been identified as a public health priority[90]. To our knowledge, no study has been conducted to explore screening uptake and barriers among women in Southern Vietnam. HPV self-sampling for cervical cancer screening has a potential to improve screening in Southern Vietnam. This strategy has been shown to be effective to improve screening attendance[91-99] and to be highly acceptable in low- and middle-income countries[100-117], including

urban areas in Northern Vietnam[118]. There are no data available on the acceptability of HPV self-sampling in Southern Vietnam.

Aim 3: To perform a comprehensive evaluation of HPV and cervical cancer knowledge and attitudes in Southern Vietnam. The sub-aims included:

- *Sub-aim 3.1:* To conduct a cross-sectional survey to explore the awareness of, experiences with, and attitudes toward cervical cancer prevention among women in rural and urban areas in Southern Vietnam;
- *Sub-aim 3.2:* To evaluate the acceptability of HPV self-sampling for cervical cancer screening among women in rural and urban areas in Southern Vietnam;
- *Sub-aim 3.3:* To explore disparities in these above factors between rural and urban areas in Southern Vietnam.

Chapter 2. Background

2.1. Background of ovarian cancer

2.1.1. Ovarian cancer classification

Ovarian, tubal, or primary peritoneal cancers are a heterogenous group of malignancies[16,19,119,120], including three main types which are germ cell, stromal, and epithelial, based on the cells in which the tumor develops. About 90% of tumors are epithelial cancers which are typically more aggressive than non-epithelial cancers[121]. Epithelial tumors can be classified as borderline or invasive cancers. Borderline (or low-malignant potential) tumors are slower-growing with no evidence of stromal invasion and represent about 10-15% of epithelial ovarian cancers. Invasive (or malignant) tumors represent 85% of epithelial cancers[122,123]. This dissertation focuses on invasive epithelial ovarian, tubal and primary peritoneal cancers (hereafter referred to as ovarian cancer).

Ovarian cancers can be classified by stage and grade. The stage describes the spread of the cancer. There are two clinical systems used for staging ovarian cancer: **FIGO** (International Federation of Gynecology and Obstetrics) and **AJCC TNM** (American Joint Committee on Cancer: Tumor, Nodes, Metastasis). Additionally, the **SEER** (Surveillance, Epidemiology and End Results) system classifies spread as localized, regional or distant. The relationship among these systems is presented in Table 2-1.

Tumor grade describes the degree of differentiation from normal cells; lower grade tumors look more similar to normal cells. Low grade tumors tend to grow slowly, while high grade tumors are generally more aggressive. Ovarian cancer can also be classified by histotype. The five main histotypes of ovarian cancer include: high-grade serous (serous grade 2-4; endometrioid grade 3-4), low-grade serous (serous grade 1), endometrioid (endometrioid grade 1-2), mucinous, and clear cell cancers[124]. High-grade serous is the most common histotype (~70%), followed by endometrioid (~15%), clear cell (~10%), low-grade serous (~3%) and mucinous cancers (~2%)[125]. These histotypes have different proposed origins. High-grade serous cancer is believed to most commonly originate from fallopian tube fimbria or ovarian cortical inclusion cysts. Low-grade serous cancer is hypothesized to originate from large tubal-type cortical inclusion cysts. Endometrioid and clear cell cancers are thought to arise from endometriosis[126]. Mucinous ovarian cancer is thought to originate from primary colorectal or endocervical adenocarcinoma[127].

2.1.2. Ovarian cancer statistics

Ovarian cancer is the deadliest gynecologic cancer. It is estimated that there will be about 20,000 new cases and 13,000 deaths by ovarian cancer in the US in 2022, comprising 17% of new gynecologic cancer cases but ~40% of deaths among all gynecologic cancers[1].

In the US, high-grade serous cancer is most common among non-Hispanic White women and its incidence decreased during 2000-2018 regardless of race/ethnicity (Phung et al. – under review). Some possible explanations include: the decline of menopausal hormone therapy (MHT) use following the results of the Women's Health Initiative (WHI)[128] including estrogen therapy (ET) use which is a risk factor for high-grade serous histotype[23,24], and the increase in

opportunistic salpingectomy which is the removal of the fallopian tubes during abdominal surgery or in lieu of tubal ligation[14]. In contrast, clear cell cancer is more common among Asian/Pacific Islanders, and its incidence increased during 1992-2018 among all racial/ethnic groups, particularly among Asian/Pacific Islanders and Hispanic women. Possible explanations include the decline in combined oral contraceptive (COC) use and parity which are preventive factors for clear cell cancer and a shift in diagnosis from "carcinoma, not otherwise specified" to clear cell cancer among Asian/Pacific Islanders (Phung et al. – under review). The incidence of endometrioid cancer decreased among non-Hispanic White women but increased among Hispanic women during 1992-2018, which may be partially explained by racial/ethnic differences in the decline in parity and COC use which are preventive factors for endometrioid cancer (Phung et al. – under review).

In the US, ovarian cancer mortality declined 33% from 1976 (10.0 per 100,000) to 2015 (6.7 per 100,000)[121], possibly due to the advances in chemotherapy, particularly the use of paclitaxel (Taxol) as an anti-cancer drug in ovarian cancer treatment[129]. Five-year survival for ovarian cancer in 2011-2017 was 49%[2]. The reason for such a low survival rate is that at least half of the cases are diagnosed at distant stage when the five-year survival rate is very low (~30%). Conversely, less than 20% of the cases are diagnosed at localized stage, when five-year survival is much higher (93%)[2].

Survival rates also vary by histotype and race/ethnicity. At localized or regional stage, the survival rate is highest among endometrioid and low-grade serous cancers, followed by mucinous, clear cell, and lowest in high-grade serous cancers. At distant stage, the survival rate is highest among low-grade serous cancer, followed by endometrioid, high-grade serous, clear

cell, and mucinous cancers[124]. In the US, Asian/Pacific Islander women have highest five-year survival (57%), followed by Hispanic (52%), and non-Hispanic White women (47%)[121]. This is probably because clear cell cancer is more common among Asian/Pacific Islanders; clear cell is more likely to be diagnosed at early stage. Although non-Hispanic Black women have lowest incidence rate, they have highest mortality among all racial/ethnic groups (five-year survival at 35%)[121], possibly because they are less likely to receive optimal treatment and more likely to have comorbidities[130,131].

2.1.3. Risk factors for ovarian cancer

Genetic factors: Family history of ovarian cancer is associated with two to three times increased risk of the disease[16,19,132,133]. Genetic familial predisposition is associated with about 20% of all ovarian cancer cases[134,135]. Germline mutations in the *BRCA1* and *BRCA2* tumor suppressor genes are related to about 65-85% of hereditary cancer cases[6,135]. The risks of developing ovarian cancer by the age of 70 among *BRCA1* and *BRCA2* mutation carriers are 40% and 20%, respectively[136]. Other rare genes associated with familial ovarian cancer are Lynch syndrome, hereditary non-polyposis colon cancer caused by germline mutations in mismatch repair genes (*MLH1*, *MSH2* and *MHS6*), and other DNA repair genes (such as *BRIP1*, *RAD51C*, *RAD51D*, *PALB2*)[137,138]. Genome-wide association studies (GWAS) have identified 36 low-penetrance but common variants for ovarian cancer, which in total account for approximately 6.4% of the polygenic risk in the population[52].

Parity: Many studies have found that parity has a protective role against ovarian cancer[16,19,29-32]. Compared to nulliparous women, women with one birth have an approximate 24% decrease in

ovarian cancer risk and women with two or more births have an approximate 42% risk reduction[19].

Incomplete pregnancies: Several studies have reported a decreased risk of ovarian cancer among women with incomplete pregnancies (i.e., pregnancies that last less than six months)[31,33-37]. Ever having incomplete pregnancies is associated with a 16% risk reduction compared to those without any incomplete pregnancies (OR=0.84, 95% CI 0.79-0.89), and there is a trend of decreasing risk with increasing number of incomplete pregnancies[36].

Breastfeeding: Ever breastfeeding is associated with a 24-30% lower risk of ovarian cancer compared to never breastfeeding[38-40]. Breastfeeding duration of 1-3 months is associated with an 18% lower risk (OR=0.82, 95% CI, 0.76-0.88), and breastfeeding for 12+ months is associated with a 34% lower risk (OR=0.66, 95% CI 0.58-0.75), compared to never breastfeeding[40].

Endometriosis: Women with endometriosis have about 46% increased risk of ovarian cancer compared to those without a personal history of endometriosis (OR=1.46, 95% CI 1.31-1.63)[16,19,139-142]. Endometriosis is associated with an increased risk of low-grade serous, endometrioid and clear-cell ovarian cancers, but not associated with risk of mucinous or high-grade serous ovarian cancers[139].

Tubal ligation: Tubal ligation is associated with an approximate of 30% reduced risk of ovarian cancer[15-19].

COC use: COC use is associated with a decreased risk of ovarian cancer, and there is a trend of decreasing risk with increasing duration of use[16,19,21,29,143]. COC use for five years is associated

with a 50% reduced risk of ovarian cancer, while using it for 10+ years is associated with a 70% reduced risk compared to never use[19].

MHT use: Lee et al. found use of ET to be associated with an increased risk of serous and endometrioid ovarian cancers, but not associated with risk of mucinous and clear cell cancers[23]. Although the literature on estrogen-plus-progestin combined therapy (EPT) use is inconsistent[24,54,144,145], a recent paper found that EPT use was not associated with an increased risk of ovarian cancer[54].

Hysterectomy: Some studies found that hysterectomy was associated with decreased risk of ovarian cancer[146-151], some did not find a significant association[152-156], while one study even found an increased risk[157]. The inconsistent results could be explained by the interactions between hysterectomy and MHT use and endometriosis. Recent studies have focused on these interactions. A population-based study with more than 800,000 Australian women found that hysterectomy was associated with substantially decreased ovarian cancer risk among women with endometriosis (HR=0.17, 95% CI 0.12-0.24), although it was not associated with ovarian cancer risk in the overall population (HR=0.98, 95% CI 0.85-1.11)[158]. Similarly, a pooled analysis of more than 5,000 ovarian cancer cases and 7,500 controls found that among women without a history of endometriosis, having hysterectomy was not associated with risk of ovarian cancer, after adjusting for the duration of ET and EPT use[159]. On the other hand, hysterectomy was associated with reduced risk of ovarian cancer among women with a history of endometriosis, possibly because some participants had their ovaries and/or fallopian tubes removed during their hysterectomy but did not know it[159].

Body mass index (BMI): BMI is associated with an increased risk of endometrioid, mucinous, and low-grade serous, but not high-grade serous ovarian cancers[25-28]. For every 5 kg/m^2 increase in BMI, the risk increases by 17% (95% CI 1.11-1.23) for endometrioid, 19% for mucinous (95% CI 1.06-1.32) and 13% for low-grade serous cancers (95% CI 1.03-1.25)[28].

Other factors: Use of the injectable contraceptive depot-medroxyprogesterone acetate (DMPA)[20], use of progestin-releasing intrauterine devices (IUDs)[22,160], older age at first childbirth[161,162] and older age at last birth[53] are associated with a reduced risk of ovarian cancer; use of talcum powder in the genital area is associated with an increased risk[163].

Interactions between risk factors: Literature on the interactions between risk factors for ovarian cancer is inconsistent. Some studies found that higher BMI was associated with an increased risk of ovarian cancer among nulliparous women and had no association with risk among parous women[164,165], whereas other studies did not find any interaction between BMI and parity[166,167]. Furthermore, the Collaborative Group on Epidemiological Studies of Ovarian Cancer found a BMI-MHT use interaction[166], while another study found no interaction[28]. Similarly, one study suggested that COC use was associated with a greater decreased risk among individuals with lower BMI compared to those with a higher BMI (i.e., BMI<24kg/m^2 vs BMI≥24kg/m^2)[167], while other studies found no interaction between BMI and COC use[166,168]. There are some limitations to previous studies, including small sample size of cases[164,165,167,168] and not stratifying by menopausal status[165-167]. It is suggested that the associations between some factors and ovarian cancer risk are different among pre- and post-menopausal individuals[133,169].

2.1.4. Mechanisms for ovarian cancer risk factors

Hormonal factors: It used to be widely believed that the damage and repair of ovarian surface epithelium after ovulation caused ovarian cancer[170,171] as evident by the positive association between the lifetime number of ovulatory cycles and ovarian cancer risk[172,173]; this was known as the "incessant ovulation" hypothesis[171]. However, the "incessant ovulation" hypothesis has largely fallen out of favor given that the majority of ovarian cancer cases are now thought to originate from fallopian tube fimbriae rather than the ovarian surface epithelium[126]. A modified explanation for this "incessant ovulation" hypothesis is that ovarian cancer develops because of the exposure of both the fallopian tube fimbriae and ovarian surface epithelium to a pro-inflammatory environment caused by follicular fluid and reactive oxygen species after ovulation[174,175]. However, the modified "incessant ovulation" hypothesis is insufficient in explaining ovarian cancer etiology: one birth or one year of COC use suppresses ovulation for a year, but the risk reduction in ovarian cancer associated with these preventive factors (~24% for the first birth and ~14% for one year of COC use[19]) is much greater than the expected risk reduction associated with one year of no ovulation (~5%)[170].

It is now more commonly believed that hormones have direct effects on ovarian cancer development as evident by a rapid increasing rate in age-specific risk of ovarian cancer during pre-menopausal years compared to a slower rate during post-menopausal years[44,176-178]. Estrogen may stimulate the transformation or proliferation of premalignant cells of endometriosis and fallopian tube fimbriae, increasing the risk of malignancy transformation[23]. It is evident that the proliferation rate of fallopian tube fimbriae is higher in the follicular phase of the menstrual cycle when estrogen is high, whereas the proliferation rate is lower during the luteal phase when

progesterone is relatively high[179,180]. This suggests a protective role of progesterone, possibly because progesterone clears genetically abnormal cells in the fallopian tube fimbriae[181]. The direct effects of hormones can explain the protective roles against ovarian cancer of the factors that are associated with an increased level of progesterone, such as parity[16,19,29-32], incomplete pregnancy[31,33-37], use of COCs[16,19,21,29,143], DMPA[20] or progestin-releasing IUDs[22,160]. Additionally, the direct effects of hormones can explain an increased risk of ovarian cancer among ET users[23], but no increased risk among EPT users[54].

Breastfeeding is a hormonal factor associated with reduced risk of ovarian cancer, however the mechanism underlying this inverse association is unknown. Estrogen levels are lower among breastfeeding mothers compared to non-breastfeeding mothers at least until seven weeks after delivery[182]. It is also evident that breastfeeding mothers have fewer ovulatory cycles, which are associated with a lower risk of ovarian cancer, compared to non-breastfeeding mothers; breastfeeding mothers have later resumption of ovulation and their ovulation frequency does not return to normal until stopping breastfeeding[183]. Another possible mechanism is that breastfeeding is associated with a lower inflammation environment, which is protective against ovarian cancer[40,184].

Endometriosis: The mechanism linking endometriosis with increased risk of ovarian cancer is unclear. Endometrioid and clear cell cancers are thought to originate from endometriosis[126]. However, they likely arise from different stages of endometriosis cells; while almost all endometrioid cancers express estrogen receptor protein, clear cell carcinomas lack expression of estrogen and progesterone receptors[185].

It is also possible that endometriosis does not cause ovarian cancer but shares the same pathogenesis as ovarian cancer through inflammatory and hormonal mechanisms. Systemic estrogen is associated with the growth and invasion of endometriosis. Endometriotic foci promote a local estrogen environment by converting systemic androstenedione to estradiol, which increases prostaglandin E_2 and creates a pro-inflammation environment that stimulates the development of endometriosis[186]. Conversely, progesterone is associated with a reduced risk of endometriosis by blocking the positive loop of estrogen above and also by promoting endometrial cell apoptosis[186]. Estrogen and progesterone play important roles in ovarian cancer etiology as described above.

BMI: The positive association between BMI and ovarian cancer risk can be explained through hormonal mechanisms. It is evident that the association between BMI and ovarian cancer risk is stronger among pre-menopausal women compared to post-menopausal women[28]. Endogenous estrogen among post-menopausal obese women increases due to the synthesis of estrogen in body fat[187]. On the other hand, estrogen synthesized by body fat does not significantly affect the total estrogen level among pre-menopausal obese women because the ovaries produce more estrogen. However, obesity among pre-menopausal women can cause anovulation, which is associated with a lower progesterone level[188], increasing ovarian cancer risk.

Tubal ligation: Two primary mechanisms have been hypothesized to explain the association between tubal ligation and a reduced risk of ovarian cancer. First, tubal ligation may reduce the exposure of the ovaries to hormones by preventing "the retrograde flow of carcinogenic or inflammatory agents from the vagina into the peritoneal cavity"[15]. Second, the procedure may obstruct endometriotic cells from seeding the ovaries[15]. Tubal ligation is associated with a

greater risk reduction for endometrioid and clear cell cancers than serous cancers[15], and as mentioned above, endometriosis is believed to be the origin cell of endometrioid and clear cell cancers[126].

2.1.5. Risk stratification models for ovarian cancer

At least ten risk stratification tools based on risk factors for ovarian cancer have been developed in nine studies to identify women at higher-than-average risk of ovarian cancer (Table 2-2). The most commonly used predictor in these models was COC use (n=10), followed by parity (n=9), tubal ligation (n=7), a family history of ovarian cancer (n=7), endometriosis (n=5), and MHT use (n=5). One model incorporated *BRCA1* and *BRCA2* mutation status, and three models included low-penetrance but common genetic variants of ovarian cancer. The relative risk for each predictor was calculated using data from case-control studies (n=5), cohort studies (n=3), or was obtained from literature (n=2). Absolute risk of ovarian cancer for each woman was calculated based on public data (such as SEER) (n=6), or was calculated directly from the cohorts (n=2), or was not calculated (n=2). Models were validated internally (n=5), externally (n=3), or not validated (n=2). Area under the receiving operating curve (AUC) ranged from 0.59-0.66 for internal validation, and 0.55-0.59 for external validation.

Pearce et al. quantified the population distribution of ovarian cancer risk among women in the US based on combinations of five lifestyle factors and 11 common but low-penetrance inherited genetic variants of ovarian cancer[41]. Although average lifetime risk is just 1.3%, the authors found risks as high as 8% among women without a family history of the disease, but who had an unfavorable combination of lifestyle factors and common genetic variants. Clyde and colleagues used data from 11 US-based case-control studies from the Ovarian Cancer

Association Consortium (OCAC) to develop two models, one with 14 epidemiologic factors only, and one with additional 17 common and low-penetrance variants[48]. They found that adding the genetic variants in the model did not increase the discriminatory ability: the AUC was 0.65 for the model with 14 epidemiologic factors only, and 0.66 for the model with both the 14 epidemiologic factors and the additional 17 common single nucleotide polymorphisms (SNPs)[48]. They also found that AUC was higher for women aged <50 compared to women aged 50+. When including only 14 epidemiologic factors in the models, the AUC was 0.71 and 0.62 for the models for women aged <50 and 50+, respectively. When adding 17 common genetic variants into the models, the AUC was 0.71 and 0.64, respectively[48]. These two studies assumed that there were no interactions between the risk factors.

The online CanRisk tool (https://www.canrisk.org/) is the only model that has been approved for clinical use within the European Economic Area[51]. The model is based on eight epidemiologic factors (BMI, height, tubal ligation, parity, COC use duration, MHT use ever/never, family history of ovarian cancer, and endometriosis), a polygenic risk score of 36 common genetic variants associated with ovarian cancer, and five pathogenic variants (i.e., *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, and *BRIP1*)[52]. This model misses some well-known risk factors, such as breastfeeding, incomplete pregnancy, DMPA use and MHT type. Another limitation of this model is that it assumes no interactions among the risk factors or between the risk factors and menopausal status and age.

2.1.6. Ovarian cancer primary prevention

There are some surgical and medical primary prevention strategies for ovarian cancer.

Risk-reducing salpingo-oophorectomy (RRSO) is the surgical removal of the fallopian tubes and ovaries. It is evident that RRSO can reduce ovarian cancer risk by 80-90% among high risk women[7-9] and by ~95% among average or low risk women[7,10,11]. However, there are some significant consequences of RRSO including early menopause, osteoporosis, cardiovascular disease and increased mortality[189]. Therefore, RRSO is recommended for women at high genetic risk only but not the general population[190].

Bilateral salpingectomy with ovarian retention (BSOR) is the removal of the fallopian tubes but leaving the ovaries intact. BSOR offers significant protection against ovarian cancer in the general population. A recent study on about 26,000 women who underwent bilateral salpingectomy with ovarian retention found not a single case of serous ovarian cancer and 5 or fewer epithelial ovarian cancer cases after a median of 3.2 years of follow-up. The number of observed cases was much smaller than the expected 5.27 serous cases and 8.68 epithelial ovarian cancer cases[5]. Women undergoing hysterectomy or requesting permanent irreversible contraception should be offered BSOR[14].

Tubal ligation has been historically the most widely used contraceptive method; data from the 2017-2019 National Survey of Family Growth showed that ~18% of US women aged 15-49 currently used tubal ligation (or female sterilization), followed by COCs (~14%)[191]. Tubal ligation can reduce the risk for ovarian cancer in both high-risk and general populations[18].

Endometriosis debulking surgery: Since endometriosis is a risk factor for ovarian cancer[16,19,139-142], treatment for endometriosis has a potential to reduce risk of the disease. A matched case-control study in Sweden found that among the surgical treatment options for endometriosis, one-

side oophorectomy and complete extirpation of the endometriotic tissue were significantly associated with an 80% and a 70% reduced risk of ovarian cancer, respectively[192].

COC use is an alternative to surgical interventions for the prevention of ovarian cancer for both the general population (as described above) and high-risk populations[193]. A meta-analysis of six studies in *BRCA1* and/or *BRCA2* mutation carriers found a significant inverse association between COC use and risk of ovarian cancer (OR=0.58, 95% CI 0.46-0.73)[193]. However, COC use is not officially recommended as a primary prevention strategy for ovarian cancer.

Use of progestin-only contraceptives: An analysis of about 8,000 ovarian cancer cases and 12,000 control women found that ever use of DMPA, an injectable progestin-only contraceptive, was associated with a 35% decreased risk (OR= 0.65, 95% CI 0.50-0.85)[20]. A meta-analysis of nine studies found that ever use of IUDs was associated with 23% decreased risk (OR=0.67, 95% CI 0.60-0.74); and use of progestin-releasing IUDs was associated with 42% decreased risk (OR= 0.58, 95% CI 0.47-0.71)[22]. These progestin-only contraceptives may be considered as prevention strategies for ovarian cancer.

2.1.7. Ovarian cancer screening

No screening method for ovarian cancer has been recommended. Trials of screening methods based on annual transvaginal ultrasound (TVU) and serum CA125 testing have not been shown to be effective. The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) randomized more than 78,000 women aged 55-74 years into the intervention arm (annual screening with CA125 and TVU) or control arm (usual care) and found that mortality was not significantly different among the two arms (RR=1.18, 95% CI 0.82-1.71)[194]. Similarly, the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) randomized

more than 200,000 postmenopausal women aged 50-74 years into three groups: annual screening with serum CA125 testing and TVU; annual screening with TVU alone; and no screening. They found no benefit in survival: the mortality reduction over 14 years was not significant (15%, 95% CI -3 to 30, p=0.10 with both CA125 and TVU, and 11%, 95% CI -7 to 27, p=0.21 with TVU alone, compared to no screening arm)[195]. A Japanese study in which more than 80,000 postmenopausal women were randomized into the intervention arm (annual screening with serum CA125 test and TVU) and control arm found that the proportion of stage I ovarian cancers in the two arms was not statistically significantly different[196].

2.1.8. Ovarian cancer treatment and risk of residual disease

The two standards of care for ovarian cancer are (1) primary cytoreductive surgery (PCS) followed by chemotherapy, and (2) neoadjuvant chemotherapy (NACT) followed by interval debulking surgery and then additional chemotherapy. A fundamental question in ovarian cancer care remains whether a patient's initial treatment should be PCS followed by chemotherapy, or instead NACT followed by interval debulking surgery and then additional chemotherapy. Based on the results of randomized clinical trials comparing PCS and NACT[55-60], current guidelines state that women who are at high risk for perioperative complications or whose surgery is unlikely to result in residual disease <1cm (and preferably no macroscopic residual disease- R0) should receive NACT[61]. Currently, the initial assessment of the feasibility of PCS involves "computed tomography (CT) scan of the abdomen and pelvis and chest imaging"[61]. "Women who have evidence of disease that has spread to the lungs or mediastinum, unresectable parenchymal liver metastasis, bulky periportal lymph nodes, mesenteric retraction, or nonresectable extra abdominal lymph nodes are best treated with initial NACT"[61]. Magnetic resonance imaging (MRI), positron emission tomography (PET) and laparoscopy have been

suggested as alternative methods to assess the likelihood of achieving residual disease <1cm (and preferably R0) after PCS, but there is insufficient validation evidence for being recommended[61].

Previously, the goal of PCS was to achieve optimal cytoreduction, which is defined as residual disease <1 cm (or sometimes defined as <2 cm)[61]. However, it is now clear that complete cytoreduction (i.e., no macroscopic residual disease or R0) leads to better survival than optimal cytoreduction[62]. A multivariate analysis showed improved progression-free survival (PFS) and overall survival (OS) for patients with R0 compared to patients with any residual disease ($p<0.0001$)[62]. Similarly, a meta-analysis of more than 13,000 patients in 18 studies found that each 10% increase in the proportion of patients with R0 was associated with a significant 2.3 month increase in cohort median survival (95% CI 0.6-4.0, $p=0.011$)[63]. Therefore, it is recommended that the goal of PCS is to achieve R0.

Studies have examined the associations between several factors and having residual disease after PCS. The factors can be classified as epidemiologic[64-78,197-199], clinical factors[64,65,67-72,74-76,198-210], serum biomarkers[64-67,69-76,198,199,201-204,206,210-219], protein expression [198,200,208,220-232], gene expression[229,233-246], CT [64,66,67,69,72,75,202,204,205,209,212,214,215,247-254], PET/CT[67,201,255], MRI[254], and laparoscopy[252,253,256,257].

Previous studies on factors associated with residual disease after PCS were not consistent in the definitions of the outcome. Some studies defined the outcome as complete cytoreduction (R0: no macroscopic residual disease) versus any macroscopic residual disease[233,235]. Some dichotomized the outcome as optimal cytoreduction (residual disease ≤1 cm) versus suboptimal cytoreduction (residual disease >1 cm)[70,73,201]. Other studies chose 2 cm as the cut point for optimal and suboptimal cytoreduction[200,221,226,240,243,249,254].

Epidemiologic factors: Most studies have found that patients with older age at diagnosis are less likely to have complete cytoreduction[64-68] or optimal cytoreduction after PCS[69-74]. Patients with higher BMI are less likely to have complete cytroduction[67,75] or optimal cytoreduction after PCS[76]. It is possible that older age patients as well as those with higher BMI are less likely to withstand an extensive surgery. Post-menopausal women have been found to be less likely to have complete cytoreduction[77] or optimal cytoreduction[76,78] compared to pre-menopausal women, but that could be a proxy for older ages because these analyses did not adjust for age. In contrast, a study that included both early and advanced stage ovarian cancer patients (N=172) found that women with a personal history of endometriosis or those with a family history of cancer are more likely to have optimal cytoreduction[73], but that could be because those people might be younger or more likely to visit physicians and be diagnosed at early stages (i.e., FIGO stages I and II rather than stages III and IV).

Furthermore, MHT use prior to ovarian cancer diagnosis was strongly associated with having complete cytoreduction in one study ($p=0.009$)[79]. In addition, it is suggested that tobacco smokers are less likely to have optimal cytoreduction compared to non-smokers[76]. Estrogen at high concentrations has anti-inflammatory properties[80-82] whereas smoking is a pro-inflammatory factor; these findings may suggest that an anti-inflammatory milieu is beneficial for resection. It is also possible that MHT users have better healthcare access, which is associated with better surgical outcomes, compared to non-users, and that smokers are more likely to have comorbidities and less likely to withstand an extensive surgery compared to non-smokers.

Clinical factors: Most studies have found that patients with advanced stage[64,65,68-71,74,76,200-202], poorer performance status[64,68,69,72,75,201,203-207], and higher grade[70,74,76,208] are less likely to have

complete cytoreduction or optimal cytoreduction after PCS, possibly because they are less likely to withstand extensive surgeries. Larger tumor sizes[68,76] and greater ascites[65,67,70,71,74,76,199,200,203,205,207-210] are also associated with a lower likelihood of having complete cytoreduction after PCS, possibly because these features make it more difficult to resect the tumors[258,259].

Serum biomarkers: Increased serum CA125[64-67,69-74,76,198,199,201-204,210-217] and human epididymis protein 4 (HE4) levels[71,198,203,213] are associated with a lower likelihood of having complete cytoreduction or optimal cytoreduction after PCS, probably because the elevated levels of these biomarkers are proxies of a larger tumor size, which makes the surgery more difficult[198].

Protein expression: A lower likelihood of having complete cytoreduction or optimal cytoreduction after PCS is also associated with an increased expression of proteins that are related to a higher grade of ovarian cancer (i.e., Maspin[222], COX-2[223], EphA2[224], Twist[226], TNFAIP8[230]), with a higher stage (i.e., COX-2[223], Cyclin E[225], Twist[226]), larger volume of ascites (i.e., COX-2[223], Twist[226]), a larger tumor size (i.e., Twist[226]), or metastasis (i.e., TNFAIP8[230]).

Gene expression: Complete cytoreduction or optimal cytoreduction after PCS is found to be negatively associated with the expression of some genes that are related to more advanced stage of ovarian cancer (i.e., *NUAK1*[233,234]) or genes with a pro-inflammatory property (i.e., *TNFAIP6*[236]). Berchuck et al. used microarray to screen more than 22,000 genes in 44 patients to obtain a list of the top 120 genes that were negatively associated with optimal cytoreduction[245]. A larger study conducted by Bonome et al. in 185 patients found that only 21 of these above ~22,000 genes were differentially expressed between patients with optimal cytoreduction and those with suboptimal cytoreduction at the 0.001 significance level, which is less than what

would be expected by chance alone[246]. They concluded that expression profiling could not distinguish between tumors with optimal cytoreduction and tumors with suboptimal cytoreduction[246].

CT scan, PET/CT, MRI and laparoscopy: The imaging factors found to be inversely associated with complete cytoreduction or optimal cytoreduction after PCS include the presence of large-volume ascites, bowel involvement, omental cake, diffuse peritoneal thickening, pleural effusion, lymphadenopathy, and diaphragm, liver, and splenic involvement.

Limitations of previous studies: Most of the studies examining factors associated with having residual disease after PCS carried out univariate analyses instead of adjusting for potential confounders. Moreover, the inclusion criteria were different between studies. Some included all epithelial ovarian cancer patients, some restricted to invasive tumors only[71,213], whereas others restricted to serous ovarian cancer patients[223,235] or advanced ovarian cancer patients only[70,201,209].

Additionally, as mentioned above, previous studies on factors associated with having residual disease after PCS were not consistent in the definitions of the outcome, including complete cytoreduction to R0 versus any macroscopic residual disease[233,235], and optimal cytoreduction versus suboptimal cytoreduction[70,73,201]. In a study of 279 advanced stage epithelial ovarian cancer patients, Janco et al. found that the factors that were significantly associated with having complete cytoreduction (R0) after PCS did not mirror those associated with having optimal cytoreduction (<1 cm)[75]. While age was the only clinical factor independently associated with achieving R0, performance status was the only one independently associated with having optimal cytoreduction[75]. In addition, previous studies on risk factors for residual disease after

PCS defined exposures differently. For example, some studies used log of serum CA125 levels, some treated it as a continuous variable, while others dichotomized it with different cut-points, such as 100 [67], 313.60 [198], 420 [199], 500 [69], 600 [64], 1467 IU/L [70].

2.1.9. Summary

Invasive epithelial ovarian cancer is the deadliest gynecologic cancer with more than half of cases diagnosed at a distant stage which is associated with very low survival. Screening for ovarian cancer has proved elusive, with the most recent clinical trial showing no survival benefit in the screening arm. It is important to focus on primary prevention for ovarian cancer, given that primary prevention strategies are available. There are several well-established risk factors for ovarian cancer, but only a number of them have been included in risk stratification models. These previous risk stratification models did not consider pairwise interactions between the risk factors as well as the interactions between the risk factors and age or menopausal status. Therefore, there is a need of a risk stratification model that incorporates well-established factors and considers pairwise interactions as well as interactions between risk factors and age and menopausal status.

Current guidelines state that ovarian cancer patients who are at high risk for perioperative complications or whose PCS is unlikely to result in no macroscopic residual disease should receive NACT followed by interval debulking surgery. Many studies have been conducted to identify factors associated with having residual disease after PCS, but their findings are difficult to interpret due to a failure of control for confounding as well as the heterogeneity in inclusion criteria and definitions of exposures and outcomes. Thus, a comprehensive analysis to identify factors associated with having residual disease after ovarian cancer PCS is needed.

2.2. Background of cervical cancer

2.2.1. Human Papillomavirus and the natural history of cervical cancer

Human Papillomavirus (HPV) is a small double-stranded DNA virus that infects human squamous epithelia[260]. There are about 130 HPV types identified, which can be separated into high- or low-risk oncogenic potential[260]. Low-risk types include HPV 6, 11, 40, 42, 43, 44, 54, 61, 70, 72 and 81. High-risk types include HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82[261]. Cancer sites that are attributed to HPV include: cervix (percentage attributable to HPV: 91-100%), anus (88-91%), vagina (40-78%), oropharynx (12-70%), vulva (24.9-69%), and penis (40-63%)[260,262,263].

It is well established that HPV is the primary cause of cervical cancer. A pooled analysis of about 2,500 women with invasive cervical cancer and 2,500 control women from 11 case-control studies found that women with HPV infections had 90 times higher risk of developing cervical cancer compared to those without an HPV infection (OR=90.0, 95% CI 71.3-113.5)[261,264]. The International Agency for Research on Cancer (IARC) found that of about 1,000 women with histologically verified invasive cervical cancer, 99.7% were HPV positive[265,266]. The eight most common HPV types detected in cervical cancer include HPV 16, 18, 45, 31, 33, 52, 58, and 35, which are responsible for about 90% of all cervical cancer cases worldwide[267]. HPV 16 and HPV 18 are the most important high-risk types, found in 50-70% and 7-20% of cases, respectively[268,269].

About 70% of HPV infections can be cleared by the body itself in one year and 90% in two years[270]. An effective immune response is needed for clearance. A failure of the immune response could lead to a persistent infection with high-risk HPV, which in turns increases the risk

of a cervical intraepithelial neoplasia (CIN)[260,271,272]. CIN1 is a low-grade squamous intraepithelial lesion (LSIL). Without treatment, about 70–80% of CIN1 lesions can be cleared by the body itself[273,274]. CIN2 and CIN3 are high-grade squamous intraepithelial lesion (HSIL). The annual regression rate for CIN2 lesions is 15%-23% and can be up to 55% by 4–6 years; while only 2% of CIN2 lesions develop to CIN3 during the same time[274,275]. Within 12 months, about 0.2-4% CIN3 lesions can progress to cervical cancer[274,276]. If not treated, about 30% of CIN3 will progress to invasive cancer within 30 years. In contrast, if treated, only about 1% of CIN3 will progress to invasive cancer[260,274,276,277]. Since the pre-cancer stage for cervical cancer lasts for many years before becoming invasive cancer, there are abundant opportunities for early detection[278].

2.2.2. Cervical cancer statistics

Cervical cancer is the most common gynecologic cancer among women worldwide, with more than 600,000 new cases and 340,000 deaths in 2020[84]. More than 80% of all cervical cancer cases and deaths occurred in developing countries (or countries with Human Development Index <0.8)[279]. The incidence rate in the richest countries (Human Development Index ≥0.8) was three times lower than that in the poorest countries (Human Development Index <0.55) (age-standardized incidence rates at 9.6 and 26.7 per 100,000 women, respectively), and the mortality rate was seven times lower (3.0 and 20.0 per 100,000 women, respectively)[279]. A possible explanation for the disparity is the lower screening level in developing countries.

The most common histotype of cervical cancer is squamous cell cancer which originates in the transformation zone of the ectocervix and is the site of 80-90% of cervical cancer cases. The second most common histotype is adenocarcinoma for which the cell of origin is the

grandular columnar layer of the endocervix and comprises 10-20% of cervical cancers[278]. It is evident that the incidence of squamous cell cancer has been decreasing while incidence for adenocarcinoma has been increasing since the 1970s[280]. The reason for this trend is unclear. A possible explanation is that screening methods are less effective to detect adenocarcinoma as squamous cell cancer. Squamous cell cancer mainly originates from the ectocervix while adenocarcinoma mainly originates from the endocervical canal, which is easily to be missed by screening by Papanicolaou (Pap) smear. Survival for adenocarcinoma is lower than squamous cell cervical cancer[281]. Five-year survival rates for cervical cancer diagnosed at a distant stage is very low (<20%) compared to that at a localized stage (>90%)[282]. Therefore, prevention and screening for cervical cancer is important to control the disease burden and minimize mortality.

2.2.3. Risk factors for cervical cancer

As HPV is the cause of cervical cancer, risk factors for cervical cancer align with risk factors for HPV infection.

Age: The incidence rate of cervical cancer starts rising after age 25. The rate peaks around the age of 40 years in the richest countries, but continues to rise up to ages 55–69 years in poorest countries[279]. The difference in the trends is possibly due to the better screening and prevention in developed countries. The age trend in cervical cancer incidence reflects the trends of HPV infection and the latency period between an HPV infection and cervical cancer development. An analysis of about 2,000 women aged 14-59 in the National Health and Nutrition Examination Survey (NHANES) 2003-2004 found a significant increasing trend for HPV prevalence with each additional year of age from 14 to 24 ($p<0.001$), followed by a gradual decline from the age of 25 through 59 ($p=0.06$)[283].

Sexual behaviors and reproductive factors: Women with a greater number of sex partners[284] or those whose partners have a greater number of sex partners[285,286] are more likely to have a higher risk of cervical cancer, as well as a higher risk of HPV infection[287-300]. Young age at first birth and having a greater number of pregnancies and births are reported to be associated with an increased risk of cervical cancer[278,301,302]. A potential explanation is that the transformation zone on the ectocervix during puberty and pregnancy is large, making women more susceptible to HPV infection during these periods[278]. Additionally, women who have sex at younger ages have a longer duration of exposure to HPV and a higher risk of exposure to different types of HPV, which increases their risk of cervical cancer.

Lifestyle factors: Several studies found that both active and passive smoking is associated with a statistically significant increase in cervical cancer risk[264,303], because smoking may affect how effective the immune response to HPV infection, thus lowering the possibility of HPV clearance[264]. A meta-analysis found that women who had used COCs for ten years or more had twice the risk of invasive cervical cancer compared to never users, even among the studies that adjusted for number of sexual partners[304]. The mechanism is unclear, but there is experimental evidence that estrogen exposure may influence the progression from the pre-cancer stage to a malignant stage among HPV-infected women[264]. It is possible that COCs change the cervical mucus and immune system, making women more susceptible to HPV infection[305,306].

Health factors: Immunosuppression or *Human immunodeficiency virus* (HIV) infection is associated with a higher risk of cervical cancer[307,308] as well as a higher HPV prevalence[294,309], because of a failure of the immune response against HPV infection. Coinfections with sexual transmitted infections (STIs) such as HSV-2[310] or Chlamydia[311] are associated with an increased

risk of cervical cancer even after adjusting for number of sexual partners, possibly because these STIs weaken the immune systems, or because of residual confounding of sexual behavior.

2.2.4. Cervical cancer primary prevention

There are three commercial HPV vaccines available, including: Cervarix (a bivalent vaccine against HPV16 and HPV18), Gardasil (a quadrivalent vaccine against HPV 6, 11, 16, and 18), and Gardasil 9 (9-valent vaccine against HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58)[312]. As research found that it was most effective to provide HPV vaccines to girls prior to the onset of sexual activity, the target population for the HPV vaccine is girls aged 9-13 and prior to sexual activity, according to the World Health Organization (WHO) recommendation[278]. However, it is also important to vaccinate boys[278]. HPV vaccine has been shown to be effective in preventing cervical cancer in several studies in different countries[313-317]. However, there are some barriers to HPV vaccination, including the three-dose schedule, high cost, and potential communication challenges around HPV being a sexually transmitted infection[312].

2.2.5. Cervical cancer screening

Cytology is the most common screening method. Cytology is conducted by a healthcare provider who uses a small brush to take a sample of cervical cells, and then fixes the sample onto slides (i.e., Papanicolaou "Pap" smear) or places it in a transport medium (i.e., liquid-based cytology). The sample will then be examined under a microscope[278]. Cytology has been used for cervical screening for decades[278]. However, cytology requires trained providers and laboratories, thus, it is more difficult to implement on a large scale in developing countries or low resourced areas[278]. Newer screening methods have been developed, including visual inspection with acetic acid (VIA) and HPV screening tests[278,318]. To conduct VIA, a healthcare provider applies acetic

acid 3-5% to the cervix and visualizes the changes on the cervix after at least one minute[278]. For HPV testing, a healthcare provider uses a small brush, swab, tampon or lavage device to collect a cervico-vaginal sample and sends the sample to a laboratory to test for HPV[278]. There is an option for women to HPV self-sample at the healthcare provider's office; women can also self-sample at home and send the samples to a laboratory in some countries. Target populations and recommended screening frequency for each method are presented in Table 2-3.

All screening methods, except for HPV testing on self-samples, require trained providers to collect samples, and thus, require women to visit hospitals/clinics/health centers. This may discourage women to attend screening, especially those who have access barriers to hospitals/clinics and those who feel uncomfortable visiting physicians. HPV testing on self-collected samples is useful for screening in places where cultural and program barriers may limit acceptance of and access to other clinician-based cervical cancer screening. Additionally, HPV self-sampling is cost-effective, as it does not require an initial visit to health centers[319].

Self-sampling has shown to improve cervical cancer screening uptake. In many studies, non-responders of regular cervical cancer screening programs were sent either an HPV self-sampling kit or contacted a second time to come to the medical facility for conventional cytology. The authors found that uptake rates in the former group were significantly higher than the latter[91-99]. HPV self-sampling is also highly accepted in several settings, from developed[320-329] to developing countries[100-117], urban[100,110,325,328,329] to rural areas[102,104,105,110,113,115,320,330,331], as well as special populations such as ethnic minority or indigenous women[102,109,329,330,332-334], immigrants[335,336], religious groups[337], women living with HIV[338,339], and female sex workers[340]. A meta-analysis of 37 studies from 24 countries across North America, South America, Europe,

Africa, and Asia estimated that 97% of more than 18,000 women found self-sampling to be acceptable (95% CI 95-98%)[341]. The most common reasons for preferring self-sampling were ease of use, not embarrassing, privacy, comfort, ability to sample on their own, and convenience[341]. The most common reasons for not liking self-sampling were fear of self-sampling incorrectly, painful or uncomfortable, anxiety, and not wanting to touch themselves[341].

Although some women are concerned about the accuracy of self-sampling, previous studies found that HPV testing on self-samples has a much higher sensitivity than cytology. A meta-analysis of six studies found that the sensitivity to detect CIN3+ on HPV testing of self-samples was 7% lower than that of HPV testing on physician-collected samples (relative sensitivity=0.93, 95% CI 0.84-1.04) but 19% higher than that of cytology (relative sensitivity=1.19, 95% CI 1.09-1.29)[342]. Similarly, a meta-analysis of 14 studies in a primary screening setting found that the pooled sensitivity to detect CIN2+ of HPV testing on self-samples was 16% lower than that of HPV testing on physician-collected samples (relative sensitivity= 0.84, 95% 0.77-0.92), but 19% higher than that of cytology (relative sensitivity= 1.19, 95% CI 0.97-1.47)[342].

A limitation of HPV self-sampling is a low specificity compared to cytology. The specificity to detect CIN2+ of HPV testing on self-samples is 2% lower than HPV testing on physician-collected samples (relative specificity=0.98, 95% CI 0.97-0.99) and 11% lower than cytology (relative specificity=0.89, 95% CI 0.87-0.91)[342]. The specificity to detect CIN3+ of HPV testing on self-samples is 2% lower than HPV testing on physician-collected samples (relative specificity=0.98, 95% CI 0.97-0.99) and 10% lower than cytology (relative specificity=0.90, 95% CI 0.87-0.94)[342].

2.2.6. Cervical cancer diagnosis

The most common diagnostic tests for cervical cancer are colposcopy, biopsy and endocervical curettage. Colposcopy is a procedure where an instrument that provides strong light and magnifies a field to examine the cervix, vagina and vulva in order to further assess for cervical cancer in women with positive screening results. During colposcopy, biopsies are taken and examined under the microscope to examine a sample of abnormal tissues to determine the degree of abnormality in order to rule out cancer. Endocervical curettage is also conducted[343].

2.2.7. Summary

Cervical cancer is the most common gynecologic cancer worldwide, particularly among low and middle-income countries. HPV vaccine and cervical cancer screening methods are available. Additionally, the cervical cancer pre-clinical stage is long, opening the opportunity to detect the disease early. WHO has set the goal to eliminate cervical cancer within the next century. To eliminate cervical cancer, WHO recommended all countries, particularly low and middle-income country, to achieve the "90-70-90" goal by 2030[344]. This includes three targets: 90% girls vaccinated by age 15; 70% women screening by age 35 and again by age 45; and 90% women with pre-cancer and cancer being treated or managed[344].

2.3. Cervical cancer in Vietnam

2.3.1. Profile of Vietnam and Southern Vietnam

Vietnam is a middle-income country in Southeast Asia with gross domestic product per capita around US $2,800 in 2020[345]. The population of Vietnam in 2019 was more than 96 million people, of whom ~50% were female and about two-third lived in rural areas[346]. It is

evident that rural areas have poorer socioeconomic status, limited healthcare access and poorer health outcomes compared to urban areas[83]. Compared to people living in urban areas, those living in rural areas are more likely to be illiterate, have lower education levels and income[83]. Children in rural areas are more likely to die before one year old, be malnourished and out-of-school. The death rate in rural areas is higher and life expectancy is shorter. People living in rural areas are less likely to have access to hygienic water and toilets[83] (Table 2-4).

There are three historic, geographic and cultural regions within Vietnam, including Northern, Center and Southern. During 1954-1975, Vietnam was divided into two separate nations: North Vietnam was socioeconomically isolated while South Vietnam was more exposed to Western culture. Although the country has been reunited for almost 50 years, cultural differences between the two regions remain. **Aim 3 was carried out in women in Southern Vietnam only.** The population of Southern Vietnam in 2019 was more than 35 million people, of whom more than 50% were female and about 56% lived in rural areas[346].

2.3.2. Cervical cancer in Vietnam

Cervical cancer is the second most common and the deadliest gynecologic cancer in Vietnam, with more than 4,000 incident cases and about 2,200 deaths from cervical cancer in 2020[84]. According to data from the International Agency for Research on Cancer (IARC), the age-standardized incidence rate of cervical cancer in Vietnam in 2020 was 6.6 per 100,000, which is the lowest of all Southeast Asian countries and is much lower than that in Indonesia (24.4), Thailand (16.4), and the Philippines (15.2)[84]. However, the reported number in Vietnam was based on the data from two cancer registries in the two largest cities (i.e., Ha Noi in the

North and Ho Chi Minh City in the South), which may not represent the whole population, possibly due the differences in cervical cancer risk factors and screening rates[86].

Since 2000, besides the registries in Ha Noi and Ho Chi Minh City, there are four additional cancer registries that have reported data to the Vietnam National Cancer Institute, but not to IARC[86]. All of these registries are located in urban areas. Figure 2-1 presents the age-adjusted incidence rate by time period and by cancer registry, whenever and wherever data are available. The graph highlights three points. First, the incidence rate of cervical cancer in Northern urban settings is lower than that in Southern urban areas in all periods. In the period 2004-2008, the incidence in Northern urban were about 3.5-10.5 per 100,000 women, which was much lower than in Southern urban at 15.3-19.6[86]. A reason is the flourishment of sex services in Southern Vietnam during the Vietnam War, which was due to the stationing of millions of local and foreign soldiers in this region[347]. A study found that women in Northern Vietnam whose husbands joined the military during the Vietnam War and were stationed in the South during the war had about four times higher risk of developing cervical cancer (OR=3.9, 95% CI 1.5-10.4), while women whose husbands joined the army but were stationed in the North during the war had no significantly increased risk (OR=1.3, 95% CI 0.8-4.2)[348]. The cultural differences during the war may still affect the patterns of risk factors for cervical cancer in the two regions. Second, the incidence rate in Southern Vietnam has decreased slightly, while the incidence in Northern Vietnam has increased over time, which indicates an erosion of the separation's effects. Third, the incidence rates in the largest cities (i.e., Ha Noi, Ho Chi Minh City, Can Tho) are higher than those in smaller and less urban areas (i.e., Hai Phong, Thai Nguyen, Hue). Although none of these registries are located in rural areas, the difference may imply that the incidence rate of

cervical cancer is higher in urban areas compared to rural areas because socioeconomic status in urban areas is higher.

It is estimated that the treatment cost for a cervical cancer patient in Vietnam ranges from US $200-9,200, depending on cancer stage and treatment type[349]. This is 1.5-62 times and 1-35 times higher than the average personal monthly income in rural and urban areas, respectively. In 2012, the total direct burden of cervical cancer in Vietnam was about US$ 76 million, and the indirect burden was about US$ 18 million[318]. Therefore, cervical cancer was listed as one of the national public health priorities[90].

2.3.3. HPV vaccination and awareness in Vietnam

The two vaccines Cervarix and Gardasil have been approved to be used in Vietnam since 2008[318]. However, very few Vietnamese women are HPV vaccinated. Population-based studies in Northern and Central Vietnam found that the proportion of women aged 15-49 years that were HPV vaccinated was 1.7%[350] and 2.3%[351], respectively; there were no reports on HPV vaccination uptake in finer age groups. No population-based survey on HPV vaccination uptake has been conducted in Southern Vietnam, but a survey of female students at a university in the South in 2016 found that the proportion of vaccination was 7.5%[352], but this convenience sample raises the question of generalizability to the whole population.

The two main reasons for the low HPV vaccination uptake in Vietnam are the high price and lack of awareness[353,354]. HPV vaccines are not listed in the national vaccination program. Women have to pay out-of-pocket for HPV vaccination. The price of three doses of vaccines is US $106.8 (Cervarix) and $167.4 (Gardasil) [355], which is unaffordable for most Vietnamese women[87].

The knowledge of HPV and cervical cancer among Vietnamese people is very low. There have been six studies on the awareness of Southern Vietnamese people about HPV and cervical cancer, which were conducted in women (n=2), parents of daughters aged 10-18 years (n=3), girls aged 11-14 years (n=2), and college students (n=1) [88,352,356-359] (Table 2-5). All these studies found that Southern Vietnamese people lack knowledge of HPV and cervical cancer[88,352,356-359]. The most recent population-based study in Southern Vietnam that was conducted in 2010-2011 found that ~50% married women aged 18-49 years had never heard of HPV, ~55% were not aware that HPV is a cause of cervical cancer, and ~55% had never heard of HPV vaccine[88]. A study conducted in 2016 among students at a university in Southern Vietnam and students at a university in the US found that Vietnamese students had lower levels of knowledge about HPV compared to US counterparts[352]. A limitation of these studies is that they did not report rural and urban areas separately.

2.3.4. Cervical cancer screening in Vietnam

The available cervical cancer screening methods in Vietnam include cytology, visual inspection with acetic acid (VIA), and HPV testing on physician-samples or self-collected samples. HPV self-sampling is available[360] but not popular. The recommended target population for screening in Vietnam is women aged 21-65 years who have had sexual intercourse, with a priority for women aged 30-50 years[318]. The recommended target population for HPV testing is women aged 25-65 years with a three-year frequency[318] (more details in Table 2-3).

A national survey in 2015 showed that about 30% of women aged 30-49 years had ever been screened for cervical cancer[89], which is much lower than the target of WHO of 70%[344]. A reason for such the low screening uptake is that there is no national cervical cancer screening

program. Another barrier is the low awareness of cervical cancer. No studies have been conducted to identify barriers to cervical cancer screening among Southern Vietnamese women.

As HPV self-sampling has been shown to improve screening uptake in other settings[100-117,320-340], it may have potential to increase screening uptake among Southern Vietnamese women. There was one study about HPV self-sampling in an urban area in Northern Vietnam, which found that women preferred HPV self-sampling to physician-sampling and Pap test[118]. No study has been conducted to explore the attitudes toward cervical cancer screening methods and the acceptability of HPV self-sampling among women in Southern Vietnam.

2.3.5. Summary

Cervical cancer screening uptake in Vietnam is low due to low awareness and barriers in accessibility. Cervical cancer incidence rate in Southern Vietnam is higher than the national average, and there is evidence of a disparity in socioeconomic status and healthcare access between rural and urban areas. However, little is known about the awareness of HPV and cervical cancer, cervical cancer screening uptake, barriers to cervical cancer screening, as well as the attitudes toward cervical cancer screening methods and the acceptability of HPV self-sampling among women in Southern Vietnam, particularly in rural areas.

Table 2-1: Staging systems for ovarian cancer

AJCC/TNM	FIGO (2012)	SEER	Description
T1a, N0, M0	IA	Localized	One ovary or one fallopian tube, capsule intact.
T1b, N0, M0	IB	Localized	Both ovaries or fallopian tubes, capsule intact.
T1c, N0, M0	IC	Regional	Capsule broke. Cancer on the outer surface. Cancer cells in the fluid (ascites) or washings from the abdomen and pelvis.
T2a, N0, M0	IIA	Regional	Spread to or invaded to uterus or fallopian tubes, or ovaries.
T2b, N0, M0	IIB	Regional	Cancer on outer surface of or grown into bladder, the sigmoid colon, or the rectum.
T1 or T2, N1, M0	IIIA1	Distant	Spread to the retroperitoneal lymph nodes.
T3a, N0 or N1, M0	IIIA2	Distant	Invisible tiny deposits of cancer in the lining of the abdomen.
T3b, N0 or N1, M0	IIIB	Distant	Deposits of cancer ≤2 cm.
T3c, N0 or N1, M0	IIIC	Distant	Deposits of cancer >2 cm.
Any T, Any N, M1a	IVA	Distant	Fluid around the lungs.
Any T, Any N, M1b	IVB	Distant	Inside of the spleen or liver, to lymph nodes other than the retroperitoneal lymph nodes, to other organs or tissues outside the peritoneal cavity.

Abbreviations: AJCC/TNM: American Joint Committee on Cancer/Tumor, Nodes, Metastasis; FIGO: International Federation of Gynecology and Obstetrics; SEER: Surveillance, Epidemiology and End Results.

Table 2-2: Risk prediction models for ovarian cancer

Study	Model development						Model validation			Limitations
	Study design Place and time of recruitment	**Outcome**	**Participants and Sample size**	**Methods**	**Predictors**	**Absolute risk**	**Validation**	**AUC (95% CI)**	**Calibration**	
Hartge et al. (1994) [42]	7 case-control studies US 1980s	Invasive epithelial ovarian cancer	White women 1,122 cases and 5,359 controls	Logistic regression	Family history of ovarian cancer, full-term pregnancies, COC use	Risk by age 65 and age 85 (using SEER data)	No			Limited generalizability to other races/ ethnicities; No validation; Miss some well-known factors.
Harvard Cancer Risk Index [43]		Ovarian cancer		Selected predictors based on expert opinion. Relative risks were obtained from literature.	Family history of ovarian cancer, parity, COC use, tubal ligation, hysterectomy, breastfeeding	10-year risk (using SEER data)	External validation Kim et al. (2004) [361] 71,778 participants aged 40-70, with no prior cancer	0.59 (0.56-0.62)	Observed/ Expected: 0.73 (0.52-0.95) among people below the average risk 0.82 (0.57-1.08) among people about the average risk 1.20 (1.02-1.38) among people above the average risk	Not consider interaction; Miss some well-known factors.

Study	Model development						Model validation			Limitations
	Study design Place and time of recruitment	Outcome	Participants and Sample size	Methods	Predictors	Absolute risk	Validation	AUC (95% CI)	Calibration	
Rosner et al. (2005) [44]	Cohort (NHS) US 1976-2000	Both invasive and borderline epithelial ovarian cancer	No previous cancer. No bilateral oophorectomy or hysterectomy. NHS: 78,504 participants, 382 cases. NHS II: 106,618 participants, 90 cases.	Assumed the incidence of ovarian cancer proportional to the number of ovarian cell divisions. The rate of cell divisions was assumed to be a linear function of risk factors.	Age, age at menopause, age at menarche, parity, COC use, tubal ligation	Cumulative risk by age 70	Internal validation	Test in the whole dataset: 0.60 (0.57-0.62). Model development in 50% of sample and test in 50%: Mann-Whitney= 0.59	Chi-square=7.04 (p=0.63)	Miss some well-known factors; Not consider interaction.
Vitonis et al. (2011) [45]	Case-control study US 1992-2003	Invasive epithelial ovarian cancer	Aged 40+ years. No hysterectomy. No prior breast cancer. No family history of ovarian cancer or breast cancer. 1,098 cases and 1,363 controls	Unconditional logistic regression, adjusting for age and study site.	Jewish ethnicity, COC use, parity, breastfeeding, tubal ligation, endometriosis, obesity, and genital talc use.	Risk by age 85 years (using SEER data)	Internal validation		Significant trend of increasing risk with increasing number of conditions	Limited generalizability to other races/ ethnicities; No validation; Not consider interaction.
Pfeiffer et al. (2013) [46]	Prospective cohorts: PLCO and NIH-AARP US 1993-2001	Invasive epithelial ovarian cancer	Non-Hispanic White aged 50-74 at baseline. 143,409 in NIH-AAPR (570 cases)	Cox models with age as the timescale. Final models included only variables and interactions that were	Family history of breast or ovarian cancer, duration of MHT use, parity, COC use.	5-, 10-, and 20- years risks (using SEER data)	External validation NHS 56,638 participants (377 cases) aged 50+ years	0.59 (0.56-0.63)	Expected/ Observed= 1.08 (0.97-1.19)	Restricted to women age 50+; Limited generalizability to other races/ ethnicities; Miss some

Study	Model development						Model validation			Limitations
	Study design Place and time of recruitment	Outcome	Participants and Sample size	Methods	Predictors	Absolute risk	Validation	AUC (95% CI)	Calibration	
			56,564 in PLCO (274 cases)	significant in multivariable models with p<0.01			External validation Li et al. (2015) [47] 66,493 participants	0.55 (0.52-0.59)	Expected/ Observed= 1.35 (95% CI 1.12-1.63)	well-known risk factors.
Pearce et al. (2015) [41] and Pearce et al. (2013) [19]	US 1999-2009	Invasive epithelial ovarian cancer	Non-Hispanic White	Odds ratios for each factor were obtained from 11 case-control studies. Absolute risk was calculated by scaling the relative risk with the average absolute risk.	Family history of ovarian cancer, endometriosis, parity, COC use, tubal ligation, 11 common susceptibility alleles	Lifetime risk by age 85	No			Limited generalizability to other races/ ethnicities; No validation; Miss well-known factors; Not consider interactions.
Li et al. (2015) [47]	Cohort study Western Europe 1992-2000	Ovarian cancer, including fallopian tube and peritoneal cancer.	Age 45+ No prior cancer. 202,206 participants (791 cases)	Weibull model, adjusting for competing risk. Backward stepwise selection of predictors with p≤0.1	Menopausal status, age at menopause, MHT use, COC use, parity, unilateral oophorectomy, BMI	5-year absolute risk	Internal validation Five-fold cross-validation	0.64 (0.57-0.70)	Expected/ Observed= 0.90 (95% CI 0.81-1.01) Hosmer-Lemeshow test p=0.14 Calibration slope= 0.9 (95% CI 0.66-1.15)	Miss well-known factors; Not consider interaction.

Study	Model development						Model validation			Limitations
	Study design Place and time of recruitment	**Outcome**	**Participants and Sample size**	**Methods**	**Predictors**	**Absolute risk**	**Validation**	**AUC (95% CI)**	**Calibration**	
Clyde et al. (2016) [48]	11 case-control studies US 1992-2010	Invasive epithelial ovarian cancer	Age 30+ No prior cancer. Non-Hispanic White. 80% of sample (4,662 cases, 7,586 controls)	Generalized additive models separately for women aged <50 years and 50+ years	Age, age at menarche, COC use, aspirin use, full-term pregnancies, non-full-term pregnancies, breastfeeding, age at end of last pregnancy, tubal ligation, hysterectomy, endometriosis, BMI, menopause status, MHT use, first degree family history of breast or ovarian cancer 17 commons alleles	No	Internal validation 20% of sample (1,131 cases, 1,926 controls)	Only epidemiologic factors: All ages: 0.65 <50: 0.71 50+: 0.62 epidemiologic factors+ 17 alleles: All ages: 0.66 <50: 0.71 50+: 0.64	Well calibrated	Limited generalizability to other races/ ethnicities; Not consider interaction.

Study	Model development						Model validation			Limitations
	Study design Place and time of recruitment	Outcome	Participants and Sample size	Methods	Predictors	Absolute risk	Validation	AUC (95% CI)	Calibration	
CanRisk tool[52]		Ovarian cancer		An explicit genetic model incorporating epidemiologic factors. Relative risk of epidemiologic factors obtained from other studies.	High penetrance genes (*BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, *BRIP1*). Polygenic risk score of 36 common susceptible variants. BMI, height, tubal ligation, parity, COC use duration, MHT use ever/never, family history of ovarian cancer, and endometriosis.	5 and 10-year risk Risk by age 80	External validation UKCTOCS self-reported European ancestry 1961 participants (374 cases) 5 years follow-up	0.61 (0.58 to 0.64)	Expected/ Observed= 1.05 (95% CI, 0.94-1.16). Hosmer-Lemeshow p=0.08	Not consider interactions; Miss some well-known risk factors.

Abbreviations**:** AUC: area under the receiving operating curve; BMI: body mass index; CI: confidence interval; COC: combined oral contraceptive; MHT: menopausal hormonal therapy; NHS: Nurses' Health Study; NIH-AARP: National Institutes of Health-American Association of Retired Persons; PLCO: Prostate, Lung, Colorectal, and Ovarian Cancer Screening trial; SEER: Surveillance, Epidemiology, and End Results; UKCTOCS: United Kingdom Collaborative Trial of Ovarian Cancer Screening; US: United States.

Table 2-3: World Health Organization (WHO) 2014 and Vietnam 2019 recommendations for cervical cancer prevention

Recommended by		Primary prevention		Secondary prevention		
		HPV vaccination		Cervical cytology	Visual inspection with acetic acid (VIA)	HPV testing
WHO [278,312]	Target population	Girls aged 9-13 AND Prior to sexual activity	Girls aged 15+ OR Immunocompromised individuals	Women aged 30-49	Women aged 30-49	Women aged 30-49
	Frequency and interval	2 doses 6 months and not greater than 12-15 months	3 doses 0, 1-2, 6 months	3-5 years	3-5 years	5+ years
Vietnam Ministry of Health [318,362]	Target population	Same as WHO recommendations		Women who have had sex Prioritize women aged 30-50	Women aged 21-65 who have had sex Prioritize women aged 30-50	Women aged 25-65 who have had sex
	Frequency and interval			2 years	2 years	3 years

Table 2-4: Disparities in socioeconomic status and health between urban and rural areas in Vietnam in 2019

	Urban	Rural	Entire country
Proportion of population aged 15+ literate [a]	98.3%	94.3%	95.8%
Average number of education years [a]	10.9	8.1	9.0
Proportion of out-of-school children [a]	5.7%	9.5%	8.3%
Highest education level [a]			
Less than primary school	4.7%	12.5%	9.8%
Primary school	14.8%	25.0%	21.4%
Secondary school	26.5%	35.5%	32.3%
High school	22.4%	14.6%	17.3%
Some college	13.9%	7.7%	9.9%
College or above	17.7%	4.7%	9.3%
Unemployment rate [a]	3.1%	1.7%	2.2%
Average monthly personal income (US$) [b]	262	148	214
Proportion of poverty household (in 2016) [b]	2.0%	7.5%	5.8%
Crude death rate (per 1000) [a]	5.1	6.9	6.3
Infant mortality rate (per 1000) [a]	8.2	16.7	14
Life expectancy at birth (years) [a]	76.2	72.6	73.6
Proportion of children aged under 5 years old with malnutrition [b]	6.3%	15.7%	12.4%
Proportion of households with access to hygienic water [b]	99.4%	94.7%	96.3%
Proportion of households with hygienic toilets [b]	98.4%	89.6%	92.7%

[a] Vietnam population and housing census 2019 [346]

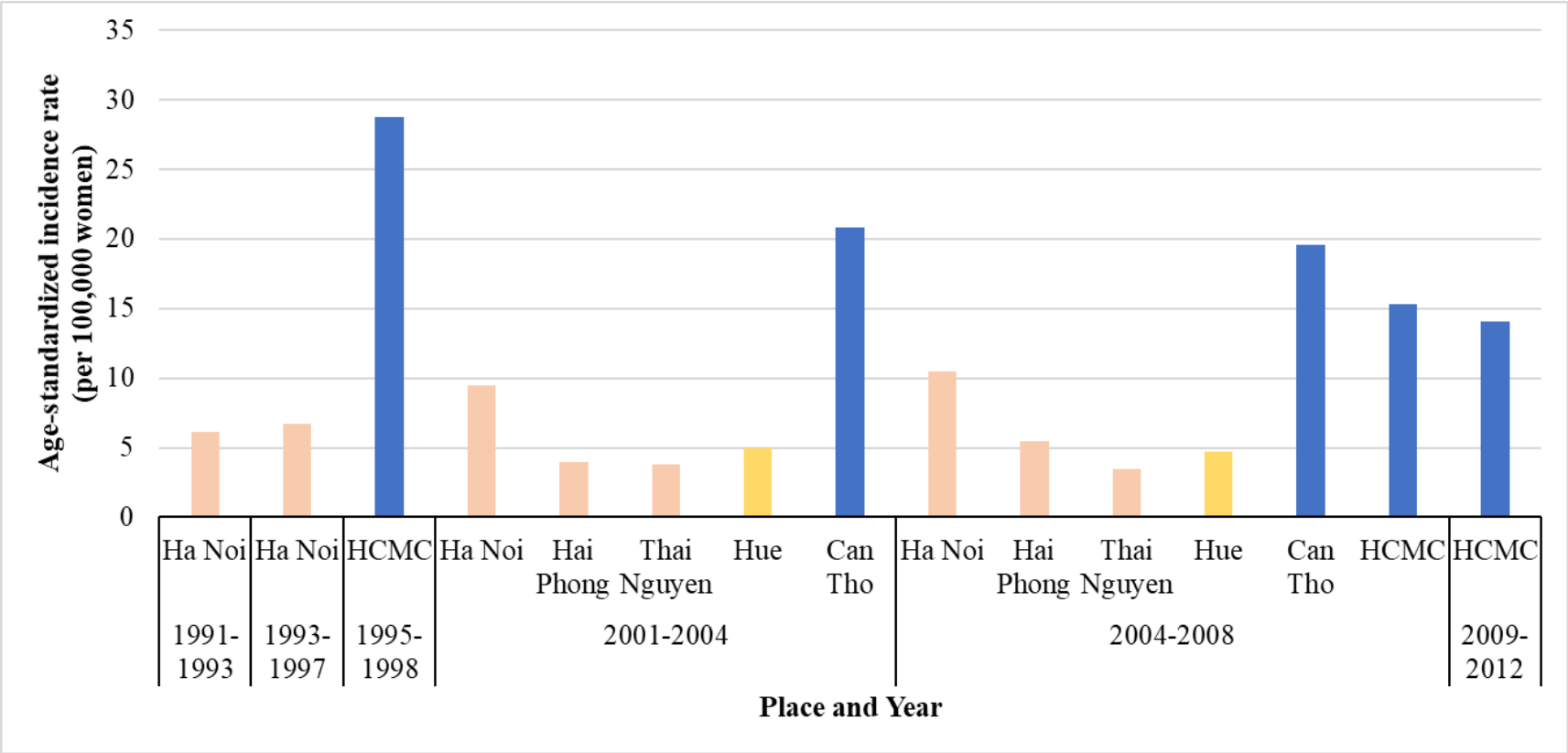
[b] General Statistics Office of Vietnam [363]

Table 2-5: Studies about awareness of HPV and cervical cancer among people in Southern Vietnam

Study	Sampling method	Participants	Location and sample size	Area	Year of recruitment	Findings	Limitations
Loi & Nhu (2014) [356]	Population-based	Women aged 40-65 who had had sex	Ho Chi Minh City (South) N=1,615	Urban	2003	43% never heard of cervical cancer 45% not know cervical cancer was fatal 51% not know cervical cancer could be detected early 82% never heard of Pap test	Not included rural women
Mai et al. (2010) [357]	Population-based	Mothers and fathers of daughters aged 11-14 years	Ho Chi Minh City (South): n=108 Dong Thap (South): n=218	Not clear	2007	22-30% never heard of cervical cancer 53-58% not know symptoms of cervical cancer 80-82% never heard of HPV 96-98% not know how HPV infected 83-85% never heard of Pap test 79-81% never heard of HPV vaccine	Not reported rural and urban separately
Nghi et al. (2010) [358]	Population-based	Parents and girls aged 11-14 years old	Ha Noi, Thai Binh (North). Ho Chi Minh City, Dong Thap (South). Nghe An (Center) n=875 parents n=879 daughters	Not clear		Majority of girls never heard of cervical cancer Participants had limited knowledge of cervical cancer, etiology, and risk factors	No detailed reports of rural and urban separately
Paul et al. (2012) [359]	Population-based	Mothers and daughters (grade 6)	Thanh Hoa (Center) Can Tho (South) N=536 pairs	Urban	2010-2011	38% not know cervical cancer fatal 85% not know symptoms of cervical cancer 78% not know risk factors for cervical cancer 40% not know how to prevent cervical cancer 49% not know HPV caused cervical cancer 51% not know how HPV infected 22% not know the purpose of HPV vaccine 31% not know who should receive HPV vaccine	Not report rural and urban areas separately Research conducted after the implementations of HPV vaccinations in these communities.
Vu et al. (2013) [88]	Population-based	Women aged 18-65 years Married	Ho Chi Minh City (South) n=750 Can Tho (South) n=1000	Urban	Ho Chi Minh City (2010) Can Tho (2011)	46-50% never heard of HPV 54-58% not know HPV caused cervical cancer 52-58% never heard of HPV vaccine	No information on rural areas
Kamimura et al. (2018) [352]	Convenient sample	College students (both males and females) aged 18-30 years in one Vietnamese and one US universities.	Ho Chi Minh City (South) n=495 Salt Lake City n=437	Urban	2016	Vietnamese students had poorer knowledge than US participants Both Vietnamese and US participants had correct answers for less than half of the questions testing HPV knowledge	Sample not representative general population No information on rural areas

Figure 2-1: Cervical cancer incidence reported by cancer registries in Vietnam

Cities in Northern Vietnam are in pink. Cities in Central Vietnam are in yellow. Cities in Southern Vietnam are in blue.



Source: IARC (2020) [85] and Thi Nguyen et al. (2019) [86]

Chapter 3. A Comprehensive Evaluation of Interactions for Ovarian Cancer Risk Factors and Development of a Risk Stratification Model

Introduction

Ovarian cancer is the deadliest gynecologic cancer. The high death rate is due to at least 50% of ovarian cancer cases being diagnosed at an advanced stage when five-year survival is ~30%[2]. The search for an early detection method has proved elusive, with the most recent trial showing no survival benefit for screen-detected cancers[3]. However, primary prevention to reduce the burden of ovarian cancer is feasible for women at average and high risk[4,5].

Multiple primary prevention strategies for ovarian cancer are available. Risk-reducing salpingo-oophorectomy (RRSO) is recommended for individuals carrying pathogenic variants for ovarian cancer (e.g. in *BRCA1/2, RAD51C, RAD51D, BRIP1)*[6] as it reduces risk by 71-96% in this population[7-12]. Bilateral salpingectomy with ovarian retention may offer significant protection against ovarian cancer in the general population[5,13] and has been recommended for individuals undergoing hysterectomy or requesting permanent, irreversible contraception[14]. Tubal ligation[15] and hormonal contraceptives[19,21] are also associated with reduced risk of ovarian cancer although they have never been specifically recommended for prevention purposes in average risk women.

There are significant additional ovarian cancer risk and protective factors. A first-degree family history of ovarian cancer[19], low-penetrance common genetic variants[19], a personal history

of endometriosis[139], menopausal estrogen therapy (ET) use[23,24], and obesity[25-28] are associated with increased risk of the disease. Conversely, parity[16,19,29-32], incomplete pregnancy[31,33-37] and breastfeeding[38-40] are all associated with substantial reductions in ovarian cancer risk.

Lifetime risk of ovarian cancer in the general population is ~1.3%, but some individuals have a much higher than average risk of developing ovarian cancer, even among those who are not known to carry a pathogenic variant for ovarian cancer or do not have a first-degree family history of the disease[41]. Various risk stratification efforts have been undertaken to identify individuals at a substantially elevated risk[41-50]. The online CanRisk tool (https://canrisk.org/), which provides risk prediction models for breast and ovarian cancers, is the only model that has been approved for use by healthcare professionals within the European Economic Area[51]; no other models have been approved for clinical use in other areas in the world to our knowledge. The CanRisk model for ovarian cancer was developed based on five rare high-penetrance mutations, a polygenic risk score (PRS) of 36 common genetic variants, and eight environmental risk factors (including body mass index [BMI], height, tubal ligation, parity, combined oral contraceptive [COC] use duration, menopausal hormone therapy [MHT] use, family history of ovarian cancer, and endometriosis); age-specific risk and risk to age 80 are estimated[52].

A limitation to the CanRisk model is that it assumes no interactions among the risk factors for ovarian cancer or between the risk factors and menopausal status or age. Additionally, the model does not account for several well-accepted risk/protective factors for ovarian cancer (breastfeeding, incomplete pregnancy, age at last pregnancy, age at menopause, and use of depot-medroxyprogesterone acetate [DMPA]). Also, MHT formulation is not considered, but may be important given recent data suggesting that ET and estrogen plus progestin therapy

(EPT) have different effects on ovarian cancer risk[23,54]. We undertook a comprehensive analysis using data from the Ovarian Cancer Association Consortium (OCAC) to address these limitations so that a user-friendly online ovarian cancer risk stratification tool can be developed to provide the most accurate risk estimates.

Methods

Study populations

This analysis used data from nine case-control studies in OCAC, including one study from Australia[364], one from Germany[365], and seven from the US[366-372] (Supplemental Table 3-1 and Table 3-1). Data were self-reported and collected through self-completed questionnaires or in-person or telephone interviews using structured questionnaires. Each study's data were sent to the OCAC data-coordinating center (Duke University) for central harmonization[373]. Institutional review board approval was obtained by each study and informed consent was provided by all participants.

Cases were women with invasive epithelial ovarian, tubal, or primary peritoneal cancers, hereafter referred to as ovarian cancer. Controls were women without a personal history of ovarian cancer who had at least one intact ovary. A total of 20,700 participants were considered for the analysis from the nine studies. Participants with missing data on menopausal status (n=389) and those aged 85 years or more at diagnosis for cases/at reference age for controls (n=67) were excluded from all analyses, leaving 20,244 participants (7,984 cases and 12,260 controls) in the analytic dataset.

Risk factors and Covariates

The risk/protective factors of interest included 14 environmental factors and a PRS for ovarian cancer (15 factors total). The 14 environmental factors considered for this analysis included: BMI, height, age at menarche, parity, breastfeeding, incomplete pregnancy, age at last pregnancy, tubal ligation, age at menopause, COC use duration, DMPA use, MHT use, first-degree family history of ovarian cancer, and endometriosis. The PRS was developed by OCAC and included 36 genome-wide significant common genetic variants for ovarian cancer[374]. Model covariates included age at diagnosis for cases/reference age for controls, menopausal status (pre-menopause [including peri-menopause] vs post-menopause), race/ethnicity, attained education level, and OCAC study site. The categorization scheme for the environmental factors, the PRS, and the covariates is shown in Supplemental Table 3-2.

Multiple imputation

There was limited missing data for most of the environmental factors (≤2.7% missingness), with the exception of DMPA use (11.5% missing), family history of ovarian cancer (21.6% missing), and age at menopause (38.2% missing among post-menopausal participants; Supplemental Table 3-2). The PRS was missing for 26.3% of study participants (Supplemental Table 3-2).

Multiple imputation was conducted separately for cases and controls and by country (i.e., Australia, Germany, and US) to generate 50 imputed datasets using the *mice* package in R. OCAC study site was included as a predictor in the imputation for US studies. Multiple imputation was carried out for all risk factors except age at menopause (due to the large proportion of missing values) and the PRS (because we did not have information on individual

genetic variants). We conducted analyses for age at menopause and the PRS in study participants with information on these variables and excluded participants with missing data.

Evaluation of risk factors by menopausal status and age group

Two of our major goals with this analysis were to determine whether age and/or menopausal status modifies the associations between 15 risk/protective factors (14 environmental factors and a PRS) and ovarian cancer risk and to evaluate whether pairwise interactions exist between these 15 factors. Therefore, the initial analyses in this study were conducted in the following five age and menopausal status strata:

(1) participants aged <45 years and pre-menopausal (965 cases and 2,111 controls)
(2) participants aged 45-54 and pre-menopausal (1,269 cases and 2,109 controls)
(3) participants aged 45-54 and post-menopausal (903 cases and 1,214 controls)
(4) participants aged 55-64 and post-menopausal (2,493 cases and 3,502 controls)
(5) participants aged 65-84 years and post-menopausal (2,226 cases and 3,148 controls).

Pre-menopausal study participants aged 55+ (75 cases and 116 controls) and post-menopausal participants aged <45 (53 cases and 60 controls) were excluded from this aspect of the analysis as the sample sizes of these groups were too small for evaluation.

To assess the menopausal status and age interactions with the 13 environmental risk factors, the odds ratios (ORs) for each of the factors were evaluated across the five menopausal status/age groups described above using logistic regression. There were 13 risk factors rather than 15 because age at menopause and the PRS were not included in this aspect of the analysis because there was substantial missing data for these variables and they were not imputed. All

models included all the 13 factors and were adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, and OCAC study site. The risk/protective factors and covariates were fit as shown in Supplemental Table 3-2. For age at last pregnancy, the reference group included study participants who were never pregnant and those who had age at last pregnancy <25, based on the methods described by Heuch et al.[375] and McKnight et al.[376]. ORs across the 50 imputed datasets were pooled using Rubin's rule[377] to obtain a single point estimate. Confidence intervals (CIs) were calculated from pooled standard errors which were derived from within and between imputation variances[377,378]. Within imputation variance is the average of the variance estimates within each imputed dataset. Between imputation variance reflects the extra variance in parameter estimates due to the uncertainty in imputation[377,378].

Potential interactions between menopausal status and age with the risk factors were evaluated using three methods: (1) a likelihood ratio test comparing a model without the interaction term versus the same model including the interaction term of interest; (2) comparing the ORs of a factor across the levels of the other factor; and (3) considering biological plausibility of the effect modification. Menopausal status interactions were assessed by considering the effect estimates for the risk/protective factors among women of the same age (i.e., 45-54) who were pre-menopausal or post-menopausal. Further, the associations with the risk/protective factors for pre-menopausal individuals were assessed within two age groups (<45 and 45-54) and for post-menopausal individuals within three age groups (45-54, 55-64, 65-84). Because the results of these analyses affect our subsequent methods, we summarize these findings here: we observed evidence of effect modification by menopausal status for some of the risk/protective factors (discussed in the results section below). When conducting analyses among

pre- and post-menopausal women separately, we did not observe any evidence of interactions between the risk factors and age groups (also discussed in the results section below).

Pairwise interactions between risk factors, by menopausal status

Pairwise interactions between the risk factors for ovarian cancer were assessed separately among pre- and post-menopausal participants following the same schema used for the age/menopausal status interaction analyses described above. Because age at menopause and the PRS were not imputed, separate models were fit to evaluate the interactions with these exposures whereas the other 13 environmental risk factors were fit in the same models. The models for the PRS were fit in study participants with complete data on the PRS; the models included the 13 environmental risk factors, adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, and OCAC study site and further adjusted for genetic ancestry principal components (but not age at menopause). The models for age at menopause were conducted among post-menopausal participants who had data on age at menopause and had not had a hysterectomy. The models included the 13 environmental risk factors, adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, and OCAC study site, and further adjusted for duration of ET use and EPT use (but not the PRS). Since all nulliparous individuals had never breastfed, the interaction between the number of children and breastfeeding duration was fit among parous participants only. As described below in the results, there was no evidence of pairwise interactions between the risk factors among pre- or post-menopausal participants (Supplemental Tables 3-3 and 3-17 show the p-values for pairwise interactions among pre- and post-menopausal participants, respectively; Supplemental Tables 3-4 to 3-16 show the ORs for pairwise interactions among pre-menopausal participants;

Supplemental Tables 3-18 to 3-32 show the ORs for pairwise interactions among post-menopausal participants).

Development of the Risk Stratification Model

To develop and evaluate a risk stratification model using the 15 factors (14 environmental and the PRS), the dataset was split into a training set and a test set. The test set comprised 20% of participants randomly selected from those who had not had a hysterectomy and had complete data on all 14 environmental factors and the PRS. The remaining 80% of participants made up the training set. We used the approach described in Pearce et al. (2015)[41] to develop the risk stratification model.

- *Ovarian cancer risk estimates in the training set*

After splitting the data, the next step was to determine the association between each risk/protective factor and ovarian cancer risk in the training set. We fit logistic regression models separately for pre- and post-menopausal participants. All models were adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, and OCAC study site (see Supplemental Table 3-2 for coding scheme). Because age at menopause and the PRS were not imputed, separate models were fit to obtain the estimates for these exposures whereas the other 13 risk/protective factors were fit in the same models. The models for age at menopause were conducted among post-menopausal participants without hysterectomy who had data on age at menopause. The ORs across the 50 imputed training datasets were pooled using Rubin's rule[377] to obtain a single point estimate.

To estimate absolute risks of developing ovarian cancer, we needed to use publicly available ovarian cancer rates which are available by age, but not menopausal status. Therefore, we further evaluated whether age <50 could be a proxy for pre-menopausal status and age 50+ for post-menopausal status. No pairwise interactions were observed between the risk factors in these two age groups, indicating again that a multiplicative model fits these data. As described below in the results, the ORs for pre-menopausal participants and participants <50 were very similar to each other as were those for post-menopausal participants and participants 50+ (Table 3-2). We therefore decided to develop the risk stratification model using age <50 and age 50+ as proxies for pre-menopausal and post-menopausal statuses, respectively, and with no pairwise interaction terms. We used all of the factors (i.e., 14 environmental factors and the PRS) in the risk stratification model.

- *Absolute risk estimation and risk factor profiles in the test set*

Control participants in the test set were stratified into risk profiles, which were the unique combinations of the risk factors. The profiles are created by multiplying the number of categories of the 15 risk factors for women 50+ and 13 factors for women <50 (MHT use and age at menopause are not included as these are not relevant for women <50) (Supplemental Table 3-2). We observed 898 profiles among 945 controls aged <50 in the test set. For controls who were 50+ but coded as pre-menopausal (n=466), we set their age at menopause as their reference age. We observed 1,499 profiles among 1,507 controls aged 50+ in the test set.

The beta coefficients for the risk factors among participants <50 and 50+ obtained in the training set (Table 3-4) were used to calculate a multiplicative relative risk estimate for each profile in the test set assuming no departure from multiplicativity. Since all risk factors were

coded as categorical variables, the beta coefficients were summed to calculate a log relative risk for each profile; the relative risk was the exponent of that value. The variance associated with the log relative risk for each profile was obtained by summing the variances for each factor; this approach assumed independence of the risk estimates for each factor as described in Pearce et al. (2015)[41]. To convert relative risks to absolute risks, the frequency-weighted average of all the profile-specific relative risks was scaled to the average absolute risk in the population (see below), and then this scaling factor was applied to each profile-specific relative risk and its 95% confidence interval (CI).

The average absolute risks of developing ovarian cancer by age 50 and between ages 50-84 in the population were estimated using DevCan, a software developed by the National Cancer Institute to calculate the probability of developing cancer accounting for competing risks[379]. The input for DevCan was the publicly available data on ovarian cancer incidence, cancer-specific mortality, all-cause mortality, and population size by country[379]. For the US-based studies, we calculated the average absolute risk of developing invasive epithelial ovarian cancer by race/ethnicity using data from the Surveillance, Epidemiology and End Results (SEER) 13 registry during the period of 1992-2010, which was the period of participant recruitment of these studies in this analysis (Table 3-1). We also calculated the average absolute risk for the populations in Australia and Germany using publicly available data from these countries in the periods that matched the time of participant recruitment in the studies (Table 3-1). For these non-US studies, we calculated the risk of developing ovarian cancer overall in the combined race/ethnicity group, since there were no detailed data on tumor behavior (i.e., borderline/invasive and epithelial/non-epithelial) and race/ethnicity in the public cancer registry data. We made this decision for non-US studies given that the majority of ovarian cancers are

invasive epithelial (~90%)[121]. This provided us with the absolute risk for each of the risk profiles observed among controls in the test set.

Comparison of our 15-variable risk stratification model to the nine-variable reduced model

We compared our risk stratification results using the 14 environmental factors (BMI, height, age at menarche, parity, breastfeeding, incomplete pregnancy, age at last pregnancy, tubal ligation, age at menopause, COC use duration, DMPA use, MHT use, first-degree family history of ovarian cancer, and endometriosis) and the PRS to results of the nine-factor reduced model to determine the impact of adding additional risk factors on the absolute risk for a given profile. The reduced model includes only the eight environmental factors (BMI, height, tubal ligation, parity, COC use duration, MHT use, family history of ovarian cancer, and endometriosis) and the PRS used in CanRisk. We applied the estimated odds ratios generated from our training set to the factors in the reduced model. We also validated our newly reported model and the reduced model in the test set. We reported the areas under the receiving operating curve (AUCs), Hosmer-Lemeshow goodness of fit tests, and Brier scores.

Data were analyzed using R version 4.0.3.

Results

Study populations

Data from 7,984 cases and 12,260 controls were used in the analysis (Table 3-1). The average age at diagnosis for cases was 57.3 years (SD=11.3 years). The majority of participants were post-menopausal (71.1% among cases and 64.6% among controls) and non-Hispanic White (82.3% of cases and 84.9% of controls; Table 3-1).

Evaluation of risk factors by menopausal status and age group

In evaluating whether ovarian cancer risk factors differ by menopausal status, the associations within the same age strata (45-54) for pre- and post-menopausal participants were examined (Tables 3-2 and 3-3). Applying the three methods to assess interactions (likelihood ratio tests, comparing ORs, and biological plausibility), we found that menopausal status appeared to modify the associations between ovarian cancer risk and *first-degree family history of ovarian cancer* and *endometriosis*. Based on the likelihood ratio test assessment, only the interaction between menopausal status and endometriosis (p=0.044) was significant, while the interaction between menopausal status and family history was not (p=0.38; Table 3-3). However, both family history and endometriosis were associated with a greater increase in risk of ovarian cancer among pre-menopausal participants (family history OR=2.44; endometriosis OR=1.93) compared to post-menopausal participants (family history OR=1.83; endometriosis OR=1.33; Table 3-2). Further, as explained below in the Discussion, these interactions satisfied the third method of biological plausibility.

None of the other risk factors appeared to have different effects among pre- and post-menopausal participants. Also, considering all three methods of assessing interactions, we did not find convincing evidence that age modified the associations between ovarian cancer risk and the 13 environmental risk factors within menopausal status group (pre versus post) (Tables 3-2 and 3-3).

Pairwise interactions between risk factors by menopausal status

Applying the three methods of assessing interactions, we did not find strong evidence of any pairwise interactions between the risk factors within menopausal status.

Among pre-menopausal women, based on the likelihood ratio assessment, four pairwise interactions were statistically significant, including: (1) *breastfeeding-parity* (among parous women) (p=0.037), (2) *breastfeeding-endometriosis* (p=0.041), (3) *family history-incomplete pregnancy* (p=0.023), and (4) *family history-parity* (p=0.024), and there were four possible interactions, including (5) *BMI-incomplete pregnancy* (p=0.064), (6) *family history-endometriosis* (p=0.066), (7) *parity-tubal ligation* (p=0.061), and (8) *COC use-tubal ligation* (p=0.067) (Supplemental Table 3-3). The observed interaction between family history of ovarian cancer and endometriosis could be due to small sample size (16 cases and 13 controls with both family history of ovarian cancer and endometriosis; Supplemental Table 3-15). For other pairs of interactions, there were no patterns across the ORs for one factor and the categories of the other factor (ORs for breastfeeding across the categories of parity: Supplemental Table 3-7; ORs for breastfeeding across the categories of endometriosis: Supplemental Table 3-15; ORs for incomplete pregnancy and parity across the categories of family history of ovarian cancer: Supplemental Table 3-14; ORs for BMI across the categories of incomplete pregnancies: Supplemental Table 3-9; ORs for parity across the categories of tubal ligation: Supplemental Table 3-11; ORs for tubal ligation across the categories of COC use: Supplemental Table 3-12).

Among pre-menopausal participants, although the interactions between *BMI-endometriosis, incomplete pregnancy-endometriosis* and *tubal ligation-endometriosis* were not statistically significant based on likelihood ratio tests (p=0.96, p=0.0.9, and p=0.10, respectively; Supplemental Table 3-3), there were some patterns of the ORs for BMI, incomplete pregnancy and tubal ligation across the categories of endometriosis (Supplemental Table 3-15). The ORs for BMI were higher (indicative of greater increased risk) while the ORs for tubal ligation and incomplete pregnancy were smaller (indicative of greater reduced risk) among study participants

with endometriosis (OR=1.68 for BMI 30+kg/m^2 vs BMI 18.5-24.99 kg/m^2; OR=0.44 for having tubal ligation vs no tubal ligation; OR=0.60 for having 2+ incomplete pregnancies vs no incomplete pregnancies) compared to those without endometriosis (ORs=1.34, 0.65, and 0.94 for BMI 30 kg/m^2, tubal ligation, and 2+ incomplete pregnancies, respectively; Supplemental Table 3-15); however, that could be due to the small sample size of participants with endometriosis. Overall, considering our knowledge of ovarian cancer biology, none of the potential interactions among pre-menopausal women were supported by an underlying biologic mechanism.

Among post-menopausal participants, based on the likelihood ratio test assessment, five pairwise interactions were statistically significant (Supplemental Table 3-17), including: *age at menarche-endometriosis* (p=0.037), *age at menarche-PRS* (p=0.027); *BMI-breastfeeding* (p=0.019), *MHT use-parity* (p=0.038), and *COC use duration-tubal ligation* (p=0.004); and there was one possible pairwise interaction: *breastfeeding-age at last pregnancy* (p=0.064). However, there were no patterns of the ORs for one factor across the categories of the other factor in each pair of interaction (ORs for age at menarche across the categories of endometriosis: Supplemental Table 3-30; ORs for age at menarche across the categories of the PRS: Supplemental Table 3-31; ORs for BMI across the categories of breastfeeding: Supplemental Table 3-22; ORs for MHT use across the categories of parity: Supplemental Table 3-21; ORs for COC use across the categories of tubal ligation: Supplemental Table 3-25).

Among post-menopausal participants, no other pairwise interactions were statistically significant based on the likelihood ratio test assessment (p>0.05; Supplemental Table 3-17), but there were patterns of the ORs for some risk factors across the levels of family history of ovarian cancer (including age at last pregnancy, age at menarche, COC use duration, DMPA use, ET use,

and endometriosis- Supplemental Table 3-29) or across the levels of endometriosis (including BMI, age at last pregnancy, incomplete pregnancy, and DMPA use- Supplemental Table 3-30). However, these differences could be due to small sample sizes of participants with a family history of ovarian cancer or a personal history of endometriosis. None of the potential interactions among post-menopausal women were supported by an underlying biologic mechanism.

Ovarian cancer risk estimates in the training set

Although some pairwise interactions among the risk factors were suggested by one or two of the methods (i.e., likelihood ratio test, qualitatively comparing the ORs, and biological plausibility), we found no convincing pairwise interactions using all three methods (see the above section). Therefore, we did not include any pairwise interactions to risk stratification modeling. To measure individual risk factor-ovarian cancer associations, we used data from the training set (6,388 cases and 9,808 controls). Table 3-4 demonstrates that the use of age <50/50+ approximates the risk estimates for pre-menopausal and post-menopausal participants, respectively, justifying our use of age <50/50+ as proxies for menopausal status.

Absolute risk estimation and risk factor profiles in the test set

The average risk of developing invasive epithelial ovarian cancer by age 50 among non-Hispanic White women in SEER13 1992-2010 was 0.15% (Supplemental Table 3-33). We observed 625 risk profiles of the 13 risk factors (MHT use and age at menopausal were not included for this age group) among 652 non-Hispanic White controls aged <50 from the US study sites in the test set. The risk by age 50 calculated by our newly developed model ranged from 0.02%-0.99% (Figure 3-1 & Supplemental Table 3-33) based on the risk profiles. Among

this age group, there were 24 profiles with a risk at least three times higher than the population average risk (0.46-0.99%; Table 3-5). Only 25% of the 24 risk profiles (n=6) included a positive family history of ovarian cancer, while 50% of the profiles (n=12) had a PRS higher than the median. As expected, the factors associated with strong risk reductions, such as use of exogenous hormones (COCs or DMPA) and pregnancies, were uncommon in the high-risk groups (Table 3-5).

The average risk of developing invasive epithelial ovarian cancer between ages 50-84 among non-Hispanic White women in SEER13 1992-2010 was 0.98% (Supplemental Table 3-33). We observed 1,130 risk profiles of the 15 risk factors among 1,134 non-Hispanic White controls aged 50+ from the US study sites in the test set. The risk between ages 50-84 in our newly developed model ranged from 0.17%-4.10% (Figure 3-2 & Supplemental Table 3-33). Among this group, eight profiles had a risk at least three times higher than the population average risk of 0.98% (range 2.96%-4.10%; Table 3-6). Four of the high-risk profiles (50%) included a family history of ovarian cancer, and all eight had a PRS higher than the median. Again, the protective hormonal exposures were uncommon in the higher risk groups. Five of the eight profiles (63%) included having age at menopause at or after 55 (Table 3-6).

The ranges of the risks calculated for control women of other racial/ethnic groups or other countries are presented in Supplemental Table 3-33.

Comparison of our 15-variable risk stratification model to the nine-variable reduced model

Among the observed profiles in the test set, the ranges of the risk estimates using the reduced model (including eight environmental factors and the PRS) were narrower than the risk estimated by our 15-factor model. For non-Hispanic White controls in the US sites test set, the

ranges of the risk by age 50 were 0.02%-0.99% and 0.03%-0.79% using the 15-factor model and the reduced model, respectively (Supplemental Table 3-33 & Figure 3-1). The ranges for risk between ages 50-84 were 0.17%-4.10% and 0.20%-3.29%, respectively, for our 15-factor model and the reduced model (Supplemental Table 3-33 & Figure 3-2). The controls with very high risk estimated by the 15-factor model were generally predicted to have modest risk using the reduced model (Tables 3-5 and 3-6).

Since our full 15-factor model has six additional factors compared to the reduced model (risk factor: age at menopause; preventive factors: age at menarche, breastfeeding, incomplete pregnancy, age at last pregnancy, and DMPA use), our full 15-factor model more finely stratifies at-risk individuals. Figure 3-3 presents the range of the risk predicted by our 15-factor model for each of 10,240 possible profiles of the nine-factor reduced model for individuals aged <50. Our 15-factor model shows a wide variation (heterogeneity) in risk for those with a given risk profile and level of risk according to the reduced model. Our 15-factor model stratifies each profile of the reduced model into up to 288 finer profiles. Similarly, Figure 3-4 presents the range of risk predicted by our 15-factor model for each of 40,960 possible profiles of the nine factors in the reduced model for individuals aged 50+. Our 15-factor model stratifies each profile of the nine factors used in the reduced model into up to 1,152 finer profiles.

Figure 3-5 presents an example of a possible profile that was not observed in our test set (i.e., non-Hispanic White women in the US with BMI >30 kg/m^2, height of 170-174 cm, no tubal ligation, one parity, no COC use, no MHT use, a family history of ovarian cancer, no personal history of endometriosis and PRS in the 4^{th} quartile). The risk of developing ovarian cancer between ages of 50-84 estimated by the nine-factor reduced model for this profile is 4.00%.

However, with the six additional factors, our 15-factor model further stratifies this reduced model risk profile into 1,152 finer profiles with risk estimates ranging from 1.63-6.20%, of which 25 have risk estimated at 5% or higher (Figure 3-5). For example, a finer profile including age at menarche ≥15, no breastfeeding, no incomplete pregnancy, age at last pregnancy <25, age at menopause ≥55 and never use DMPA had a risk of 6.20%.

Our 15-factor model showed similar AUCs to the nine-factor reduced model, both among participants aged <50 (AUC=0.72, 95% CI 0.69-0.74, and AUC=0.71, 95% CI 0.68-0.74, respectively) and participants 50-84 (AUC=0.64, 95% CI 0.62-0.66, and AUC=0.64, 95% CI 0.61-0.66, respectively). The Brier scores for accuracy were the same for both the full and reduced models (Brier scores=0.20 among participants <50 and 0.23 among participants 50+). However, our 15-factor model showed better calibration compared to the reduced model. Hosmer-Lemeshow goodness of fit for our 15-factor model was not statistically significant (p=0.12 and 0.30 among participants aged <50 and 50-84, respectively), indicating that the observed and predicted risks were similar. In contrast, Hosmer-Lemeshow goodness of fit for the reduced model was statistically significant (p=0.011 and p<0.001 among participants aged <50 and 50-84, respectively).

Discussion

To our knowledge, this is the first study to comprehensively evaluate the interactions between menopausal status and age with the 15 unequivocal risk/protective factors for ovarian cancer, as well as the pairwise interactions between these factors. Using three methods of assessing interactions (i.e., likelihood ratio tests, comparing ORs, and checking biological plausibility), we found that menopausal status rather than age appeared to modify the

associations between ovarian cancer and first-degree family history of the disease and endometriosis, but that using age as a proxy for menopausal status (<50/50+) was reasonable. We found no strong evidence of pairwise interactions between the risk factors stratified by menopausal status or age and thus developed a risk stratification model for ovarian cancer stratified by age <50/50+. Our 15-factor model more finely stratifies individuals into risk profiles compared to a reduced model that included the eight environmental risk factors and the PRS used in the online CanRisk tool, which is the only model currently in clinical use by healthcare professionals within the European Economic Area.

Our finding of a stronger association between first-degree family of ovarian cancer and ovarian cancer risk among pre-menopausal women maybe explained via two mechanisms[380]. The first mechanism is through chronic inflammation: during ovulation, reactive oxygen species levels increase, which can cause DNA damage in the fallopian tube epithelium and possibly contribute to the mutations in the tumor suppressor *p53* (*TP53*)[380]; *TP53* mutations are likely required for the early pathogenesis of high-grade serous cancer[381]. Among *BRCA* mutation carriers, *BRCA* deficient cells cannot detect DNA damage to repair, thus predisposing the normal fallopian tube to develop lesions[380]. Another possible mechanism is through elevated estrogen levels released to the fallopian tube epithelium during ovulation, which stimulates the expression of many genes promoting cell proliferation, motility/invasion, and apoptosis inhibition, such as *IL6*, TGF-α, *EGF*, *PI3K/Akt*, *IGF-1* and *Bcl-2* [382]. Although endogenous estrogen is not a strong risk factor for ovarian cancer among normal women, its effect may be exacerbated among *BRCA* mutation carriers because (1) DNA repairs by *BRCA* genes are dysfunctional[380], and (2) *BRCA1* expression increases serum estradiol levels by modulating aromatase expression in ovarian granulosa cells and primary preadipocytes[380,383,384]. To our knowledge, our study is the first to

examine the interaction between family history of ovarian cancer and menopausal status. Some previous studies have suggested that the magnitude of the association between family history of ovarian cancer and risk of the disease was greater among women aged <50 compared to those 50+[133,169], which might be a proxy for menopausal status as shown by our finding.

We also observed that having a personal history of endometriosis was associated with a higher risk of ovarian cancer among pre-menopausal individuals compared to post-menopausal individuals. Endometriosis is a chronic inflammatory condition[385], and inflammation plays a role in ovarian cancer tumorigenesis and progression[386]. Ovulation is an inflammatory process, as the luteinizing hormone (LH) surge in the follicle initiates inflammation[387]. Thus, it is plausible that ovulation may enhance the harmful effect of endometriosis on ovarian cancer among pre-menopausal women through an inflammatory mechanism. Endometriosis usually resolves once women go through the menopausal transition[388], which may explain why the effect of endometriosis on ovarian cancer among post-menopausal women is not as strong as among pre-menopausal women.

We did not find strong evidence for pairwise interactions between the risk factors stratified by menopausal status. The literature on this is inconsistent. Some studies found higher BMI to be associated with increased ovarian cancer risk among nulliparous individuals but to have no association among parous individuals[164,165], while others found no evidence for the BMI-parity interaction[166,167]. The Collaborative Group on Epidemiological Studies of Ovarian Cancer found that BMI was associated with an increased risk of ovarian cancer among never users of MHT[166], while Olsen et al. (2013) found that the BMI-ovarian cancer association did not differ by MHT use[28]. Similarly, one study suggested that COC use was associated with a greater

decreased risk among individuals with BMI<24kg/m^2 compared to those with BMI≥24kg/m^2 [167], while others found no convincing evidence for the BMI-COC use interaction[166,168]. The limitations of the previous studies include small numbers of ovarian cancer cases[164,165,167,168] and not stratifying by menopausal status[165-167]. By using a large sample size of ~8,000 cases and ~12,000 controls, assessing the pairwise interactions within menopausal status, and applying three methods of assessing interactions (i.e., likelihood ratio tests, comparing ORs, and biological plausibility), we elucidated the inconsistencies in the literature. Further well-powered studies should examine the interactions within histotype. Evaluating histotype-specific associations was not the focus of this body of work as it is not relevant for risk stratification models.

Our newly developed risk stratification model has the potential to improve CanRisk, which is the only model currently approved for use by healthcare professionals within the European Economic Area[51]; no other models have been approved for clinical use in other parts of the world to our knowledge. With the six additional factors, our model identifies profiles with substantially higher risk than the average population compared to the nine-factor model. Women belonging to such profiles may want to consider having conversations with their doctors to consider the risks/benefits of primary prevention strategies for ovarian cancer.

The strengths of our study include a large sample size, the application of three methods of assessing interactions, and the ability to take a training and test set approach. There are also a few limitations to this study. First, although we have a large sample size, which was enhanced by multiple imputation to address missing data, the sizes of some strata (such as participants with a family history of ovarian cancer, endometriosis, or DMPA use) were still small; thus, the

findings of possible pairwise interactions with these variables should be interpreted with caution. To mitigate this limitation, we applied several methods to assess interactions including carefully reviewing OR patterns across strata and considering biological plausibility. Also, we only included the OCAC study sites that collected data on all risk factors and covariates, which may limit our generalizability. Third, when estimating the absolute risk, we assumed that the control participants from our OCAC study sites represented the countries where they were recruited; only the study in Australia (AUS) recruited controls that were nationally representative. Lastly, the denominators for SEER incidence rate calculations include women who have had an oophorectomy (because they do not know who has had this procedure), making these rates artificially low by including women who are not at risk of developing ovarian cancer. As we used the SEER data to calculate the population average risk, the absolute risks used in our calculations are likely underestimated.

The results from this study build on the understanding of ovarian cancer etiology by finding that menopausal status modifies the associations between some factors and ovarian cancer risk and by elucidating the inconsistencies in the literature on the pairwise interactions between the risk factors. Furthermore, our newly developed model has the potential to be applied in ovarian cancer prevention practice to identify individuals with higher-than-average risk who may be candidates for many primary prevention strategies. Given that our model is multiplicative and some risk factors (e.g. COC use and MHT use) are modifiable, it is straightforward for physicians and women to see how much their risks would be reduced when exposures change. The next step of this scope of work is to validate our risk stratification model in a population external to the OCAC and then to develop a user-friendly online ovarian cancer risk calculator.

Table 3-1: Characteristics of participants included in Aim 1 analysis based on the unimputed dataset

	All		Training set		Test set	
	Cases (N=7984)	Controls (N=12260)	Cases (N=6388)	Controls (N=9808)	Cases (N=1596)	Controls (N=2452)
OCAC study (country)						
AUS (Australia)	1353 (16.9%)	1499 (12.2%)	1039 (16.3%)	1096 (11.2%)	314 (19.7%)	403 (16.4%)
DOV (US)	1090 (13.7%)	1709 (13.9%)	789 (12.4%)	1273 (13.0%)	301 (18.9%)	436 (17.8%)
GER (Germany)	184 (2.3%)	517 (4.2%)	163 (2.6%)	454 (4.6%)	21 (1.3%)	63 (2.6%)
HAW (US)	695 (8.7%)	1088 (8.9%)	626 (9.8%)	1001 (10.2%)	69 (4.3%)	87 (3.5%)
HOP (US)	693 (8.7%)	1720 (14.0%)	491 (7.7%)	1253 (12.8%)	202 (12.7%)	467 (19.0%)
NEC (US)	1470 (18.4%)	2099 (17.1%)	966 (15.1%)	1419 (14.5%)	504 (31.6%)	680 (27.7%)
NJO (US)	222 (2.8%)	444 (3.6%)	222 (3.5%)	363 (3.7%)	0 (0%)	81 (3.3%)
UCI (US)	373 (4.7%)	599 (4.9%)	373 (5.8%)	599 (6.1%)	0 (0%)	0 (0%)
USC (US)	1904 (23.8%)	2585 (21.1%)	1719 (26.9%)	2350 (24.0%)	185 (11.6%)	235 (9.6%)
Age at diagnosis for cases/ reference age for controls						
Mean (SD)	57.3 (11.3)	55.7 (12.3)	58.1 (11.1)	56.4 (12.2)	54.3 (11.4)	53.2 (12.3)
Median [Min, Max]	58.0 [20.0, 84.0]	56.0 [18.0, 84.0]	59.0 [20.0, 84.0]	57.0 [18.0, 84.0]	54.0 [20.0, 84.0]	53.0 [20.0, 84.0]
Menopausal status						
Pre-menopause	2309 (28.9%)	4336 (35.4%)	1609 (25.2%)	3147 (32.1%)	700 (43.9%)	1189 (48.5%)
Post-menoapause	5675 (71.1%)	7924 (64.6%)	4779 (74.8%)	6661 (67.9%)	896 (56.1%)	1263 (51.5%)
Race/ethnicity						
Non-Hispanic White	6573 (82.3%)	10404 (84.9%)	5183 (81.1%)	8179 (83.4%)	1390 (87.1%)	2225 (90.7%)
Hispanic White	372 (4.7%)	464 (3.8%)	323 (5.1%)	410 (4.2%)	49 (3.1%)	54 (2.2%)
Black	180 (2.3%)	238 (1.9%)	160 (2.5%)	206 (2.1%)	20 (1.3%)	32 (1.3%)
Asian	524 (6.6%)	590 (4.8%)	437 (6.8%)	512 (5.2%)	87 (5.5%)	78 (3.2%)
Other	306 (3.8%)	532 (4.3%)	256 (4.0%)	469 (4.8%)	50 (3.1%)	63 (2.6%)
Missing	29 (0.4%)	32 (0.3%)	29 (0.5%)	32 (0.3%)	0 (0.0%)	0 (0.0%)
Education level						
Less than high school	1058 (13.3%)	1083 (8.8%)	859 (13.4%)	908 (9.3%)	199 (12.5%)	175 (7.1%)
High school	1880 (23.5%)	2792 (22.8%)	1479 (23.2%)	2233 (22.8%)	401 (25.1%)	559 (22.8%)
Some college	2325 (29.1%)	3565 (29.1%)	1884 (29.5%)	2846 (29.0%)	441 (27.6%)	719 (29.3%)
College graduate or above	2501 (31.3%)	4474 (36.5%)	1946 (30.5%)	3475 (35.4%)	555 (34.8%)	999 (40.7%)
Missing	220 (2.8%)	346 (2.8%)	220 (3.4%)	346 (3.5%)	0 (0.0%)	0 (0.0%)
Body mass index (BMI)						
<18.5 kg/m2	186 (2.3%)	238 (1.9%)	153 (2.4%)	184 (1.9%)	33 (2.1%)	54 (2.2%)
18.5-24.99 kg/m2	3612 (45.2%)	5877 (47.9%)	2915 (45.6%)	4683 (47.7%)	697 (43.7%)	1194 (48.7%)
25-29.99 kg/m2	2228 (27.9%)	3521 (28.7%)	1770 (27.7%)	2842 (29.0%)	458 (28.7%)	679 (27.7%)
30+ kg/m2	1805 (22.6%)	2535 (20.7%)	1397 (21.9%)	2010 (20.5%)	408 (25.6%)	525 (21.4%)
Missing	153 (1.9%)	89 (0.7%)	153 (2.4%)	89 (0.9%)	0 (0.0%)	0 (0.0%)
Height (m)						
<1.60	2387 (29.9%)	3505 (28.6%)	1944 (30.4%)	2879 (29.4%)	443 (27.8%)	626 (25.5%)
1.60-1.64	2170 (27.2%)	3358 (27.4%)	1748 (27.4%)	2685 (27.4%)	422 (26.4%)	673 (27.4%)

	All		Training set		Test set	
	Cases (N=7984)	Controls (N=12260)	Cases (N=6388)	Controls (N=9808)	Cases (N=1596)	Controls (N=2452)
1.65-1.69	1895 (23.7%)	2998 (24.5%)	1490 (23.3%)	2369 (24.2%)	405 (25.4%)	629 (25.7%)
1.70-1.74	1053 (13.2%)	1657 (13.5%)	832 (13.0%)	1287 (13.1%)	221 (13.8%)	370 (15.1%)
1.75+	431 (5.4%)	684 (5.6%)	326 (5.1%)	530 (5.4%)	105 (6.6%)	154 (6.3%)
Missing	48 (0.6%)	58 (0.5%)	48 (0.8%)	58 (0.6%)	0 (0.0%)	0 (0.0%)
Age at menarche						
<12 years	1624 (20.3%)	2572 (21.0%)	1271 (19.9%)	2078 (21.2%)	353 (22.1%)	494 (20.1%)
12-14 years	5333 (66.8%)	8052 (65.7%)	4260 (66.7%)	6408 (65.3%)	1073 (67.2%)	1644 (67.0%)
15+ years	961 (12.0%)	1528 (12.5%)	791 (12.4%)	1214 (12.4%)	170 (10.7%)	314 (12.8%)
Missing	66 (0.8%)	108 (0.9%)	66 (1.0%)	108 (1.1%)	0 (0.0%)	0 (0.0%)
Parity						
0	1997 (25.0%)	2010 (16.4%)	1475 (23.1%)	1536 (15.7%)	522 (32.7%)	474 (19.3%)
1	1123 (14.1%)	1662 (13.6%)	871 (13.6%)	1343 (13.7%)	252 (15.8%)	319 (13.0%)
2	2211 (27.7%)	3893 (31.8%)	1803 (28.2%)	3069 (31.3%)	408 (25.6%)	824 (33.6%)
3+	2636 (33.0%)	4666 (38.1%)	2222 (34.8%)	3831 (39.1%)	414 (25.9%)	835 (34.1%)
Missing	17 (0.2%)	29 (0.2%)	17 (0.3%)	29 (0.3%)	0 (0.0%)	0 (0.0%)
Breastfeeding						
Never	4317 (54.1%)	5218 (42.6%)	3410 (53.4%)	4167 (42.5%)	907 (56.8%)	1051 (42.9%)
<12 months	2157 (27.0%)	3721 (30.4%)	1758 (27.5%)	2999 (30.6%)	399 (25.0%)	722 (29.4%)
12-23 months	860 (10.8%)	1599 (13.0%)	692 (10.8%)	1254 (12.8%)	168 (10.5%)	345 (14.1%)
24+ months	549 (6.9%)	1388 (11.3%)	427 (6.7%)	1054 (10.7%)	122 (7.6%)	334 (13.6%)
Missing	101 (1.3%)	334 (2.7%)	101 (1.6%)	334 (3.4%)	0 (0.0%)	0 (0.0%)
Incomplete pregnancy						
0	5296 (66.3%)	7571 (61.8%)	4212 (65.9%)	5983 (61.0%)	1084 (67.9%)	1588 (64.8%)
1	1586 (19.9%)	2698 (22.0%)	1260 (19.7%)	2186 (22.3%)	326 (20.4%)	512 (20.9%)
2+	972 (12.2%)	1806 (14.7%)	786 (12.3%)	1454 (14.8%)	186 (11.7%)	352 (14.4%)
Missing	130 (1.6%)	185 (1.5%)	130 (2.0%)	185 (1.9%)	0 (0.0%)	0 (0.0%)
Age at last pregnancy						
Never pregnant	1509 (18.9%)	1406 (11.5%)	1080 (16.9%)	1046 (10.7%)	429 (26.9%)	360 (14.7%)
<25 years	1109 (13.9%)	1460 (11.9%)	915 (14.3%)	1184 (12.1%)	194 (12.2%)	276 (11.3%)
25-29 years	1957 (24.5%)	3186 (26.0%)	1606 (25.1%)	2620 (26.7%)	351 (22.0%)	566 (23.1%)
30-34 years	1922 (24.1%)	3410 (27.8%)	1555 (24.3%)	2724 (27.8%)	367 (23.0%)	686 (28.0%)
35+ years	1337 (16.7%)	2662 (21.7%)	1082 (16.9%)	2098 (21.4%)	255 (16.0%)	564 (23.0%)
Missing	150 (1.9%)	136 (1.1%)	150 (2.3%)	136 (1.4%)	0 (0.0%)	0 (0.0%)
Tubal ligation						
No	6705 (84.0%)	9221 (75.2%)	5337 (83.5%)	7325 (74.7%)	1368 (85.7%)	1896 (77.3%)
Yes	1231 (15.4%)	2709 (22.1%)	1003 (15.7%)	2153 (22.0%)	228 (14.3%)	556 (22.7%)
Missing	48 (0.6%)	330 (2.7%)	48 (0.8%)	330 (3.4%)	0 (0.0%)	0 (0.0%)
Age at menopause						
Pre-menopause	2309 (28.9%)	4336 (35.4%)	1609 (25.2%)	3147 (32.1%)	700 (43.9%)	1189 (48.5%)
<45 years	458 (5.7%)	646 (5.3%)	342 (5.4%)	487 (5.0%)	116 (7.3%)	159 (6.5%)
45-49 years	1048 (13.1%)	1423 (11.6%)	794 (12.4%)	1074 (11.0%)	254 (15.9%)	349 (14.2%)

	All		Training set		Test set	
	Cases (N=7984)	**Controls (N=12260)**	**Cases (N=6388)**	**Controls (N=9808)**	**Cases (N=1596)**	**Controls (N=2452)**
50-54 years	1553 (19.5%)	2200 (17.9%)	1140 (17.8%)	1644 (16.8%)	413 (25.9%)	556 (22.7%)
55+ years	446 (5.6%)	625 (5.1%)	333 (5.2%)	426 (4.3%)	113 (7.1%)	199 (8.1%)
Missing	2170 (27.2%)	3030 (24.7%)	2170 (34.0%)	3030 (30.9%)	0 (0.0%)	0 (0.0%)
COC use duration						
<1 year	4396 (55.1%)	5040 (41.1%)	3561 (55.7%)	4178 (42.6%)	835 (52.3%)	862 (35.2%)
1-4.99 years	1737 (21.8%)	2943 (24.0%)	1361 (21.3%)	2318 (23.6%)	376 (23.6%)	625 (25.5%)
5-9.99 years	1019 (12.8%)	2110 (17.2%)	802 (12.6%)	1624 (16.6%)	217 (13.6%)	486 (19.8%)
10+ years	784 (9.8%)	2107 (17.2%)	616 (9.6%)	1628 (16.6%)	168 (10.5%)	479 (19.5%)
Missing	48 (0.6%)	60 (0.5%)	48 (0.8%)	60 (0.6%)	0 (0.0%)	0 (0.0%)
DMPA use						
No	6976 (87.4%)	10628 (86.7%)	5403 (84.6%)	8230 (83.9%)	1573 (98.6%)	2398 (97.8%)
Yes	90 (1.1%)	228 (1.9%)	67 (1.0%)	174 (1.8%)	23 (1.4%)	54 (2.2%)
Missing	918 (11.5%)	1404 (11.5%)	918 (14.4%)	1404 (14.3%)	0 (0.0%)	0 (0.0%)
MHT use						
Never use	5530 (69.3%)	8701 (71.0%)	4188 (65.6%)	6687 (68.2%)	1342 (84.1%)	2014 (82.1%)
ET only	891 (11.2%)	1046 (8.5%)	854 (13.4%)	999 (10.2%)	37 (2.3%)	47 (1.9%)
EPT only	1079 (13.5%)	1874 (15.3%)	903 (14.1%)	1557 (15.9%)	176 (11.0%)	317 (12.9%)
Others	287 (3.6%)	475 (3.9%)	246 (3.9%)	401 (4.1%)	41 (2.6%)	74 (3.0%)
Missing	197 (2.5%)	164 (1.3%)	197 (3.1%)	164 (1.7%)	0 (0.0%)	0 (0.0%)
Family history of ovarian cancer						
No	5846 (73.2%)	9313 (76.0%)	4351 (68.1%)	6942 (70.8%)	1495 (93.7%)	2371 (96.7%)
Yes	403 (5.0%)	311 (2.5%)	302 (4.7%)	230 (2.3%)	101 (6.3%)	81 (3.3%)
Missing	1735 (21.7%)	2636 (21.5%)	1735 (27.2%)	2636 (26.9%)	0 (0.0%)	0 (0.0%)
Endometriosis						
No	7141 (89.4%)	11372 (92.8%)	5680 (88.9%)	9048 (92.3%)	1461 (91.5%)	2324 (94.8%)
Yes	786 (9.8%)	822 (6.7%)	651 (10.2%)	694 (7.1%)	135 (8.5%)	128 (5.2%)
Missing	57 (0.7%)	66 (0.5%)	57 (0.9%)	66 (0.7%)	0 (0.0%)	0 (0.0%)
Polygenic risk score (PRS) quartile						
1st	1088 (13.6%)	2269 (18.5%)	811 (12.7%)	1680 (17.1%)	277 (17.4%)	589 (24.0%)
2nd	1272 (15.9%)	2268 (18.5%)	921 (14.4%)	1633 (16.6%)	351 (22.0%)	635 (25.9%)
3rd	1506 (18.9%)	2268 (18.5%)	1071 (16.8%)	1647 (16.8%)	435 (27.3%)	621 (25.3%)
4th	1975 (24.7%)	2269 (18.5%)	1442 (22.6%)	1662 (16.9%)	533 (33.4%)	607 (24.8%)
Missing	2143 (26.8%)	3186 (26.0%)	2143 (33.5%)	3186 (32.5%)	0 (0.0%)	0 (0.0%)

Abbreviation: BMI, body mass index; COC, combined oral contraceptive; DMPA, depot medroxyprogesterone acetate; EPT: estrogen plus progestin therapy; ET: estrogen therapy; OCAC: the Ovarian Cancer Association Consortium; MHT: menopausal hormone therapy; PRS, polygenic risk score; SD: standard deviation.

Table 3-2: Associations between risk factors and ovarian cancer risk by menopausal status and age group

A. Comparing pre- and post-menopausal women within the same age group 45-54

Risk factors	Pre-menopausal women aged 45-54			Post-menopausal women aged 45-54		
	Cases (N=1269)*	Controls (N=2109)*	OR** (95% CI)	Cases (N=903)*	Controls (N=1214)*	OR** (95% CI)
Body mass index (BMI)						
<18.5 kg/m2	24	37	1.23 (0.70-2.16)	19	16	1.63 (0.78-3.40)
18.5-24.99 kg/m2	590	1107	1.0	426	602	1.0
25-29.99 kg/m2	319	530	1.13 (0.94-1.37)	219	329	0.91 (0.73-1.15)
30+ kg/m2	321	428	1.35 (1.11-1.65)	225	261	1.27 (1.00-1.62)
Height (m)						
<1.60	349	518	1.0	252	332	1.0
1.60-1.64	345	603	0.92 (0.74-1.13)	233	314	1.06 (0.82-1.37)
1.65-1.69	320	512	1.06 (0.85-1.32)	219	316	1.03 (0.79-1.35)
1.70-1.74	169	340	0.80 (0.62-1.04)	138	173	1.19 (0.87-1.63)
1.75+	80	133	0.85 (0.60-1.21)	54	77	1.04 (0.68-1.59)
Age at menarche						
<12 years	274	414	0.98 (0.81-1.19)	208	290	0.88 (0.70-1.10)
12-14 years	858	1413	1.0	600	786	1.0
15+ years	129	275	0.76 (0.59-0.97)	91	133	0.87 (0.64-1.19)
Parity						
0	414	365	1.0	279	223	1.0
1	208	343	0.80 (0.59-1.09)	174	191	1.02 (0.72-1.43)
2	380	741	0.74 (0.55-0.99)	259	437	0.70 (0.51-0.98)
3+	265	660	0.61 (0.44-0.85)	191	363	0.59 (0.41-0.86)
Breastfeeding						
Never	693	763	1.0	519	515	1.0
<12 months	327	595	0.78 (0.62-0.98)	224	383	0.71 (0.55-0.92)
12-23 months	141	348	0.64 (0.48-0.84)	86	162	0.69 (0.49-0.97)
24+ months	99	358	0.42 (0.31-0.57)	71	130	0.70 (0.48-1.03)
Incomplete pregnancy						
0	805	1161	1.0	556	699	1.0
1	264	518	0.94 (0.78-1.14)	192	291	1.02 (0.80-1.28)
2+	171	400	0.78 (0.62-0.99)	143	209	0.94 (0.72-1.24)
Age at last pregnancy						
<25 years or never pregnant	456	426	1.0	345	328	1.0
25-29 years	262	432	0.95 (0.73-1.25)	205	300	0.91 (0.68-1.22)
30-34 years	306	588	0.95 (0.72-1.24)	204	314	0.90 (0.67-1.22)
35+ years	220	641	0.69 (0.52-0.92)	136	263	0.72 (0.51-1.00)
Tubal ligation						

Risk factors	Pre-menopausal women aged 45-54			Post-menopausal women aged 45-54		
	Cases (N=1269)*	Controls (N=2109)*	OR** (95% CI)	Cases (N=903)*	Controls (N=1214)*	OR** (95% CI)
No	1050	1526	1.0	750	862	1.0
Yes	213	534	0.68 (0.56-0.84)	152	320	0.68 (0.53-0.86)
COC use duration						
<1 year	560	606	1.0	396	336	1.0
1-4.99 years	364	585	0.73 (0.61-0.89)	263	374	0.66 (0.52-0.83)
5-9.99 years	198	426	0.50 (0.40-0.63)	135	254	0.50 (0.38-0.66)
10+ years	140	492	0.28 (0.22-0.35)	106	248	0.32 (0.24-0.43)
DMPA use						
No	1109	1793	1.0	777	1000	1.0
Yes	10	52	0.50 (0.26-0.98)	11	24	0.80 (0.38-1.69)
Menopausal hormone therapy (MHT)						
Never use	1269	2109		683	870	1.0
ET only	0	0		52	93	0.85 (0.57-1.26)
EPT only	0	0		125	211	0.77 (0.58-1.01)
Others	0	0		25	25	1.50 (0.84-2.69)
Family history of ovarian cancer						
No	943	1633	1.0	667	915	1.0
Yes	69	48	2.44 (1.59-3.75)	50	39	1.83 (1.15-2.91)
Endometriosis						
No	1128	1981	1.0	761	1077	1.0
Yes	135	123	1.93 (1.46-2.56)	134	132	1.33 (1.00-1.76)

B. Comparing age groups within pre-menopausal women

Risk factors	Pre-menopausal women aged <45			Pre-menopausal women aged 45-54		
	Cases (N=965)*	Controls (N=2111)*	OR** (95% CI)	Cases (N=1269)*	Controls (N=2109)*	OR** (95% CI)
Body mass index (BMI)						
<18.5 kg/m2	44	74	1.29 (0.85-1.97)	24	37	1.23 (0.70-2.16)
18.5-24.99 kg/m2	504	1257	1.0	590	1107	1.0
25-29.99 kg/m2	217	465	1.15 (0.93-1.42)	319	530	1.13 (0.94-1.37)
30+ kg/m2	189	288	1.40 (1.10-1.78)	321	428	1.35 (1.11-1.65)
Height (m)						
<1.60	244	526	1.0	349	518	1.0
1.60-1.64	255	529	1.17 (0.93-1.49)	345	603	0.92 (0.74-1.13)
1.65-1.69	242	542	1.12 (0.88-1.43)	320	512	1.06 (0.85-1.32)
1.70-1.74	130	324	0.99 (0.75-1.32)	169	340	0.80 (0.62-1.04)
1.75+	93	170	1.50 (1.08-2.09)	80	133	0.85 (0.60-1.21)
Age at menarche						
<12 years	222	444	1.03 (0.84-1.26)	274	414	0.98 (0.81-1.19)
12-14 years	655	1423	1.0	858	1413	1.0
15+ years	84	218	0.84 (0.62-1.13)	129	275	0.76 (0.59-0.97)

Risk factors	Pre-menopausal women aged <45			Pre-menopausal women aged 45-54		
	Cases (N=965)*	Controls (N=2111)*	OR** (95% CI)	Cases (N=1269)*	Controls (N=2109)*	OR** (95% CI)
Parity						
0	471	579	1.0	414	365	1.0
1	166	389	0.61 (0.44-0.85)	208	343	0.80 (0.59-1.09)
2	220	681	0.48 (0.34-0.68)	380	741	0.74 (0.55-0.99)
3+	108	445	0.42 (0.27-0.63)	265	660	0.61 (0.44-0.85)
Breastfeeding						
Never	600	868	1.0	693	763	1.0
<12 months	209	592	0.96 (0.72-1.27)	327	595	0.78 (0.62-0.98)
12-23 months	94	289	0.93 (0.66-1.32)	141	348	0.64 (0.48-0.84)
24+ months	53	290	0.51 (0.34-0.76)	99	358	0.42 (0.31-0.57)
Incomplete pregnancy						
0	609	1248	1.0	805	1161	1.0
1	210	462	1.17 (0.94-1.45)	264	518	0.94 (0.78-1.14)
2+	137	353	1.04 (0.81-1.34)	171	400	0.78 (0.62-0.99)
Age at last pregnancy						
<25 years or never pregnant	483	649	1.0	456	426	1.0
25-29 years	148	436	0.76 (0.56-1.02)	262	432	0.95 (0.73-1.25)
30-34 years	190	599	0.86 (0.63-1.15)	306	588	0.95 (0.72-1.24)
35+ years	126	388	0.73 (0.52-1.04)	220	641	0.69 (0.52-0.92)
Tubal ligation						
No	885	1762	1.0	1050	1526	1.0
Yes	74	282	0.54 (0.39-0.74)	213	534	0.68 (0.56-0.84)
COC use duration						
<1 year	431	552	1.0	560	606	1.0
1-4.99 years	262	578	0.62 (0.50-0.76)	364	585	0.73 (0.61-0.89)
5-9.99 years	156	493	0.47 (0.37-0.60)	198	426	0.50 (0.40-0.63)
10+ years	116	467	0.33 (0.26-0.44)	140	492	0.28 (0.22-0.35)
DMPA use						
No	872	1797	1.0	1109	1793	1.0
Yes	41	119	0.82 (0.54-1.24)	10	52	0.50 (0.26-0.98)
Family history of ovarian cancer						
No	714	1581	1.0	943	1633	1.0
Yes	53	36	2.89 (1.77-4.73)	69	48	2.44 (1.59-3.75)
Endometriosis						
No	841	1954	1.0	1128	1981	1.0
Yes	120	136	1.89 (1.42-2.52)	135	123	1.93 (1.46-2.56)

C. Comparing age groups within post-menopausal women

Risk factors	Post-menopausal women aged 45-54			Post-menopausal women aged 55-64			Post-menopausal women aged 65-84		
	Cases (N=903)*	Controls (N=1214)*	OR** (95% CI)	Cases (N=2493)*	Controls (N=3502)*	OR** (95% CI)	Cases (N=2226)*	Controls (N=3148)*	OR** (95% CI)
Body mass index (BMI)									
<18.5 kg/m2	19	16	1.63 (0.78-3.40)	47	47	1.24 (0.81-1.89)	48	61	1.02 (0.68-1.52)
18.5-24.99 kg/m2	426	602	1.0	1034	1463	1.0	1000	1377	1.0
25-29.99 kg/m2	219	329	0.91 (0.73-1.15)	756	1101	0.96 (0.85-1.09)	685	1036	0.91 (0.79-1.04)
30+ kg/m2	225	261	1.27 (1.00-1.62)	612	866	0.98 (0.85-1.13)	424	650	0.91 (0.78-1.07)
Height (m)									
<1.60	252	332	1.0	694	930	1.0	816	1161	1.0
1.60-1.64	233	314	1.06 (0.82-1.37)	699	999	0.99 (0.85-1.14)	605	859	1.01 (0.87-1.17)
1.65-1.69	219	316	1.03 (0.79-1.35)	597	888	0.96 (0.83-1.12)	487	688	1.08 (0.92-1.26)
1.70-1.74	138	173	1.19 (0.87-1.63)	358	479	1.13 (0.94-1.36)	232	316	1.08 (0.87-1.32)
1.75+	54	77	1.04 (0.68-1.59)	129	189	0.97 (0.74-1.25)	68	108	0.96 (0.68-1.34)
Age at menarche									
<12 years	208	290	0.88 (0.70-1.10)	517	817	0.84 (0.74-0.96)	379	574	0.94 (0.81-1.10)
12-14 years	600	786	1.0	1646	2239	1.0	1487	2068	1.0
15+ years	91	133	0.87 (0.64-1.19)	305	413	0.99 (0.84-1.18)	335	470	0.97 (0.82-1.15)
Parity									
0	279	223	1.0	481	500	1.0	311	311	1.0
1	174	191	1.02 (0.72-1.43)	348	438	1.10 (0.88-1.37)	209	279	0.90 (0.68-1.19)
2	259	437	0.70 (0.51-0.98)	745	1213	0.91 (0.74-1.12)	560	750	0.90 (0.70-1.16)
3+	191	363	0.59 (0.41-0.86)	911	1344	0.91 (0.73-1.14)	1139	1803	0.78 (0.60-1.02)
Breastfeeding									
Never	519	515	1.0	1343	1589	1.0	1095	1409	1.0
<12 months	224	383	0.71 (0.55-0.92)	708	1100	0.78 (0.68-0.90)	653	996	0.88 (0.76-1.02)
12-23 months	86	162	0.69 (0.49-0.97)	255	423	0.72 (0.59-0.88)	268	350	0.97 (0.79-1.18)
24+ months	71	130	0.70 (0.48-1.03)	153	296	0.61 (0.49-0.78)	165	295	0.67 (0.53-0.85)
Incomplete pregnancy									
0	556	699	1.0	1672	2240	1.0	1575	2112	1.0
1	192	291	1.02 (0.80-1.28)	490	754	0.91 (0.80-1.05)	399	642	0.93 (0.80-1.07)
2+	143	209	0.94 (0.72-1.24)	293	453	0.87 (0.74-1.04)	210	360	0.87 (0.72-1.05)
Age at last pregnancy									
<25 years or never pregnant	345	328	1.0	779	852	1.0	508	555	1.0
25-29 years	205	300	0.91 (0.68-1.22)	700	1103	0.81 (0.68-0.96)	606	864	0.90 (0.72-1.12)
30-34 years	204	314	0.90 (0.67-1.22)	580	903	0.85 (0.71-1.02)	617	964	0.88 (0.71-1.11)
35+ years	136	263	0.72 (0.51-1.00)	393	610	0.94 (0.77-1.16)	442	734	0.84 (0.66-1.07)
Tubal ligation									
No	750	862	1.0	1944	2391	1.0	1972	2560	1.0

Risk factors	Post-menopausal women aged 45-54			Post-menopausal women aged 55-64			Post-menopausal women aged 65-84		
	Cases (N=903)*	Controls (N=1214)*	OR** (95% CI)	Cases (N=2493)*	Controls (N=3502)*	OR** (95% CI)	Cases (N=2226)*	Controls (N=3148)*	OR** (95% CI)
Yes	152	320	0.68 (0.53-0.86)	531	1018	0.70 (0.61-0.80)	237	499	0.70 (0.58-0.83)
COC use duration									
<1 year	396	336	1.0	1233	1320	1.0	1720	2163	1.0
1-4.99 years	263	374	0.66 (0.52-0.83)	580	953	0.71 (0.62-0.82)	231	409	0.76 (0.64-0.92)
5-9.99 years	135	254	0.50 (0.38-0.66)	381	638	0.67 (0.57-0.79)	127	262	0.61 (0.48-0.77)
10+ years	106	248	0.32 (0.24-0.43)	286	573	0.48 (0.41-0.58)	124	295	0.48 (0.38-0.61)
DMPA use									
No	777	1000	1.0	2199	3070	1.0	1908	2807	1.0
Yes	11	24	0.80 (0.38-1.69)	19	28	1.15 (0.64-2.07)	6	3	1.86 (0.47-7.47)
Menopausal hormone therapy (MHT)									
Never use	683	870	1.0	1265	1690	1.0	1221	1745	1.0
ET only	52	93	0.85 (0.57-1.26)	375	434	1.19 (1.01-1.41)	464	519	1.31 (1.12-1.53)
EPT only	125	211	0.77 (0.58-1.01)	616	1060	0.82 (0.72-0.94)	338	603	0.87 (0.74-1.03)
Others	25	25	1.50 (0.84-2.69)	141	230	0.89 (0.70-1.12)	121	220	0.81 (0.63-1.03)
Family history of ovarian cancer									
No	667	915	1.0	1863	2770	1.0	1554	2283	1.0
Yes	50	39	1.83 (1.15-2.91)	128	84	2.19 (1.61-2.98)	100	99	1.56 (1.10-2.21)
Endometriosis									
No	761	1077	1.0	2215	3202	1.0	2083	2998	1.0
Yes	134	132	1.33 (1.00-1.76)	262	279	1.32 (1.09-1.59)	120	136	1.20 (0.92-1.56)

* Numbers may not sum to total due to missing values.

**Pooled estimates from logistic regression models in the 50 imputed datasets, regressing on the 13 environmental risk factors, adjusted for age at diagnosis for cases/reference age for controls (<40, every five years to 74, 75-84), race/ethnicity, education level, and OCAC study.

Abbreviation: BMI, body mass index; CI, confidence interval; COC, combined oral contraceptive; DMPA, depot medroxyprogesterone acetate; EPT: estrogen plus progestin therapy; ET: estrogen therapy; OR: odds ratio; MHT: menopausal hormone therapy.

Table 3-3: P-values for pairwise interactions between risk factors and menopausal status and age at diagnosis for cases/reference age for controls

Risk factors	Interaction with menopausal status among women aged 45-54 years	Interaction with age at diagnosis for cases/reference age for controls among pre-menopausal women	Interaction with age at diagnosis for cases/reference age for controls among post-menopausal women
BMI	0.36	0.95	0.45
Height	0.37	0.19	0.97
Age at menarche	0.37	0.84	0.67
Parity	0.42	0.27	0.010
Breastfeeding	0.044	0.86	0.11
Incomplete pregnancy	0.20	0.12	1.00
Age at last pregnancy	0.28	0.17	0.35
Tubal ligation	0.54	0.14	0.45
COC use duration	0.60	0.28	0.14
DMPA use	0.35	0.17	0.42
MHT use			0.058
Family history of ovarian cancer	0.38	0.62	0.30
Endometriosis	0.044	0.89	0.88

p-value from likelihood ratio tests in the 50 imputed datasets

All models adjusted for age at diagnosis for cases/reference age for controls (<40, every five years to 74, 75-84), race/ethnicity, education level, and OCAC study.

Abbreviation: BMI, body mass index; COC, combined oral contraceptive; DMPA, depot medroxyprogesterone acetate; EPT: estrogen plus progestin therapy; ET: estrogen therapy; MHT: menopausal hormone therapy.

Table 3-4: Associations between risk factors and ovarian cancer risk by menopausal status and by age <50 versus 50+ years in the training set of Aim 1

A. Among pre-menopausal women and women aged <50

Risk factors	Pre-menopause Cases* (N=1609)	Pre-menopause Controls* (N=3147)	Pre-menopause OR (95% CI)	Age <50 Cases* (N=1404)	Age <50 Controls* (N=2758)	Age <50 OR (95% CI)
BMI (kg/m^2)**						
<18.5	62	77	1.71 (1.18-2.48)	63	76	1.76 (1.21-2.55)
18.5-24.99	792	1735	1.0	699	1584	1.0
25-29.99	377	751	1.06 (0.90-1.25)	314	637	1.14 (0.95-1.36)
30+	352	550	1.26 (1.06-1.51)	302	430	1.46 (1.20-1.78)
Height (m)**						
<1.60	433	821	1.0	378	743	1.0
1.60-1.64	443	837	1.09 (0.91-1.30)	387	699	1.25 (1.03-1.52)
1.65-1.69	386	767	1.11 (0.92-1.34)	318	676	1.12 (0.91-1.37)
1.70-1.74	223	476	0.98 (0.79-1.22)	197	418	1.02 (0.80-1.29)
1.75+	117	223	1.07 (0.80-1.41)	116	200	1.27 (0.95-1.71)
Age at menarche**						
<12 years	345	641	1.02 (0.86-1.20)	311	582	0.97 (0.81-1.16)
12-14 years	1093	2097	1.0	954	1825	1.0
15+ years	159	375	0.80 (0.64-0.99)	129	318	0.78 (0.61-0.99)
Parity**						
0	600	679	1.0	570	627	1.0
1	274	564	0.76 (0.59-0.98)	242	509	0.63 (0.48-0.83)
2	453	1046	0.69 (0.54-0.89)	370	903	0.57 (0.43-0.74)
3+	280	841	0.59 (0.44-0.79)	220	702	0.49 (0.35-0.68)
Breastfeeding**						
Never	918	1203	1.0	820	1077	1.0
<12 months	390	890	0.81 (0.66-0.99)	345	779	0.88 (0.71-1.09)
12-23 months	179	474	0.73 (0.57-0.93)	144	405	0.73 (0.56-0.96)
24+ months	103	462	0.43 (0.32-0.57)	82	387	0.45 (0.32-0.62)
Incomplete pregnancy**						
0	973	1751	1.0	855	1515	1.0
1	366	734	1.11 (0.94-1.31)	314	650	1.01 (0.84-1.21)
2+	232	583	0.88 (0.72-1.07)	213	520	0.86 (0.70-1.06)
Age at last pregnancy**						
<25 years or never pregnant	621	762	1.0	582	729	1.0
25-29 years	303	678	0.82 (0.65-1.03)	248	595	0.91 (0.71-1.16)
30-34 years	380	886	0.90 (0.72-1.14)	330	755	1.09 (0.85-1.39)
35+ years	262	759	0.71 (0.54-0.92)	209	624	0.79 (0.59-1.05)

Risk factors	Pre-menopause Cases* (N=1609)	Controls* (N=3147)	OR (95% CI)	Age <50 Cases* (N=1404)	Controls* (N=2758)	OR (95% CI)
Tubal ligation**						
No	1381	2406	1.0	1224	2132	1.0
Yes	216	625	0.63 (0.52-0.77)	168	517	0.60 (0.48-0.74)
COC use duration**						
<1 year	712	910	1.0	623	784	1.0
1-4.99 years	459	867	0.71 (0.60-0.83)	401	745	0.73 (0.61-0.87)
5-9.99 years	252	657	0.52 (0.43-0.63)	212	583	0.50 (0.40-0.61)
10+ years	178	692	0.30 (0.24-0.37)	163	625	0.31 (0.25-0.39)
DMPA use**						
No	1360	2556	1.0	1204	2217	1.0
Yes	38	128	0.74 (0.49-1.11)	41	122	0.79 (0.53-1.18)
Family history of ovarian cancer**						
No	1068	2151	1.0	917	1865	1.0
Yes	81	53	2.68 (1.76-4.10)	74	47	2.83 (1.81-4.42)
Endometriosis**						
No	1403	2918	1.0	1205	2517	1.0
Yes	196	203	1.95 (1.56-2.45)	189	217	1.68 (1.34-2.11)
PRS quartile****						
1st	216	511	1.0	189	436	1.0
2nd	230	465	1.24 (0.96-1.59)	200	413	1.11 (0.85-1.46)
3rd	251	489	1.35 (1.05-1.73)	200	408	1.21 (0.92-1.60)
4th	286	441	1.68 (1.31-2.16)	227	410	1.38 (1.05-1.80)

B. Among post-menopausal women and women aged 50-84

Risk factors	Post-menopause Cases* (N=4779)	Controls* (N=6661)	OR (95% CI)	Age 50-84 Cases* (N=4984)	Controls* (N=7050)	OR (95% CI)
BMI (kg/m^2)**						
<18.5	91	107	1.07 (0.80-1.44)	90	108	1.07 (0.80-1.44)
18.5-24.99	2123	2948	1.0	2216	3099	1.0
25-29.99	1393	2091	0.92 (0.83-1.00)	1456	2205	0.91 (0.83-0.99)
30+	1045	1460	0.99 (0.90-1.11)	1095	1580	0.97 (0.87-1.07)
Height (m)**						
<1.60	1511	2058	1.0	1566	2136	1.0
1.60-1.64	1305	1848	1.00 (0.90-1.11)	1361	1986	0.96 (0.87-1.07)
1.65-1.69	1104	1602	1.02 (0.91-1.14)	1172	1693	1.02 (0.91-1.13)
1.70-1.74	609	811	1.11 (0.97-1.27)	635	869	1.09 (0.96-1.24)
1.75+	209	307	0.97 (0.80-1.19)	210	330	0.91 (0.75-1.11)
Age at menarche**						
<12 years	926	1437	0.87 (0.79-0.96)	960	1496	0.88 (0.80-0.97)

Risk factors	Post-menopause Cases* (N=4779)	Post-menopause Controls* (N=6661)	Post-menopause OR (95% CI)	Age 50-84 Cases* (N=4984)	Age 50-84 Controls* (N=7050)	Age 50-84 OR (95% CI)
12-14 years	3167	4311	1.0	3306	4583	1.0
15+ years	632	839	1.01 (0.90-1.14)	662	896	1.01 (0.89-1.13)
Parity**						
0	875	857	1.0	905	909	1.0
1	597	779	0.98 (0.82-1.15)	629	834	1.01 (0.86-1.19)
2	1350	2023	0.88 (0.75-1.02)	1433	2166	0.91 (0.78-1.06)
3+	1942	2990	0.81 (0.69-0.96)	2002	3129	0.83 (0.71-0.98)
Breastfeeding**						
Never	2492	2964	1.0	2590	3090	1.0
<12 months	1368	2109	0.82 (0.75-0.91)	1413	2220	0.81 (0.73-0.89)
12-23 months	513	780	0.81 (0.70-0.93)	548	849	0.81 (0.71-0.93)
24+ months	324	592	0.65 (0.55-0.76)	345	667	0.63 (0.53-0.73)
Incomplete pregnancy**						
0	3239	4232	1.0	3357	4468	1.0
1	894	1452	0.87 (0.79-0.96)	946	1536	0.90 (0.81-0.99)
2+	554	871	0.88 (0.78-0.99)	573	934	0.88 (0.78-0.99)
Age at last pregnancy**						
<25 years or never pregnant	1374	1468	1.0	1413	1501	1.0
25-29 years	1303	1942	0.86 (0.75-0.98)	1358	2025	0.83 (0.73-0.95)
30-34 years	1175	1838	0.85 (0.74-0.98)	1225	1969	0.81 (0.71-0.93)
35+ years	820	1339	0.86 (0.74-1.01)	873	1474	0.82 (0.70-0.96)
Tubal ligation**						
No	3956	4919	1.0	4113	5193	1.0
Yes	787	1528	0.71 (0.64-0.78)	835	1636	0.72 (0.65-0.79)
Age at menopause***						
<45 years	296	460	0.87 (0.72-1.05)	251	394	0.87 (0.72-1.06)
45-49 years	753	1048	1.06 (0.93-1.21)	707	995	1.05 (0.92-1.20)
50-54 years	1060	1616	1.0	1060	1616	1.0
55+ years	310	415	1.16 (0.97-1.39)	310	415	1.16 (0.97-1.39)
COC use duration**						
<1 year	2849	3268	1.0	2938	3394	1.0
1-4.99 years	902	1451	0.72 (0.64-0.80)	960	1573	0.71 (0.64-0.79)
5-9.99 years	550	967	0.63 (0.55-0.72)	590	1041	0.63 (0.56-0.72)
10+ years	438	936	0.45 (0.39-0.52)	453	1003	0.44 (0.39-0.50)
DMPA use**						
No	4043	5674	1.0	4199	6013	1.0
Yes	29	46	1.01 (0.62-1.63)	26	52	0.89 (0.55-1.44)
MHT use**						
Never use	2579	3540	1.0	2789	3933	1.0
ET only	854	999	1.23 (1.10-1.38)	854	999	1.22 (1.09-1.36)
EPT only	903	1557	0.85 (0.77-0.95)	903	1557	0.85 (0.77-0.95)

Risk factors	Post-menopause Cases* (N=4779)	Post-menopause Controls* (N=6661)	Post-menopause OR (95% CI)	Age 50-84 Cases* (N=4984)	Age 50-84 Controls* (N=7050)	Age 50-84 OR (95% CI)
Others	246	401	0.90 (0.75-1.08)	246	401	0.90 (0.75-1.07)
Family history of ovarian cancer**						
No	3283	4791	1.0	3434	5077	1.0
Yes	221	177	1.81 (1.39-2.36)	228	183	1.80 (1.39-2.34)
Endometriosis**						
No	4277	6130	1.0	4475	6531	1.0
Yes	455	491	1.26 (1.10-1.45)	462	477	1.36 (1.18-1.56)
PRS quartile****						
1st	595	1169	1.0	622	1244	1.0
2nd	691	1168	1.15 (0.99-1.32)	721	1220	1.17 (1.02-1.35)
3rd	820	1158	1.40 (1.22-1.61)	871	1239	1.43 (1.25-1.64)
4th	1156	1221	1.95 (1.71-2.23)	1215	1252	2.04 (1.79-2.33)

* Numbers may not sum to total due to missing values.

** Pooled estimates from logistic regression models in the 50 imputed datasets, regressing on the 13 environmental risk factors, adjusted for age at diagnosis for cases/reference age for controls (<40, every five years to 74, 75-84), race/ethnicity, education level, and OCAC study.

*** Pooled estimates from logistic regression models in the 50 imputed datasets, regressing on the 13 environmental risk factors and age at menopause among non-hysterectomized post-menopausal women with complete data on age at menopause, adjusted for age at diagnosis for cases/reference age for controls (<40, every five years to 74, 75-84), race/ethnicity, education level, OCAC study, and duration of hormonal therapy use.

**** Pooled estimates from logistic regression models in the 50 imputed datasets, regressing on the 13 environmental risk factors and the PRS among women with complete data on PRS, adjusted for age at diagnosis for cases/reference age for controls (<40, every five years to 74, 75-84), race/ethnicity, education level, OCAC study, and genetic ancestry principal components.

Abbreviation: BMI, body mass index; CI, confidence interval; COC, combined oral contraceptive; DMPA, depot medroxyprogesterone acetate; EPT: estrogen plus progestin therapy; ET: estrogen therapy; OR: odds ratio; MHT: menopausal hormone therapy; PRS: polygenic risk score.

Table 3-5: Risk profiles (combinations of 13 factors) among Non-Hispanic White control women aged <50 in the US sites with calculated risk at three times or higher compared to the population average risk (i.e., 0.15%)

The profiles are ordered by risk.

A. The hormonal factors in the high-risk profiles

Profile number	Age at menarche (years)	Parity	Breastfeeding	Incomplete pregnancy	Age at last pregnancy (years)	COC use duration	DMPA use
1	12-14	0	Never	0	Never pregnant	<1 year	Never
2	<12	0	Never	0	Never pregnant	1-4.99 years	Never
3	12-14	0	Never	0	Never pregnant	<1 year	Never
4	12-14	0	Never	2+	30-34	<1 year	Never
5	<12	1	Never	1	30-34	<1 year	Never
6	<12	0	Never	0	Never pregnant	<1 year	Never
7	12-14	0	Never	0	Never pregnant	<1 year	Never
8	12-14	0	Never	0	Never pregnant	<1 year	Never
9	12-14	0	Never	0	Never pregnant	5-9.99 years	Never
10	12-14	1	<12 months	2+	35+	<1 year	Never
11	<12	0	Never	0	Never pregnant	<1 year	Never
12	<12	0	Never	0	Never pregnant	<1 year	Never
13	12-14	0	Never	0	Never pregnant	<1 year	Never
14	12-14	0	Never	0	Never pregnant	1-4.99 years	Never
15	12-14	2	<12 months	1	30-34	1-4.99 years	Never
16	12-14	0	Never	0	Never pregnant	<1 year	Never
17	15+	0	Never	0	Never pregnant	<1 year	Never
18	<12	0	Never	0	Never pregnant	5-9.99 years	Never
19	12-14	0	Never	0	Never pregnant	<1 year	Never
20	<12	3+	<12 months	2+	30-34	<1 year	Never
21	12-14	0	Never	0	Never pregnant	<1 year	Never
22	12-14	0	Never	0	Never pregnant	1-4.99 years	Never
23	<12	0	Never	0	Never pregnant	<1 year	Never
24	<12	2	12-23 months	0	35+	1-4.99 years	Never

B. Other factors in the high-risk profiles and calculated risks

Profile number	BMI (kg/m^2)	Height (cm)	Tubal ligation	Family history of ovarian cancer	Endometriosis	PRS quartile	Risk calculated by the newly developed model (95% CI)	Risk calculated using a reduced model that included risk factors from CanRisk* (95% CI)
1	25-29.99	160-164	No	No	Yes	4	0.99% (0.64%-1.53%)	0.78% (0.50%-1.21%)
2	30+	<160	No	Yes	No	2	0.97% (0.53%-1.79%)	0.79% (0.43%-1.46%)
3	<18.5	165-169	No	No	No	3	0.71% (0.43%-1.18%)	0.56% (0.34%-0.93%)
4	30+	160-164	No	No	No	4	0.71% (0.43%-1.17%)	0.60% (0.36%-0.99%)
5	18.5-24.99	<160	No	Yes	No	3	0.69% (0.35%-1.36%)	0.51% (0.26%-1.01%)
6	18.5-24.99	160-164	No	No	Yes	1	0.61% (0.43%-0.86%)	0.50% (0.35%-0.70%)
7	30+	160-164	No	No	No	2	0.61% (0.41%-0.89%)	0.48% (0.33%-0.71%)
8	30+	<160	No	No	No	4	0.60% (0.43%-0.84%)	0.48% (0.34%-0.67%)
9	18.5-24.99	170-174	No	Yes	No	4	0.59% (0.32%-1.08%)	0.46% (0.25%-0.85%)
10	30+	165-169	No	Yes	No	2	0.58% (0.27%-1.25%)	0.76% (0.35%-1.65%)
11	<18.5	170-174	No	No	No	2	0.58% (0.33%-0.99%)	0.47% (0.27%-0.81%)
12	30+	165-169	No	No	No	3	0.58% (0.37%-0.89%)	0.47% (0.30%-0.72%)
13	18.5-24.99	<160	No	No	Yes	2	0.56% (0.39%-0.80%)	0.44% (0.31%-0.63%)
14	30+	160-164	No	No	No	4	0.55% (0.36%-0.84%)	0.43% (0.28%-0.66%)
15	25-29.99	170-174	No	Yes	No	4	0.54% (0.25%-1.17%)	0.44% (0.20%-0.96%)
16	25-29.99	165-169	No	No	No	4	0.52% (0.36%-0.77%)	0.42% (0.28%-0.61%)
17	30+	160-164	No	No	No	3	0.52% (0.33%-0.82%)	0.53% (0.33%-0.83%)
18	30+	175+	No	No	Yes	2	0.50% (0.28%-0.88%)	0.41% (0.23%-0.72%)
19	30+	170-174	No	No	No	2	0.49% (0.33%-0.74%)	0.39% (0.26%-0.59%)
20	<18.5	160-164	No	No	Yes	2	0.48% (0.22%-1.04%)	0.48% (0.22%-1.03%)
21	25-29.99	160-164	No	No	No	2	0.47% (0.32%-0.69%)	0.37% (0.26%-0.55%)
22	<18.5	170-174	No	No	No	3	0.47% (0.27%-0.82%)	0.37% (0.22%-0.65%)
23	30+	<160	No	No	No	2	0.47% (0.32%-0.69%)	0.38% (0.26%-0.56%)
24	25-29.99	165-169	No	Yes	Yes	2	0.46% (0.20%-1.06%)	0.66% (0.29%-1.51%)

* Risk predicted with the risk factors used in CanRisk including BMI, height, tubal ligation, parity, COC use duration, family history of ovarian cancer, endometriosis and PRS, with the estimates from our model.

Abbreviation: BMI, body mass index; COC, combined oral contraceptive; CI, confidence interval; DMPA, depot medroxyprogesterone acetate; PRS, polygenic risk score

Table 3-6: Risk profiles (combinations of 15 factors) among Non-Hispanic White control women aged 50-84 in the US sites with calculated risk at three times or higher compared to the population average risk (i.e., 0.98%)

The profiles are ordered by risk.

A. The hormonal factors in the high-risk profiles

Profile number	Age at menarche (years)	Parity	Breastfeeding	Incomplete pregnancy	Age at last pregnancy (years)	Age at menopause (years)	COC use duration	DMPA use	MHT use
1	12-14	1	Never	0	<25	55+	<1 year	Never	Never use
2	12-14	2	12-23 months	0	<25	55+	<1 year	Never	Never use
3	12-14	0	Never	2+	<25	55+	<1 year	Never	Never use
4	12-14	1	Never	0	<25	45-49	<1 year	Never	Never use
5	12-14	2	Never	0	<25	55+	<1 year	Never	Never use
6	12-14	2	Never	0	25-29	<45	<1 year	Never	Never use
7	12-14	0	Never	0	Never pregnant	50-54	<1 year	Never	Estrogen therapy (ET) only
8	12-14	0	Never	0	Never pregnant	55+	<1 year	Never	Never use

B. Other factors in the high-risk profiles and calculated risks

Profile number	BMI (kg/m^2)	Height (cm)	Tubal ligation	Family history of ovarian cancer	Endometriosis	PRS	Risk calculated by the newly developed model (95% CI)	Risk calculated using a reduced model that included risk factors from CanRisk* (95% CI)
1	18.5-24.99	<160	No	Yes	No	3	4.10% (2.81%-5.99%)	2.65% (1.90%-3.71%)
2	25-29.99	165-169	No	Yes	No	4	3.95% (2.60%-6.02%)	3.14% (2.15%-4.60%)
3	25-29.99	170-174	No	No	Yes	4	3.80% (2.73%-5.29%)	2.80% (2.12%-3.70%)
4	18.5-24.99	<160	No	Yes	No	3	3.70% (2.59%-5.31%)	2.65% (1.90%-3.71%)
5	18.5-24.99	170-174	No	No	No	4	3.18% (2.36%-4.30%)	2.06% (1.62%-2.62%)
6	18.5-24.99	160-164	No	Yes	No	4	3.18% (2.10%-4.81%)	3.29% (2.28%-4.74%)
7	25-29.99	165-169	No	No	No	4	3.10% (2.48%-3.88%)	2.34% (1.87%-2.92%)
8	30+	<160	No	No	Yes	3	2.96% (2.23%-3.93%)	1.92% (1.54%-2.39%)

* Risk calculated with the risk factors used in CanRisk including BMI, height, tubal ligation, parity, COC use duration, family history of ovarian cancer, endometriosis and PRS, with the estimates from our model.

Abbreviation: BMI, body mass index; COC, combined oral contraceptive; DMPA, depot medroxyprogesterone acetate; PRS, polygenic risk score; CI, confidence interval

Figure 3-1: Risk of developing ovarian cancer by age 50 among Non-Hispanic White control women in the US sites

The y-axis presents the risk by age 50. The x-axis presents the observed risk profiles (combinations of the 13 risk factors, menopausal hormone therapy use and age at menopause are not relevant in this group). The royal blue dots (appears to be a line) are the risk calculated by our 13-factor model for each observed profile, and the light blue bars are the 95% confidence intervals. The highest observed risk calculated by our 15-factor model was 0.99% (95% CI 0.64%-1.53%). The red dots are the risk calculated by a reduced model that included eight risk factors in CanRisk (except menopausal hormone therapy use). The highest observed risk calculated by the reduced model was 0.79% (95% CI 0.43%-1.46%). The average risk to age 50 is 0.15%.

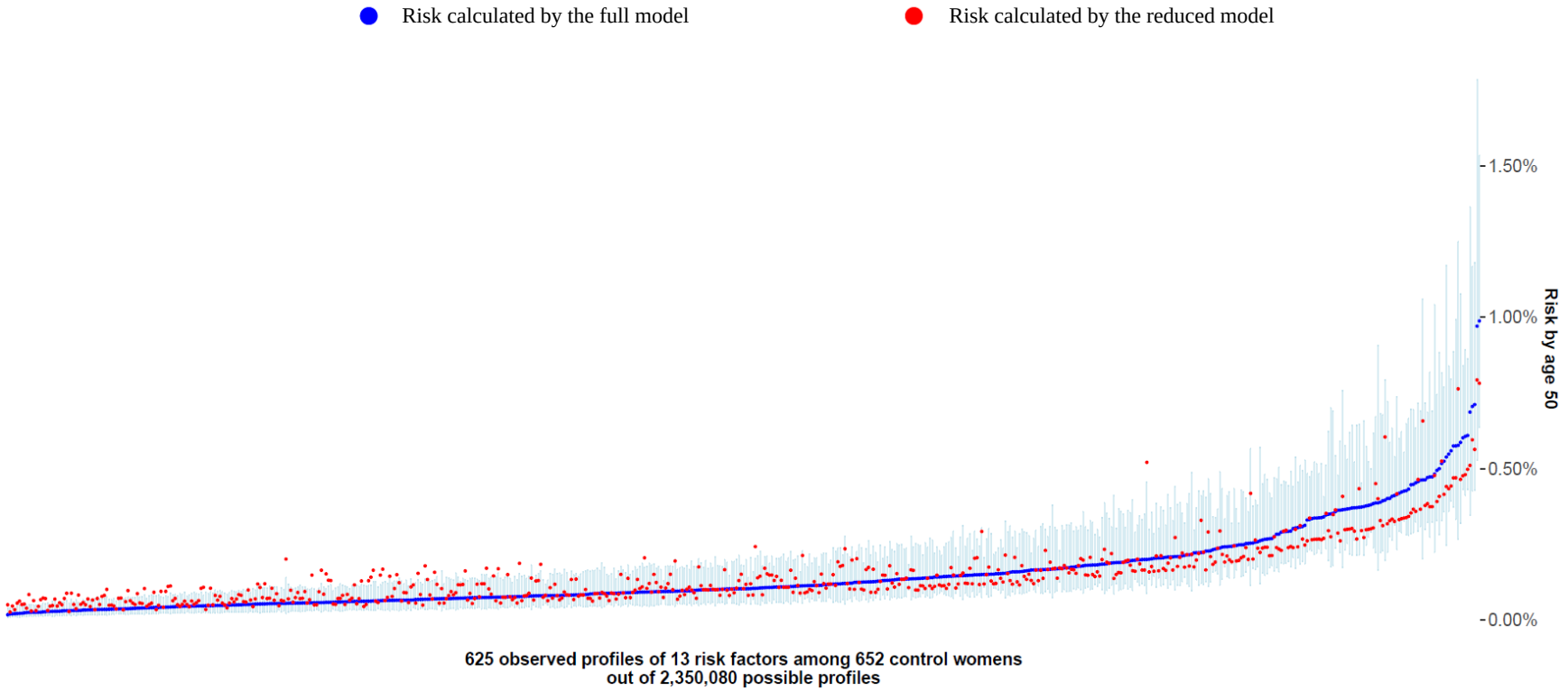


Figure 3-2: Risk of developing ovarian cancer between ages 50-84 among Non-Hispanic White control women in the US sites

The x-axis presents the observed risk profiles (combinations of the 15 risk factors). The y-axis presents the risk between age 50-84. The royal blue dots (appears as a line) are the risk calculated by our 15-factor model for each observed profile, and the light blue bars are 95% confidence intervals. The highest observed risk calculated by our 15-factor model was 4.10% (95% CI 2.81%-5.99%). The red dots are the risk calculated by a reduced model that included nine risk factors in CanRisk. The highest risk calculated by the reduced model was 3.29% (95% CI 2.21%-4.91%). The average risk between ages 50-84 is 0.98%.

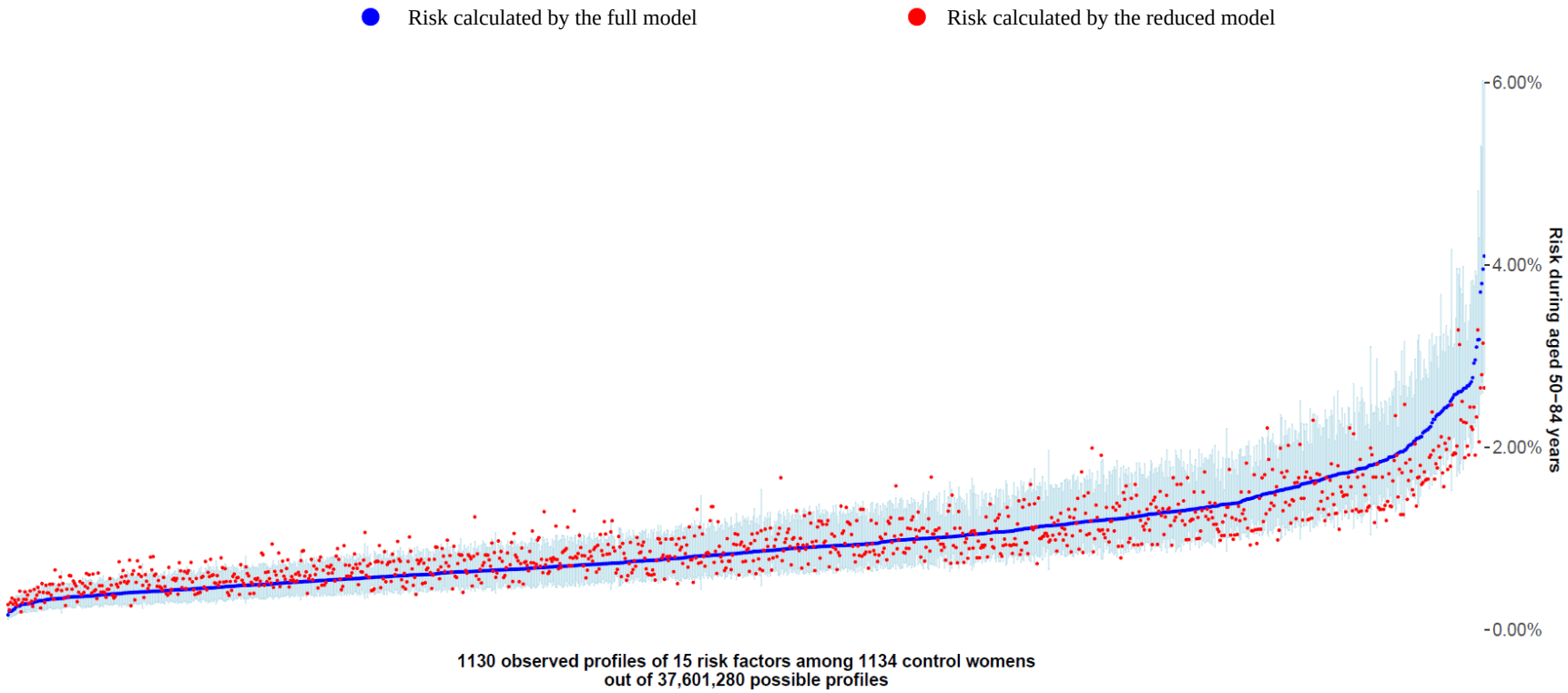


Figure 3-3: 10,240 possible risk profiles of the reduced model for non-Hispanic White women in the US and their risk estimates by age 50

The y-axis presents the risk by age 50. The x-axis presents 10,240 possible risk profiles of the reduced model that included eight factors in CanRisk (except for menopausal hormone therapy use which is not relevant in this group). The red dots (appear to be a line) are the risk calculated by the reduced model. Our 13-factor model can stratify each profile of the reduced model into up to 288 finer profiles. The light blue bars (appear as a region) are the range of the risk estimated by our 13-factor model for each profile of the reduced model.

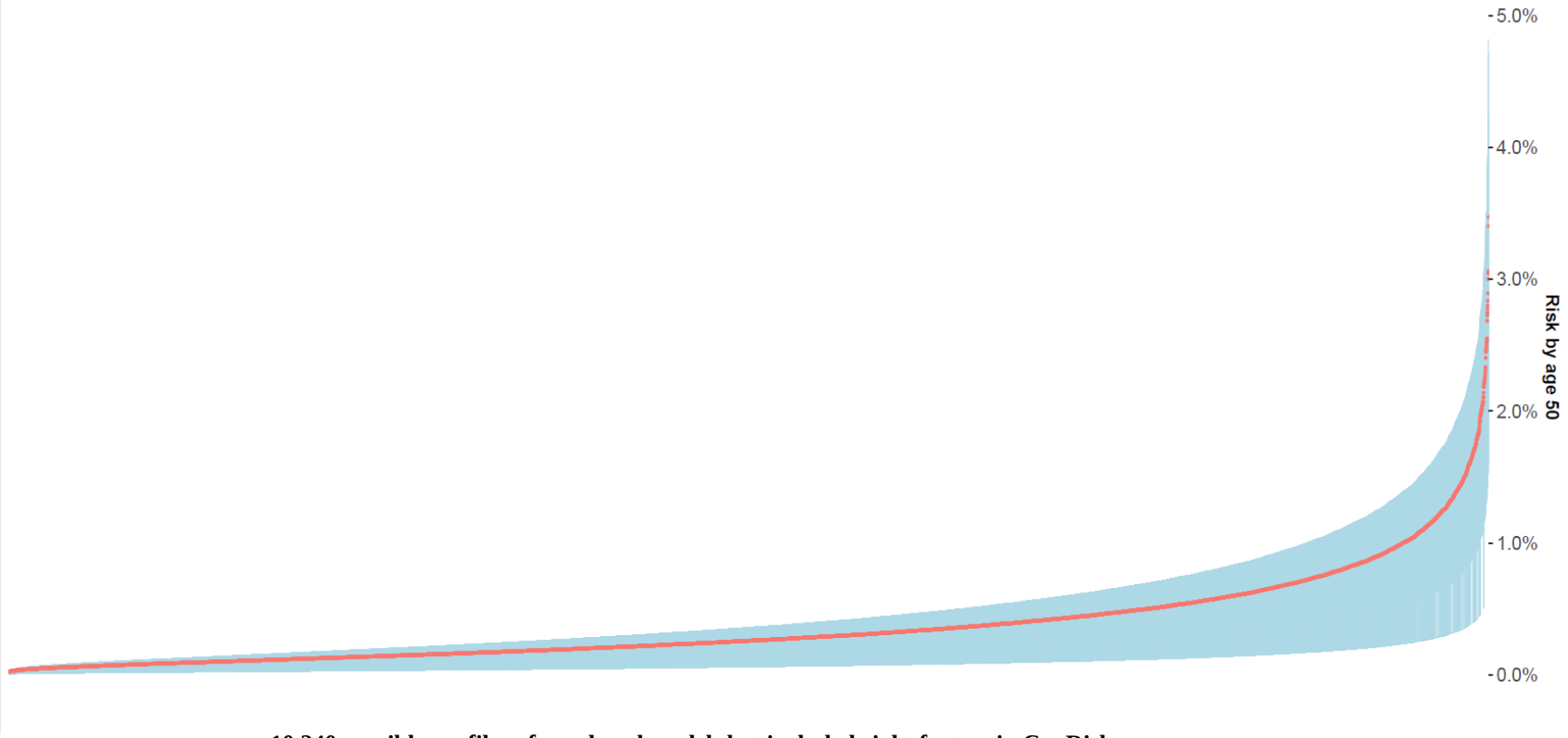


Figure 3-4: 40,960 possible risk profiles of the reduced model for non-Hispanic White women in the US and their risk estimates between ages 50-84

The x-axis presents 40,960 possible risk profiles of the reduced model that included nine factors in CanRisk. The y-axis presents the calculated risk between ages 50-84. The red dots (appear as a line) are the risk calculated by the reduced model. Our 15-factor model can stratify each profile of the reduced model into up to 1,152 finer profiles. The light blue bars (appear as a region) are the range of the risk estimated by our 15-factor model for each profile of the reduced model.

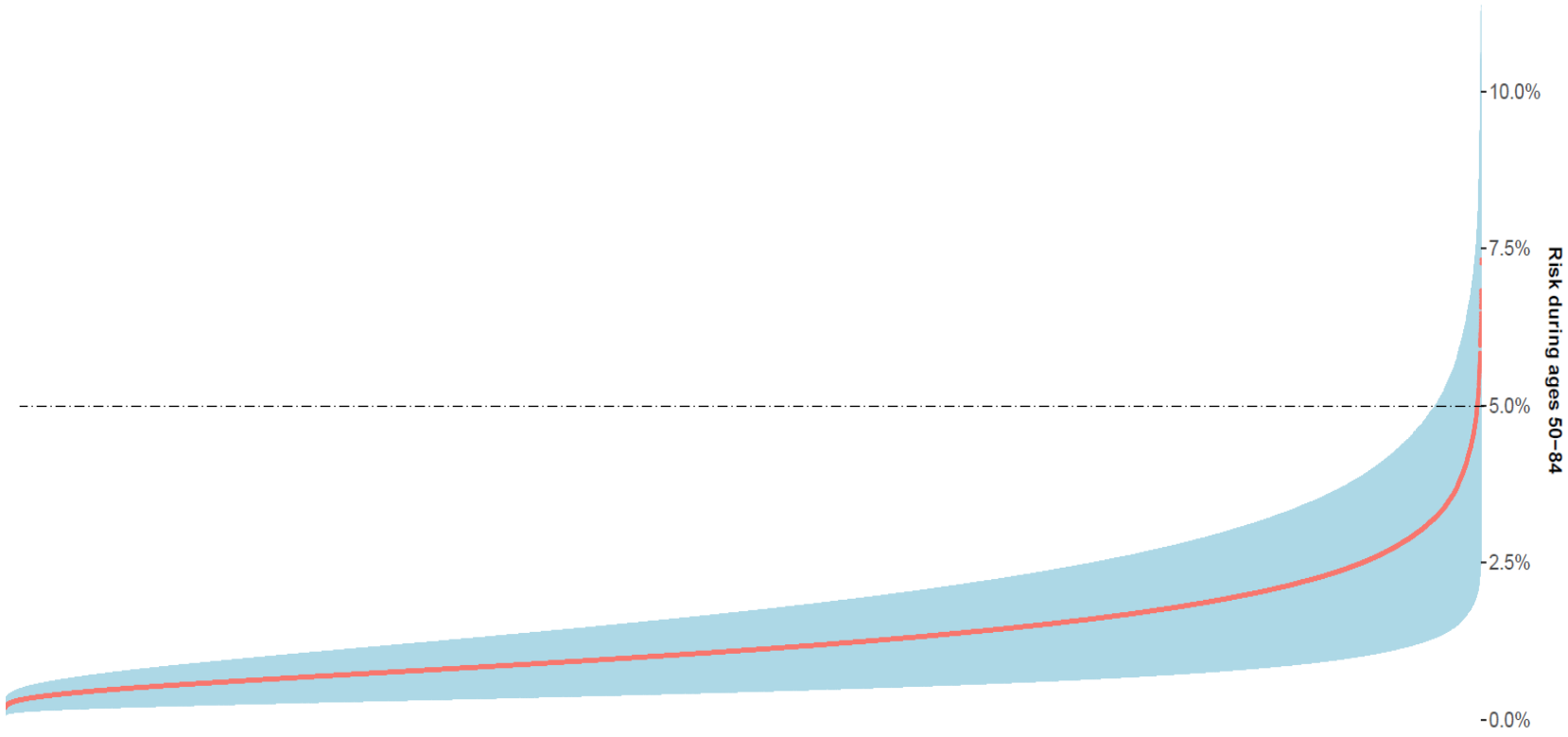
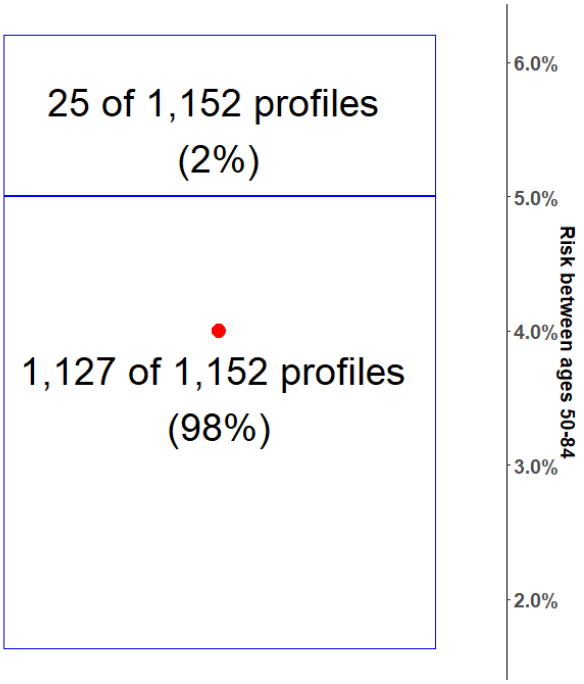


Figure 3-5: An example of a risk profile of the nine-factor reduced model which is further stratified into 1,152 finer profiles by our 15-factor model

This is the example of a profile of non-Hispanic White women in the US with body mass index (BMI) >30 kg/m2, height of 170-174 cm, no tubal ligation, one parity, no combined oral contraceptive (COC) use, no menopausal hormone therapy (MHT) use, a first-degree family history of ovarian cancer, no personal history of endometriosis and the polygenic risk score (PRS) in the 4th quartile. The y-axis presents the risk between ages 50-84. The red dot is the risk calculated by the reduced model that included nine factors used in CanRisk, which is 4.00%. Our 15-factor model stratifies this profile into up to 1,152 finer profiles. The royal blue box represents the range of the risk estimated by our 15-factor model for the 1,152 finer profiles, which is 1.63%-6.20%. The middle horizontal bar at risk of 5% is the threshold which has been showed to be cost-effective for women to consider risk reducing salpingo-oophorectomy (RRSO) for ovarian cancer prevention. Of the 1,152 finer profiles that our 15-factor model stratifies, 25 profiles have a risk at 5% or higher, while 1,127 profiles have a risk lower than 5%.



Supplemental Table 3-1: Characteristics of OCAC studies included in Aim 1 analysis

Study name	Acronym	Time period	Location	Method of data collection
Australian Ovarian Cancer Study	AUS	2001-2005	Australia	Self-completed questionnaire
Disease of the Ovary and Their Evaluation Study	DOV	2002-2009	Washington, US	In-person interview
German Ovarian Cancer Study	GER	1993-1998	Germany	Self-completed questionnaire
Hawaii Ovarian Cancer Study	HAW	1993-2008	Hawaii, US	In-person interview
Hormones and Ovarian Cancer Prediction	HOP	2003-2009	Western Pennsylvania, northeast Ohio, western New York, US	In-person interview
New England Case-Control Study of Ovarian Cancer	NEC	1992-2008	New Hampshire, eastern Massachusetts, US	In-person interview
New Jersey Ovarian Cancer Study	NJO	2002-2009	New Jersey, US	Phone interview
University of California Irvine Ovarian Study	UCI	1994-2005	Southern California, US	Self-completed questionnaire
University of Southern California, Study of Lifestyle and Women's Health	USC	1993-2010	Los Angeles, California, US	In-person interview

Supplemental Table 3-2: Description of the variables included in Aim 1 analysis

Variable	Description	Coding	Percentage of missing
Body mass index (BMI)	Risk factor	<18.5, 18.5-24.99, 25-29.99, 30+ kg/m2	1.2%
Height	Risk factor	<160, 160-164, 165-169, 170-174, 175+ cm	0.5%
Age at menarche	Risk factor	<12, 12-14, 15+ years	0.9%
Parity	Risk factor	0, 1, 2, 3+	0.2%
Breastfeeding	Risk factor	Never breastfed, breastfed 1-11 months, 12-23 months, 24+ months	2.4%
Incomplete pregnancy	Risk factor	0, 1, 2+	1.6%
Age at last pregnancy	Risk factor	<25, 25-29, 30-34, 35+ years	0.7%
Tubal ligation	Risk factor	Yes, no	1.9%
Age at menopause	Risk factor	<45, 45-49, 50-54, 55+ years	38.2%
Combined oral contraceptive (COC) use duration	Risk factor	Never use or used <1 year, 1-4.99, 5-9.99, 10+ years	0.5%
Depot-medroxyprogesterone acetate (DMPA) use	Risk factor	Yes, no	11.5%
Menopausal hormonal therapy (MHT) use	Risk factor	Never use, estrogen therapy (ET) use only, estrogen plus progestin therapy (EPT) use only, other	2.7%
First-degree family history of ovarian cancer	Risk factor	Yes, no	21.6%
Endometriosis	Risk factor	Yes, no	0.6%
Polygenic risk score	Risk factor	Quartile	26.3%
Age at diagnosis for cases/reference age for controls	Covariate	<40, every five years to 74, 75-84	No missing
Menopausal status	Covariate	Pre-menopausal (including peri-menopausal), post-menopausal	No missing
Education level	Covariate	Less than high school, high school, some college, college graduate or above	2.8%
Race/ethnicity	Covariate	Non-Hispanic White, Hispanic White, Black, Asian, other	0.3%
Ovarian Cancer Association Consortium (OCAC) study site	Covariate	9 studies	No missing

Supplemental Table 3-3: P-values for pairwise interactions between risk factors among pre-menopausal women

	BMI	Height	Age at menarche	Parity	Breastfeeding	Incomplete pregnancy	Age at last pregnancy	Tubal ligation	COC use duration	DMPA use	Family history of ovarian	Endometriosis	PRS
BMI		0.26	0.53	0.84	0.72	0.064	0.82	0.87	0.31	0.54	0.53	0.96	0.15
Height			0.38	0.68	0.78	0.14	0.29	0.70	0.75	0.65	0.81	0.24	0.41
Age at menarche				0.10	0.23	0.40	0.61	0.62	0.68	0.54	0.71	0.19	0.21
Parity					0.037*	0.10	0.52	0.061	0.93	0.69	0.024	0.68	0.83
Breastfeeding						0.46	0.58	0.77	0.84	0.59	0.28	0.041	0.92
Incomplete pregnancy							0.98	0.54	0.67	0.16	0.023	0.09	0.40
Age at last pregnancy								0.43	0.46	0.15	0.25	0.14	0.63
Tubal ligation									0.067	0.61	0.31	0.10	0.57
COC use duration										0.63	0.67	0.97	0.52
DMPA use											0.92	0.93	0.60
Family history of ovarian cancer												0.066	0.32
Endometriosis													0.47

p-value from likelihood ratio tests in the 50 imputed datasets

* Interaction among parous women only

Abbreviations: BMI: body mass index, COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; PRS: polygenic risk score.

Supplemental Table 3-4: Associations between risk factors and ovarian cancer risk among pre-menopausal women by strata of BMI

Risk factors	BMI 18.5-24.99 kg/m2			BMI 25-29.99 kg/m2			BMI 30+ kg/m2		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
Height (m)									
<1.60	265	590	1.0	163	257	1.0	146	173	1.0
1.60-1.64	311	602	1.28 (1.02-1.59)	130	290	0.73 (0.53-1.01)	139	210	0.94 (0.67-1.33)
1.65-1.69	281	611	1.21 (0.96-1.52)	132	237	0.89 (0.64-1.23)	121	166	1.04 (0.72-1.50)
1.70-1.74	149	396	0.93 (0.71-1.21)	79	145	0.86 (0.59-1.26)	60	106	0.76 (0.49-1.18)
1.75+	88	165	1.39 (0.99-1.94)	32	66	0.76 (0.45-1.29)	44	61	0.86 (0.52-1.42)
Age at menarche									
<12 years	197	370	1.12 (0.90-1.38)	135	247	0.99 (0.76-1.31)	156	217	0.91 (0.69-1.20)
12-14 years	771	1670	1.0	357	644	1.0	320	441	1.0
15+ years	121	316	0.80 (0.63-1.03)	43	99	0.72 (0.47-1.08)	31	54	0.75 (0.45-1.25)
Parity									
0	447	570	1.0	193	168	1.0	206	157	1.0
1	192	399	0.75 (0.54-1.04)	83	182	0.54 (0.34-0.85)	81	130	0.76 (0.48-1.22)
2	290	820	0.62 (0.45-0.86)	153	348	0.53 (0.34-0.82)	131	219	0.78 (0.49-1.22)
3+	165	575	0.57 (0.39-0.83)	107	297	0.45 (0.27-0.75)	91	209	0.57 (0.34-0.98)
Breastfeeding									
Never	620	910	1.0	304	351	1.0	318	310	1.0
<12 months	272	640	1.01 (0.78-1.31)	138	299	0.81 (0.58-1.14)	108	214	0.60 (0.42-0.88)
12-23 months	121	381	0.82 (0.60-1.12)	59	157	0.68 (0.45-1.04)	48	84	0.75 (0.46-1.22)
24+ months	79	374	0.51 (0.36-0.72)	34	161	0.40 (0.25-0.66)	34	95	0.46 (0.27-0.78)
Incomplete pregnancy									
0	694	1363	1.0	343	539	1.0	330	420	1.0
1	230	554	1.08 (0.88-1.32)	118	236	0.96 (0.72-1.29)	101	166	1.02 (0.74-1.41)
2+	149	418	0.96 (0.75-1.22)	67	198	0.68 (0.48-0.96)	73	121	0.95 (0.65-1.38)
Age at last pregnancy									
<25 years or never being pregnant	458	593	1.0	217	231	1.0	229	203	1.0
25-29 years	187	452	0.75 (0.56-1.01)	103	221	0.99 (0.66-1.47)	111	179	0.87 (0.58-1.31)
30-34 years	251	682	0.79 (0.59-1.05)	136	284	1.10 (0.74-1.63)	91	191	0.77 (0.50-1.18)
35+ years	178	613	0.58 (0.42-0.79)	76	246	0.79 (0.51-1.22)	74	136	0.79 (0.50-1.27)
Tubal ligation									
No	972	1904	1.0	454	754	1.0	424	519	1.0
Yes	120	404	0.60 (0.46-0.77)	78	213	0.64 (0.46-0.89)	80	182	0.66 (0.47-0.93)
COC use duration									
<1 year	486	606	1.0	230	286	1.0	229	225	1.0
1-4.99 years	311	651	0.61 (0.50-0.74)	143	275	0.73 (0.54-0.97)	151	200	0.86 (0.63-1.18)
5-9.99 years	176	523	0.44 (0.35-0.55)	91	219	0.56 (0.40-0.78)	73	151	0.56 (0.39-0.82)
10+ years	118	580	0.23 (0.18-0.30)	72	215	0.41 (0.29-0.59)	55	139	0.35 (0.23-0.53)
DMPA use									
No	981	2034	1.0	476	844	1.0	460	598	1.0
Yes	22	87	0.79 (0.48-1.30)	14	37	0.83 (0.42-1.62)	12	43	0.43 (0.21-0.87)
Family history of ovarian cancer									

Risk factors	BMI 18.5-24.99 kg/m2			BMI 25-29.99 kg/m2			BMI 30+ kg/m2		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
No	803	1799	1.0	414	759	1.0	383	553	1.0
Yes	59	38	3.24 (2.01-5.23)	26	27	2.01 (1.09-3.70)	31	16	2.86 (1.42-5.75)
Endometriosis									
No	950	2207	1.0	470	936	1.0	467	672	1.0
Yes	139	150	1.88 (1.43-2.46)	65	57	2.01 (1.33-3.03)	41	43	1.58 (0.97-2.59)

* Numbers may not sum to total due to missing values.

** Pooled estimates from logistic regression models in the 50 imputed datasets, adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, and OCAC study.

Abbreviations: BMI: body mass index, CI: confidence interval; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; OR: odds ratio; PRS: polygenic risk score

Supplemental Table 3-5: Associations between risk factors and ovarian cancer risk among pre-menopausal women by strata of height

Risk factors	Height <1.60 m			Height 1.60-1.64 m			Height 1.65-1.69 m		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI									
<18.5 kg/m2	15	20	1.32 (0.63-2.74)	14	27	0.85 (0.41-1.74)	22	39	1.19 (0.65-2.18)
18.5-24.99 kg/m2	265	590	1.0	311	602	1.0	281	611	1.0
25-29.99 kg/m2	163	257	1.46 (1.11-1.92)	130	290	0.86 (0.66-1.14)	132	237	1.04 (0.78-1.39)
30+ kg/m2	146	173	1.59 (1.17-2.16)	139	210	1.21 (0.90-1.61)	121	166	1.39 (1.01-1.91)
Age at menarche									
<12 years	148	273	0.92 (0.70-1.19)	138	227	1.12 (0.86-1.47)	128	210	1.13 (0.85-1.50)
12-14 years	382	660	1.0	400	770	1.0	387	723	1.0
15+ years	57	108	1.02 (0.70-1.49)	59	129	0.86 (0.59-1.24)	45	119	0.66 (0.44-0.98)
Parity									
0	209	226	1.0	226	236	1.0	237	249	1.0
1	98	183	0.73 (0.47-1.13)	109	190	0.75 (0.49-1.15)	77	179	0.66 (0.41-1.05)
2	180	352	0.68 (0.44-1.05)	162	408	0.58 (0.38-0.88)	151	338	0.69 (0.44-1.09)
3+	105	282	0.46 (0.28-0.77)	103	298	0.57 (0.35-0.93)	96	288	0.61 (0.36-1.03)
Breastfeeding									
Never	342	438	1.0	336	427	1.0	318	400	1.0
<12 months	143	290	0.85 (0.61-1.19)	156	320	0.90 (0.65-1.26)	137	303	0.96 (0.66-1.40)
12-23 months	57	152	0.68 (0.44-1.03)	69	169	0.86 (0.58-1.30)	61	148	0.91 (0.57-1.43)
24+ months	47	146	0.56 (0.35-0.88)	33	183	0.39 (0.24-0.63)	40	179	0.50 (0.30-0.83)
Incomplete pregnancy									
0	394	590	1.0	368	667	1.0	369	595	1.0
1	118	261	0.75 (0.56-0.99)	132	253	1.17 (0.88-1.55)	114	247	1.09 (0.82-1.46)
2+	74	180	0.65 (0.46-0.91)	89	190	1.18 (0.85-1.64)	68	202	0.74 (0.52-1.06)
Age at last pregnancy									
<25 years or never being pregnant	238	282	1.0	247	280	1.0	251	257	1.0
25-29 years	105	232	0.84 (0.56-1.24)	116	234	0.89 (0.61-1.29)	100	219	0.68 (0.45-1.01)
30-34 years	129	286	1.05 (0.70-1.56)	142	339	0.88 (0.60-1.28)	110	290	0.64 (0.42-0.97)
35+ years	112	235	0.96 (0.63-1.48)	83	266	0.57 (0.37-0.87)	91	279	0.55 (0.35-0.85)
Tubal ligation									
No	494	805	1.0	521	866	1.0	488	828	1.0
Yes	94	223	0.72 (0.53-0.99)	79	230	0.58 (0.42-0.80)	68	202	0.65 (0.46-0.93)
COC use duration									
<1 year	297	354	1.0	243	294	1.0	262	272	1.0
1-4.99 years	155	263	0.75 (0.57-0.99)	183	321	0.76 (0.57-1.00)	139	304	0.53 (0.39-0.70)
5-9.99 years	80	226	0.46 (0.33-0.63)	102	244	0.55 (0.40-0.75)	86	213	0.44 (0.32-0.62)
10+ years	59	201	0.32 (0.22-0.47)	70	271	0.31 (0.22-0.44)	73	265	0.26 (0.18-0.37)
DMPA use									
No	537	916	1.0	527	941	1.0	494	909	1.0

Risk factors	Height <1.60 m			Height 1.60-1.64 m			Height 1.65-1.69 m		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
Yes	15	48	0.69 (0.36-1.32)	19	44	0.96 (0.52-1.75)	8	38	0.53 (0.23-1.21)
Family history of ovarian cancer									
No	424	736	1.0	427	862	1.0	436	838	1.0
Yes	35	18	3.17 (1.64-6.12)	38	31	2.30 (1.35-3.91)	24	17	2.32 (1.12-4.79)
Endometriosis									
No	522	988	1.0	534	1061	1.0	500	974	1.0
Yes	70	55	2.31 (1.53-3.47)	63	67	1.76 (1.18-2.62)	59	77	1.32 (0.89-1.96)

Risk factors	Height 1.70-1.74 m			Height 1.75+ m		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI						
<18.5 kg/m2	10	17	1.53 (0.62-3.74)	7	8	1.63 (0.41-6.45)
18.5-24.99 kg/m2	149	396	1.0	88	165	1.0
25-29.99 kg/m2	79	145	1.48 (1.00-2.18)	32	66	0.90 (0.50-1.62)
30+ kg/m2	60	106	1.38 (0.89-2.13)	44	61	1.07 (0.61-1.86)
Age at menarche						
<12 years	47	111	0.62 (0.40-0.96)	35	37	1.29 (0.71-2.34)
12-14 years	221	461	1.0	119	215	1.0
15+ years	31	88	0.70 (0.42-1.16)	19	49	0.48 (0.24-0.94)
Parity						
0	128	159	1.0	83	71	1.0
1	56	110	0.72 (0.38-1.34)	33	70	0.79 (0.34-1.79)
2	69	225	0.51 (0.28-0.94)	35	98	0.80 (0.33-1.92)
3+	46	170	0.44 (0.22-0.90)	22	64	0.84 (0.29-2.39)
Breastfeeding						
Never	184	254	1.0	110	109	1.0
<12 months	63	182	0.64 (0.39-1.07)	35	89	0.60 (0.29-1.27)
12-23 months	34	119	0.54 (0.30-0.97)	14	49	0.44 (0.18-1.11)
24+ months	17	92	0.30 (0.14-0.62)	13	48	0.41 (0.15-1.11)
Incomplete pregnancy						
0	172	379	1.0	107	174	1.0
1	69	146	1.33 (0.88-2.00)	39	71	1.33 (0.76-2.33)
2+	52	129	1.07 (0.67-1.70)	24	52	1.22 (0.63-2.38)
Age at last pregnancy						
<25 years or never being pregnant	115	169	1.0	85	84	1.0
25-29 years	63	137	1.27 (0.73-2.22)	25	46	0.65 (0.29-1.47)
30-34 years	78	185	1.31 (0.75-2.27)	36	85	0.65 (0.30-1.40)
35+ years	37	164	0.71 (0.38-1.33)	21	83	0.41 (0.17-1.00)
Tubal ligation						
No	270	527	1.0	155	256	1.0
Yes	29	119	0.48 (0.28-0.80)	17	41	0.79 (0.37-1.67)

Risk factors	Height 1.70-1.74 m			Height 1.75+ m		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
COC use duration						
<1 year	118	164	1.0	66	71	1.0
1-4.99 years	98	187	0.78 (0.53-1.15)	50	87	0.63 (0.35-1.12)
5-9.99 years	52	163	0.47 (0.30-0.73)	34	72	0.54 (0.29-1.02)
10+ years	30	149	0.22 (0.13-0.38)	23	71	0.30 (0.15-0.60)
DMPA use						
No	264	561	1.0	155	258	1.0
Yes	5	33	0.44 (0.15-1.25)	4	8	0.72 (0.18-2.90)
Family history of ovarian cancer						
No	229	534	1.0	136	238	1.0
Yes	15	13	3.56 (1.47-8.62)	10	5	3.32 (0.94-11.74)
Endometriosis						
No	261	626	1.0	146	279	1.0
Yes	38	37	2.64 (1.51-4.61)	25	23	2.68 (1.32-5.45)

* Numbers may not sum to total due to missing values.

** Pooled estimates from logistic regression models in the 50 imputed datasets, adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, and OCAC study.

Abbreviations: BMI: body mass index, CI: confidence interval; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; OR: odds ratio; PRS: polygenic risk score

Supplemental Table 3-6: Associations between risk factors and ovarian cancer risk among pre-menopausal women by strata of age at menarche

Risk factors	Age at menarche <12 years			Age at menarche 12-14 years			Age at menarche 15+ years		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI									
<18.5 kg/m2	7	22	0.50 (0.20-1.22)	50	66	1.50 (1.00-2.25)	11	23	1.35 (0.54-3.36)
18.5-24.99 kg/m2	197	370	1.0	771	1670	1.0	121	316	1.0
25-29.99 kg/m2	135	247	1.12 (0.83-1.52)	357	644	1.16 (0.98-1.38)	43	99	1.05 (0.64-1.73)
30+ kg/m2	156	217	1.29 (0.95-1.76)	320	441	1.40 (1.16-1.69)	31	54	1.55 (0.87-2.77)
Height (m)									
<1.60	148	273	1.0	382	660	1.0	57	108	1.0
1.60-1.64	138	227	1.15 (0.83-1.60)	400	770	1.01 (0.83-1.22)	59	129	0.90 (0.54-1.51)
1.65-1.69	128	210	1.16 (0.83-1.63)	387	723	1.09 (0.89-1.33)	45	119	0.81 (0.46-1.42)
1.70-1.74	47	111	0.66 (0.42-1.02)	221	461	0.95 (0.76-1.20)	31	88	0.67 (0.36-1.25)
1.75+	35	37	1.31 (0.75-2.29)	119	215	1.12 (0.84-1.49)	19	49	0.65 (0.31-1.37)
Parity									
0	211	180	1.0	598	641	1.0	71	120	1.0
1	76	157	0.42 (0.26-0.67)	261	489	0.85 (0.65-1.12)	36	83	0.74 (0.35-1.54)
2	125	285	0.41 (0.26-0.66)	403	979	0.66 (0.51-0.87)	68	149	1.12 (0.56-2.25)
3+	83	236	0.37 (0.21-0.63)	251	726	0.58 (0.42-0.79)	38	141	0.76 (0.32-1.78)
Breastfeeding									
Never	302	352	1.0	869	1065	1.0	115	209	1.0
<12 months	111	225	1.06 (0.73-1.55)	368	852	0.73 (0.59-0.91)	55	105	1.26 (0.72-2.23)
12-23 months	49	126	0.81 (0.51-1.29)	162	424	0.74 (0.57-0.97)	23	83	0.51 (0.25-1.02)
24+ months	32	132	0.48 (0.28-0.81)	103	431	0.44 (0.33-0.59)	16	84	0.42 (0.19-0.91)
Incomplete pregnancy									
0	320	473	1.0	953	1644	1.0	132	279	1.0
1	100	216	0.86 (0.63-1.17)	321	653	1.08 (0.91-1.29)	51	110	1.37 (0.86-2.20)
2+	67	154	0.68 (0.47-0.99)	214	500	0.97 (0.79-1.19)	27	96	0.86 (0.48-1.54)
Age at last pregnancy									
<25 years or never being pregnant	223	223	1.0	634	726	1.0	77	121	1.0
25-29 years	92	203	0.94 (0.62-1.42)	271	564	0.84 (0.66-1.07)	44	96	0.86 (0.44-1.70)
30-34 years	108	229	1.18 (0.77-1.80)	334	827	0.83 (0.65-1.05)	51	129	0.78 (0.39-1.56)
35+ years	70	195	0.79 (0.50-1.26)	243	695	0.66 (0.50-0.86)	33	137	0.47 (0.22-1.02)
Tubal ligation									
No	426	644	1.0	1314	2267	1.0	184	368	1.0
Yes	68	193	0.63 (0.44-0.89)	189	509	0.67 (0.54-0.82)	29	110	0.47 (0.27-0.83)
COC use duration									
<1 year	212	258	1.0	670	747	1.0	106	151	1.0
1-4.99 years	154	248	0.85 (0.63-1.14)	415	773	0.65 (0.55-0.77)	56	135	0.58 (0.36-0.94)
5-9.99 years	75	166	0.63 (0.44-0.91)	251	652	0.47 (0.39-0.57)	25	97	0.42 (0.24-0.76)
10+ years	55	186	0.35 (0.24-0.52)	172	660	0.28 (0.23-0.35)	25	109	0.28 (0.15-0.50)
DMPA use									

Risk factors	Age at menarche <12 years			Age at menarche 12-14 years			Age at menarche 15+ years		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
No	445	747	1.0	1341	2425	1.0	186	409	1.0
Yes	11	37	0.55 (0.26-1.15)	34	117	0.71 (0.47-1.09)	6	15	0.82 (0.26-2.55)
Family history of ovarian cancer									
No	364	637	1.0	1134	2186	1.0	149	378	1.0
Yes	30	24	2.21 (1.20-4.10)	80	53	2.71 (1.80-4.07)	11	7	2.92 (0.91-9.34)
Endometriosis									
No	433	793	1.0	1342	2655	1.0	185	472	1.0
Yes	62	62	1.71 (1.13-2.58)	164	175	1.75 (1.37-2.24)	28	20	3.94 (1.97-7.89)

* Numbers may not sum to total due to missing values.

** Pooled estimates from logistic regression models in the 50 imputed datasets, adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, and OCAC study.

Abbreviations: BMI: body mass index, CI: confidence interval; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; OR: odds ratio; PRS: polygenic risk score

Supplemental Table 3-7: Associations between risk factors and ovarian cancer risk among pre-menopausal women by strata of parity

Risk factors	Nulliparous			Parity 1		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI						
<18.5 kg/m2	33	41	1.10 (0.66-1.85)	15	20	1.86 (0.86-4.02)
18.5-24.99 kg/m2	447	570	1.0	192	399	1.0
25-29.99 kg/m2	193	168	1.25 (0.96-1.63)	83	182	1.00 (0.71-1.42)
30+ kg/m2	206	157	1.38 (1.04-1.83)	81	130	1.29 (0.88-1.89)
Height (m)						
<1.60	209	226	1.0	98	183	1.0
1.60-1.64	226	236	1.25 (0.94-1.68)	109	190	1.10 (0.75-1.62)
1.65-1.69	237	249	1.32 (0.99-1.77)	77	179	0.88 (0.57-1.33)
1.70-1.74	128	159	1.15 (0.82-1.61)	56	110	1.03 (0.65-1.63)
1.75+	83	71	1.57 (1.03-2.37)	33	70	0.93 (0.54-1.62)
Age at menarche						
<12 years	211	180	1.18 (0.92-1.52)	76	157	0.84 (0.59-1.21)
12-14 years	598	641	1.0	261	489	1.0
15+ years	71	120	0.61 (0.43-0.87)	36	83	0.68 (0.43-1.09)
Breastfeeding						
Never				113	201	1.0
<12 months				205	387	1.14 (0.81-1.59)
12-23 months				40	78	1.06 (0.63-1.77)
24+ months				12	44	0.49 (0.23-1.05)
Incomplete pregnancy						
0	651	653	1.0	209	383	1.0
1	137	164	1.16 (0.80-1.66)	104	157	1.24 (0.89-1.73)
2+	85	121	1.04 (0.63-1.70)	55	172	0.60 (0.41-0.88)
Age at last pregnancy						
<25 years or never being pregnant	732	736	1.0	92	131	1.0
25-29 years	43	53	0.71 (0.40-1.27)	85	194	0.68 (0.45-1.02)
30-34 years	40	57	0.74 (0.41-1.33)	100	208	0.74 (0.49-1.12)
35+ years	42	64	0.50 (0.27-0.91)	94	198	0.78 (0.50-1.22)
Tubal ligation						
No	859	891	1.0	352	643	1.0
Yes	14	34	0.34 (0.17-0.67)	22	70	0.50 (0.29-0.87)
COC use duration						
<1 year	447	304	1.0	156	188	1.0
1-4.99 years	216	242	0.67 (0.52-0.86)	111	189	0.75 (0.53-1.06)
5-9.99 years	124	181	0.54 (0.40-0.73)	59	150	0.47 (0.31-0.72)
10+ years	95	215	0.29 (0.22-0.40)	47	203	0.26 (0.17-0.40)
DMPA use						
No	789	823	1.0	337	617	1.0
Yes	15	27	0.63 (0.31-1.26)	8	34	0.65 (0.28-1.46)
Family history of ovarian cancer						
No	742	829	1.0	274	538	1.0
Yes	45	11	4.14 (1.99-8.62)	7	18	0.66 (0.24-1.83)
Endometriosis						
No	762	871	1.0	323	672	1.0
Yes	120	70	1.94 (1.38-2.72)	49	60	2.10 (1.34-3.28)

Risk factors	Parity 2			Parity 3+		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI						
<18.5 kg/m2	15	31	1.52 (0.77-2.97)	5	19	0.81 (0.27-2.44)
18.5-24.99 kg/m2	290	820	1.0	165	575	1.0
25-29.99 kg/m2	153	348	1.19 (0.93-1.53)	107	297	1.07 (0.79-1.45)
30+ kg/m2	131	219	1.57 (1.18-2.10)	91	209	1.25 (0.90-1.75)
Height (m)						
<1.60	180	352	1.0	105	282	1.0
1.60-1.64	162	408	0.84 (0.63-1.11)	103	298	0.93 (0.65-1.32)
1.65-1.69	151	338	0.99 (0.74-1.33)	96	288	1.07 (0.75-1.55)
1.70-1.74	69	225	0.73 (0.51-1.04)	46	170	0.69 (0.44-1.07)
1.75+	35	98	0.94 (0.59-1.50)	22	64	0.97 (0.53-1.76)
Age at menarche						
<12 years	125	285	1.00 (0.77-1.29)	83	236	0.98 (0.71-1.35)
12-14 years	403	979	1.0	251	726	1.0
15+ years	68	149	1.09 (0.78-1.53)	38	141	0.83 (0.54-1.26)
Breastfeeding						
Never	200	291	1.0	95	195	1.0
<12 months	226	550	0.64 (0.49-0.83)	105	250	0.90 (0.62-1.31)
12-23 months	114	348	0.50 (0.36-0.69)	81	211	0.89 (0.60-1.33)
24+ months	52	192	0.42 (0.28-0.63)	88	412	0.41 (0.28-0.61)
Incomplete pregnancy						
0	360	797	1.0	194	576	1.0
1	125	358	0.91 (0.70-1.17)	108	301	1.03 (0.77-1.38)
2+	102	252	1.08 (0.81-1.45)	66	208	0.98 (0.69-1.39)
Age at last pregnancy						
<25 years or never being pregnant	92	166	1.0	23	42	1.0
25-29 years	166	360	1.01 (0.72-1.43)	116	261	1.14 (0.61-2.11)
30-34 years	210	521	1.06 (0.75-1.50)	146	401	1.10 (0.60-2.04)
35+ years	125	371	0.81 (0.55-1.20)	85	396	0.69 (0.36-1.32)
Tubal ligation						
No	470	1085	1.0	252	669	1.0
Yes	130	304	0.80 (0.62-1.04)	121	408	0.55 (0.41-0.73)
COC use duration						
<1 year	235	324	1.0	152	342	1.0
1-4.99 years	178	377	0.63 (0.49-0.83)	121	355	0.75 (0.55-1.02)
5-9.99 years	107	348	0.45 (0.33-0.60)	64	240	0.46 (0.31-0.66)
10+ years	78	373	0.30 (0.22-0.42)	36	167	0.30 (0.19-0.49)
DMPA use						
No	526	1220	1.0	328	930	1.0
Yes	14	60	0.65 (0.34-1.24)	14	50	0.93 (0.49-1.76)
Family history of ovarian cancer						
No	394	1058	1.0	246	789	1.0
Yes	46	36	2.77 (1.70-4.50)	23	19	3.23 (1.57-6.66)
Endometriosis						
No	534	1342	1.0	349	1049	1.0
Yes	62	76	1.90 (1.29-2.78)	24	53	1.38 (0.80-2.38)

* Numbers may not sum to total due to missing values.

** Pooled estimates from logistic regression models in the 50 imputed datasets, adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, and OCAC study.

Abbreviations: BMI: body mass index, CI: confidence interval; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; OR: odds ratio; PRS: polygenic risk score

Supplemental Table 3-8: Associations between risk factors and ovarian cancer risk among pre-menopausal women by strata of breastfeeding duration

Risk factors	Never breastfed			Breastfed <12 months		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI						
<18.5 kg/m2	43	52	1.26 (0.81-1.97)	16	28	1.41 (0.72-2.77)
18.5-24.99 kg/m2	620	910	1.0	272	640	1.0
25-29.99 kg/m2	304	351	1.23 (1.01-1.51)	138	299	1.06 (0.81-1.39)
30+ kg/m2	318	310	1.45 (1.17-1.80)	108	214	1.10 (0.82-1.49)
Height (m)						
<1.60	342	438	1.0	143	290	1.0
1.60-1.64	336	427	1.06 (0.85-1.32)	156	320	1.02 (0.76-1.39)
1.65-1.69	318	400	1.11 (0.88-1.40)	137	303	1.00 (0.73-1.37)
1.70-1.74	184	254	1.00 (0.77-1.31)	63	182	0.76 (0.52-1.12)
1.75+	110	109	1.32 (0.94-1.85)	35	89	0.90 (0.56-1.45)
Age at menarche						
<12 years	302	352	0.96 (0.79-1.17)	111	225	1.16 (0.88-1.54)
12-14 years	869	1065	1.0	368	852	1.0
15+ years	115	209	0.66 (0.51-0.87)	55	105	1.11 (0.76-1.61)
Parity						
0	885	944	1.0			
1	113	201	0.61 (0.46-0.82)	205	387	1.0
2	200	291	0.80 (0.60-1.05)	226	550	0.73 (0.57-0.95)
3+	95	195	0.52 (0.36-0.75)	105	250	0.70 (0.50-0.98)
Incomplete pregnancy						
0	898	1054	1.0	319	652	1.0
1	235	343	1.03 (0.82-1.28)	130	290	0.98 (0.75-1.28)
2+	140	224	0.90 (0.68-1.20)	80	239	0.72 (0.52-0.98)
Age at last pregnancy						
<25 years or never being pregnant	838	874	1.0	75	147	1.0
25-29 years	160	282	0.71 (0.53-0.95)	158	308	1.22 (0.84-1.78)
30-34 years	156	242	0.88 (0.65-1.19)	188	439	1.04 (0.72-1.50)
35+ years	111	199	0.64 (0.46-0.90)	115	293	0.91 (0.60-1.37)
Tubal ligation						
No	1160	1348	1.0	439	908	1.0
Yes	121	264	0.57 (0.44-0.75)	97	279	0.71 (0.53-0.95)
COC use duration						
<1 year	622	518	1.0	212	273	1.0
1-4.99 years	335	417	0.71 (0.58-0.87)	161	345	0.62 (0.47-0.82)
5-9.99 years	191	331	0.55 (0.43-0.69)	89	277	0.41 (0.30-0.56)
10+ years	140	362	0.30 (0.24-0.39)	74	292	0.30 (0.21-0.42)
DMPA use						
No	1155	1439	1.0	474	1035	1.0
Yes	27	60	0.68 (0.41-1.12)	13	58	0.66 (0.35-1.25)
Family history of ovarian cancer						
No	990	1280	1.0	368	865	1.0
Yes	69	33	2.62 (1.63-4.21)	25	30	1.96 (1.09-3.51)
Endometriosis						
No	1123	1522	1.0	482	1106	1.0
Yes	164	106	2.04 (1.55-2.69)	51	80	1.35 (0.91-2.00)

Risk factors	Breastfed 12-23 months			Breastfed 24+ months		
	Case *	Control *	OR** (95% CI)	Case *	Control *	OR** (95% CI)
BMI						
<18.5 kg/m2	6	14	1.54 (0.53-4.48)	3	16	0.89 (0.23-3.47)
18.5-24.99 kg/m2	121	381	1.0	79	374	1.0
25-29.99 kg/m2	59	157	0.97 (0.65-1.46)	34	161	0.96 (0.59-1.56)
30+ kg/m2	48	84	1.68 (1.05-2.71)	34	95	1.42 (0.84-2.41)
Height (m)						
<1.60	57	152	1.0	47	146	1.0
1.60-1.64	69	169	1.19 (0.76-1.89)	33	183	0.71 (0.41-1.25)
1.65-1.69	61	148	1.16 (0.72-1.87)	40	179	0.96 (0.55-1.66)
1.70-1.74	34	119	0.80 (0.46-1.40)	17	92	0.59 (0.29-1.20)
1.75+	14	49	0.77 (0.36-1.65)	13	48	1.04 (0.46-2.32)
Age at menarche						
<12 years	49	126	0.82 (0.54-1.26)	32	132	0.88 (0.53-1.44)
12-14 years	162	424	1.0	103	431	1.0
15+ years	23	83	0.69 (0.40-1.20)	16	84	0.70 (0.37-1.32)
Parity						
0						
1	40	78	1.0	12	44	1.0
2	114	348	0.68 (0.42-1.12)	52	192	1.14 (0.51-2.55)
3+	81	211	0.85 (0.49-1.45)	88	412	0.72 (0.33-1.57)
Incomplete pregnancy						
0	118	328	1.0	71	319	1.0
1	57	166	1.01 (0.68-1.51)	47	176	1.47 (0.94-2.29)
2+	56	136	1.23 (0.81-1.87)	29	151	0.98 (0.58-1.68)
Age at last pregnancy						
<25 years or never being pregnant	19	32	1.0	7	12	1.0
25-29 years	62	145	0.79 (0.38-1.62)	29	111	0.48 (0.15-1.53)
30-34 years	88	233	0.72 (0.35-1.48)	63	241	0.60 (0.20-1.82)
35+ years	66	227	0.55 (0.26-1.18)	53	284	0.40 (0.13-1.23)
Tubal ligation						
No	194	483	1.0	126	533	1.0
Yes	41	154	0.55 (0.35-0.85)	26	115	0.78 (0.45-1.34)
COC use duration						
<1 year	84	160	1.0	67	184	1.0
1-4.99 years	78	176	0.75 (0.49-1.13)	47	202	0.60 (0.38-0.96)
5-9.99 years	43	140	0.49 (0.30-0.79)	27	142	0.36 (0.20-0.64)
10+ years	30	159	0.31 (0.18-0.52)	11	120	0.21 (0.10-0.44)
DMPA use						
No	214	551	1.0	134	557	1.0
Yes	5	28	0.49 (0.17-1.40)	6	25	1.39 (0.50-3.88)
Family history of ovarian cancer						
No	179	484	1.0	115	507	1.0
Yes	14	10	4.16 (1.66-10.42)	10	7	5.71 (1.88-17.32)
Endometriosis						
No	215	594	1.0	134	620	1.0
Yes	20	41	1.48 (0.80-2.74)	18	25	4.40 (2.17-8.94)

* Numbers may not sum to total due to missing values.

** Pooled estimates from logistic regression models in the 50 imputed datasets, adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, and OCAC study.

Abbreviations: BMI: body mass index, CI: confidence interval; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; OR: odds ratio; PRS: polygenic risk score

Supplemental Table 3-9: Associations between risk factors and ovarian cancer risk among pre-menopausal women by strata of incomplete pregnancy

Risk factors	0 incomplete pregnancy			1 incomplete prengnacy			2+ incomlete pregnancies		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI									
<18.5 kg/m2	33	75	0.80 (0.51-1.26)	18	19	1.93 (0.93-3.98)	16	16	2.69 (1.25-5.82)
18.5-24.99 kg/m2	694	1363	1.0	230	554	1.0	149	418	1.0
25-29.99 kg/m2	343	539	1.21 (1.01-1.46)	118	236	1.12 (0.84-1.51)	67	198	0.86 (0.60-1.22)
30+ kg/m2	330	420	1.40 (1.15-1.70)	101	166	1.27 (0.92-1.76)	73	121	1.37 (0.93-2.02)
Height (m)									
<1.60	394	590	1.0	118	261	1.0	74	180	1.0
1.60-1.64	368	667	0.92 (0.75-1.13)	132	253	1.21 (0.87-1.68)	89	190	1.29 (0.85-1.94)
1.65-1.69	369	595	1.10 (0.89-1.36)	114	247	1.21 (0.86-1.70)	68	202	0.82 (0.53-1.27)
1.70-1.74	172	379	0.76 (0.59-0.98)	69	146	1.15 (0.77-1.70)	52	129	0.92 (0.57-1.48)
1.75+	107	174	1.05 (0.77-1.43)	39	71	1.19 (0.73-1.95)	24	52	1.14 (0.61-2.11)
Age at menarche									
<12 years	320	473	1.08 (0.90-1.30)	100	216	0.93 (0.70-1.25)	67	154	0.81 (0.56-1.16)
12-14 years	953	1644	1.0	321	653	1.0	214	500	1.0
15+ years	132	279	0.79 (0.61-1.01)	51	110	0.93 (0.63-1.36)	27	96	0.66 (0.40-1.07)
Parity									
0	651	653	1.0	137	164	1.0	85	121	1.0
1	209	383	0.71 (0.51-0.97)	104	157	0.90 (0.59-1.40)	55	172	0.58 (0.34-0.99)
2	360	797	0.59 (0.43-0.81)	125	358	0.56 (0.37-0.85)	102	252	0.88 (0.52-1.49)
3+	194	576	0.51 (0.35-0.74)	108	301	0.50 (0.31-0.80)	66	208	0.63 (0.35-1.14)
Breastfeeding									
Never	898	1054	1.0	235	343	1.0	140	224	1.0
<12 months	319	652	0.88 (0.70-1.11)	130	290	0.80 (0.56-1.14)	80	239	0.71 (0.45-1.12)
12-23 months	118	328	0.72 (0.53-0.96)	57	166	0.68 (0.44-1.03)	56	136	0.80 (0.48-1.34)
24+ months	71	319	0.42 (0.30-0.60)	47	176	0.58 (0.36-0.91)	29	151	0.36 (0.20-0.66)
Age at last pregnancy									
<25 years or never being pregnant	801	891	1.0	102	130	1.0	34	49	1.0
25-29 years	226	513	0.86 (0.64-1.14)	109	204	0.99 (0.66-1.48)	66	140	0.85 (0.48-1.52)
30-34 years	258	614	0.94 (0.71-1.26)	138	335	0.89 (0.60-1.32)	90	218	0.89 (0.50-1.56)
35+ years	122	383	0.67 (0.48-0.94)	110	292	0.74 (0.49-1.13)	111	335	0.75 (0.42-1.32)
Tubal ligation									
No	1245	1935	1.0	399	754	1.0	259	582	1.0
Yes	157	416	0.65 (0.52-0.82)	75	226	0.72 (0.52-1.00)	49	170	0.52 (0.35-0.79)
COC use duration									
<1 year	665	680	1.0	186	245	1.0	125	221	1.0
1-4.99 years	377	625	0.71 (0.59-0.86)	134	300	0.58 (0.43-0.79)	104	226	0.71 (0.50-1.00)

Risk factors	0 incomplete pregnancy			1 incomplete prengnacy			2+ incomlete pregnancies		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
5-9.99 years	218	539	0.51 (0.41-0.63)	81	211	0.46 (0.32-0.65)	48	154	0.48 (0.32-0.73)
10+ years	149	563	0.29 (0.23-0.36)	72	223	0.33 (0.23-0.47)	31	151	0.26 (0.16-0.43)
DMPA use									
No	1272	2086	1.0	425	874	1.0	283	630	1.0
Yes	20	85	0.59 (0.36-0.99)	20	38	1.13 (0.63-2.05)	11	48	0.52 (0.24-1.11)
Family history of ovarian cancer									
No	1081	1928	1.0	322	703	1.0	218	527	1.0
Yes	79	40	3.43 (2.20-5.33)	33	19	3.18 (1.70-5.96)	9	21	1.02 (0.43-2.42)
Endometriosis									
No	1250	2280	1.0	420	912	1.0	271	689	1.0
Yes	159	126	2.25 (1.72-2.94)	52	64	1.49 (0.98-2.26)	37	62	1.51 (0.95-2.41)

* Numbers may not sum to total due to missing values.

** Pooled estimates from logistic regression models in the 50 imputed datasets, adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, and OCAC study.

Abbreviations: BMI: body mass index, CI: confidence interval; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; OR: odds ratio; PRS: polygenic risk score

Supplemental Table 3-10: Associations between risk factors and ovarian cancer risk among pre-menopausal women by strata of age at last pregnancy

Risk factors	Age at last pregnancy <25 years			Age at last pregnancy 25-29 years		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI						
<18.5 kg/m2	9	8	1.32 (0.44-3.90)	8	15	1.78 (0.70-4.50)
18.5-24.99 kg/m2	130	206	1.0	187	452	1.0
25-29.99 kg/m2	72	115	0.95 (0.63-1.43)	103	221	1.21 (0.89-1.66)
30+ kg/m2	75	93	1.40 (0.91-2.17)	111	179	1.53 (1.10-2.12)
Height (m)						
<1.60	72	122	1.0	105	232	1.0
1.60-1.64	86	119	1.20 (0.77-1.89)	116	234	1.25 (0.88-1.77)
1.65-1.69	71	85	1.60 (0.99-2.59)	100	219	1.19 (0.82-1.73)
1.70-1.74	30	62	0.87 (0.48-1.55)	63	137	1.19 (0.78-1.81)
1.75+	28	34	1.62 (0.84-3.12)	25	46	1.37 (0.76-2.48)
Age at menarche						
<12 years	65	105	0.66 (0.43-0.99)	92	203	0.94 (0.69-1.28)
12-14 years	197	272	1.0	271	564	1.0
15+ years	26	42	0.69 (0.38-1.22)	44	96	0.95 (0.63-1.44)
Parity						
0	81	83	1.0	43	53	1.0
1	92	131	0.68 (0.37-1.26)	85	194	0.62 (0.35-1.11)
2	92	166	0.48 (0.25-0.89)	166	360	0.65 (0.37-1.14)
3+	23	42	0.38 (0.16-0.88)	116	261	0.64 (0.35-1.17)
Breastfeeding						
Never	187	221	1.0	160	282	1.0
<12 months	75	147	0.63 (0.41-0.98)	158	308	1.08 (0.77-1.49)
12-23 months	19	32	0.95 (0.47-1.95)	62	145	0.85 (0.56-1.28)
24+ months	7	12	0.74 (0.25-2.22)	29	111	0.42 (0.25-0.71)
Incomplete pregnancy						
0	150	238	1.0	226	513	1.0
1	102	130	0.89 (0.55-1.44)	109	204	1.16 (0.85-1.59)
2+	34	49	0.86 (0.48-1.54)	66	140	0.92 (0.63-1.33)
Tubal ligation						
No	238	310	1.0	319	617	1.0
Yes	50	104	0.62 (0.40-0.98)	91	232	0.61 (0.44-0.84)
COC use duration						
<1 year	112	121	1.0	148	228	1.0
1-4.99 years	106	138	0.75 (0.50-1.13)	142	260	0.85 (0.62-1.17)
5-9.99 years	37	83	0.40 (0.24-0.67)	80	210	0.58 (0.41-0.84)
10+ years	31	80	0.28 (0.16-0.48)	40	169	0.30 (0.19-0.47)
DMPA use						
No	257	349	1.0	381	757	1.0
Yes	10	26	0.70 (0.31-1.61)	5	44	0.33 (0.12-0.88)
Family history of ovarian cancer						
No	194	312	1.0	271	608	1.0
Yes	21	13	2.55 (1.14-5.70)	19	22	1.89 (0.94-3.77)
Endometriosis						
No	254	399	1.0	376	812	1.0
Yes	34	22	2.02 (1.10-3.72)	34	55	1.30 (0.80-2.13)

Risk factors	Age at last pregnancy 30-34 years			Age at last pregnancy 35+ years		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI						
<18.5 kg/m2	17	26	1.61 (0.82-3.17)	15	29	1.49 (0.70-3.16)
18.5-24.99 kg/m2	251	682	1.0	178	613	1.0
25-29.99 kg/m2	136	284	1.20 (0.91-1.57)	76	246	1.06 (0.75-1.51)
30+ kg/m2	91	191	1.14 (0.83-1.57)	74	136	1.62 (1.09-2.40)
Height (m)						
<1.60	129	286	1.0	112	235	1.0
1.60-1.64	142	339	1.03 (0.75-1.41)	83	266	0.75 (0.51-1.09)
1.65-1.69	110	290	0.95 (0.67-1.33)	91	279	0.76 (0.52-1.11)
1.70-1.74	78	185	0.97 (0.66-1.41)	37	164	0.50 (0.31-0.81)
1.75+	36	85	1.05 (0.64-1.73)	21	83	0.67 (0.37-1.21)
Age at menarche						
<12 years	108	229	1.15 (0.87-1.53)	70	195	0.89 (0.62-1.27)
12-14 years	334	827	1.0	243	695	1.0
15+ years	51	129	0.87 (0.60-1.27)	33	137	0.70 (0.45-1.10)
Parity						
0	40	57	1.0	42	64	1.0
1	100	208	0.79 (0.45-1.39)	94	198	0.94 (0.51-1.71)
2	210	521	0.71 (0.41-1.23)	125	371	0.78 (0.43-1.41)
3+	146	401	0.57 (0.32-1.02)	85	396	0.55 (0.29-1.04)
Breastfeeding						
Never	156	242	1.0	111	199	1.0
<12 months	188	439	0.73 (0.53-1.00)	115	293	0.80 (0.53-1.21)
12-23 months	88	233	0.66 (0.45-0.96)	66	227	0.64 (0.41-1.01)
24+ months	63	241	0.46 (0.30-0.69)	53	284	0.38 (0.24-0.62)
Incomplete pregnancy						
0	258	614	1.0	122	383	1.0
1	138	335	0.95 (0.73-1.24)	110	292	1.12 (0.80-1.58)
2+	90	218	0.84 (0.61-1.15)	111	335	0.94 (0.67-1.32)
Tubal ligation						
No	400	903	1.0	305	801	1.0
Yes	96	256	0.74 (0.55-1.00)	41	205	0.59 (0.39-0.89)
COC use duration						
<1 year	185	293	1.0	170	278	1.0
1-4.99 years	153	336	0.76 (0.57-1.02)	74	258	0.48 (0.33-0.69)
5-9.99 years	91	295	0.49 (0.35-0.67)	55	204	0.44 (0.30-0.66)
10+ years	67	262	0.35 (0.24-0.50)	47	288	0.23 (0.15-0.35)
DMPA use						
No	429	1002	1.0	311	876	1.0
Yes	19	51	1.02 (0.57-1.83)	9	33	0.85 (0.36-2.00)
Family history of ovarian cancer						
No	346	891	1.0	244	768	1.0
Yes	22	26	1.89 (1.00-3.57)	23	15	5.06 (2.26-11.34)
Endometriosis						
No	439	1118	1.0	296	959	1.0
Yes	51	65	1.79 (1.18-2.70)	50	67	2.52 (1.61-3.93)

* Numbers may not sum to total due to missing values.

** Pooled estimates from logistic regression models in the 50 imputed datasets, adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, and OCAC study.

Abbreviations: BMI: body mass index, CI: confidence interval; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; OR: odds ratio; PRS: polygenic risk score

Supplemental Table 3-11: Associations between risk factors and ovarian cancer risk among pre-menopausal women by strata of tubal ligation

Risk factors	No tubal ligation			With tubal ligation		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI						
<18.5 kg/m2	61	95	1.16 (0.81-1.65)	7	15	1.62 (0.61-4.29)
18.5-24.99 kg/m2	972	1904	1.0	120	404	1.0
25-29.99 kg/m2	454	754	1.13 (0.97-1.32)	78	213	1.23 (0.86-1.77)
30+ kg/m2	424	519	1.35 (1.14-1.60)	80	182	1.41 (0.98-2.05)
Height (m)						
<1.60	494	805	1.0	94	223	1.0
1.60-1.64	521	866	1.07 (0.90-1.27)	79	230	0.83 (0.56-1.22)
1.65-1.69	488	828	1.09 (0.91-1.30)	68	202	1.01 (0.67-1.53)
1.70-1.74	270	527	0.92 (0.75-1.13)	29	119	0.69 (0.40-1.16)
1.75+	155	256	1.11 (0.86-1.43)	17	41	1.18 (0.59-2.33)
Age at menarche						
<12 years	426	644	1.03 (0.88-1.20)	68	193	0.85 (0.60-1.22)
12-14 years	1314	2267	1.0	189	509	1.0
15+ years	184	368	0.80 (0.65-0.98)	29	110	0.67 (0.42-1.09)
Parity						
0	859	891	1.0	14	34	1.0
1	352	643	0.73 (0.57-0.93)	22	70	0.90 (0.38-2.14)
2	470	1085	0.60 (0.47-0.76)	130	304	1.26 (0.59-2.69)
3+	252	669	0.55 (0.41-0.73)	121	408	0.84 (0.38-1.86)
Breastfeeding						
Never	1160	1348	1.0	121	264	1.0
<12 months	439	908	0.86 (0.70-1.05)	97	279	0.77 (0.53-1.11)
12-23 months	194	483	0.79 (0.62-1.00)	41	154	0.60 (0.38-0.96)
24+ months	126	533	0.45 (0.34-0.59)	26	115	0.52 (0.30-0.90)
Incomplete pregnancy						
0	1245	1935	1.0	157	416	1.0
1	399	754	1.05 (0.90-1.23)	75	226	0.96 (0.68-1.35)
2+	259	582	0.92 (0.76-1.11)	49	170	0.77 (0.51-1.15)
Age at last pregnancy						
<25 years or never being pregnant	870	936	1.0	57	118	1.0
25-29 years	319	617	0.85 (0.68-1.06)	91	232	0.93 (0.59-1.47)
30-34 years	400	903	0.86 (0.69-1.07)	96	256	1.04 (0.65-1.67)
35+ years	305	801	0.68 (0.53-0.87)	41	205	0.57 (0.33-0.98)
COC use duration						
<1 year	891	904	1.0	90	227	1.0
1-4.99 years	525	871	0.66 (0.56-0.77)	100	271	0.91 (0.63-1.31)
5-9.99 years	291	729	0.45 (0.38-0.54)	63	167	0.82 (0.54-1.25)
10+ years	222	779	0.29 (0.24-0.35)	34	151	0.44 (0.26-0.73)
DMPA use						
No	1711	2861	1.0	259	723	1.0
Yes	45	134	0.74 (0.51-1.08)	6	37	0.60 (0.24-1.51)
Family history of ovarian cancer						
No	1467	2583	1.0	181	547	1.0
Yes	102	54	2.86 (1.94-4.20)	19	25	1.98 (1.01-3.91)
Endometriosis						
No	1699	3083	1.0	259	761	1.0
Yes	227	199	2.02 (1.62-2.51)	27	52	1.34 (0.79-2.27)

* Numbers may not sum to total due to missing values.

** Pooled estimates from logistic regression models in the 50 imputed datasets, adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, and OCAC study.

Abbreviations: BMI: body mass index, CI: confidence interval; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; OR: odds ratio; PRS: polygenic risk score

Supplemental Table 3-12: Associations between risk factors and ovarian cancer risk among pre-menopausal women by strata of COC use duration

Risk factors	Oral contraceptive use <1 year			Oral contraceptive use 1-4.99 years		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI						
<18.5 kg/m2	34	33	1.15 (0.68-1.96)	16	33	1.11 (0.58-2.15)
18.5-24.99 kg/m2	486	606	1.0	311	651	1.0
25-29.99 kg/m2	230	286	1.01 (0.80-1.27)	143	275	1.07 (0.82-1.39)
30+ kg/m2	229	225	1.19 (0.92-1.53)	151	200	1.50 (1.13-1.98)
Height (m)						
<1.60	297	354	1.0	155	263	1.0
1.60-1.64	243	294	1.03 (0.80-1.33)	183	321	0.98 (0.73-1.33)
1.65-1.69	262	272	1.31 (1.01-1.70)	139	304	0.86 (0.62-1.18)
1.70-1.74	118	164	0.94 (0.68-1.28)	98	187	0.91 (0.64-1.30)
1.75+	66	71	1.10 (0.73-1.67)	50	87	0.95 (0.60-1.48)
Age at menarche						
<12 years	212	258	0.88 (0.70-1.11)	154	248	1.09 (0.84-1.41)
12-14 years	670	747	1.0	415	773	1.0
15+ years	106	151	0.77 (0.57-1.03)	56	135	0.76 (0.53-1.09)
Parity						
0	447	304	1.0	216	242	1.0
1	156	188	0.68 (0.47-0.98)	111	189	0.85 (0.56-1.27)
2	235	324	0.67 (0.46-0.96)	178	377	0.67 (0.45-0.99)
3+	152	342	0.51 (0.33-0.78)	121	355	0.64 (0.40-1.03)
Breastfeeding						
Never	622	518	1.0	335	417	1.0
<12 months	212	273	0.99 (0.74-1.32)	161	345	0.73 (0.53-1.01)
12-23 months	84	160	0.78 (0.54-1.13)	78	176	0.77 (0.52-1.14)
24+ months	67	184	0.56 (0.38-0.83)	47	202	0.40 (0.26-0.64)
Incomplete pregnancy						
0	665	680	1.0	377	625	1.0
1	186	245	1.02 (0.80-1.31)	134	300	0.92 (0.71-1.20)
2+	125	221	0.85 (0.64-1.12)	104	226	0.94 (0.70-1.28)
Age at last pregnancy						
<25 years or never being pregnant	475	354	1.0	245	299	1.0
25-29 years	148	228	0.75 (0.54-1.05)	142	260	0.97 (0.69-1.38)
30-34 years	185	293	0.80 (0.57-1.13)	153	336	0.93 (0.65-1.32)
35+ years	170	278	0.72 (0.50-1.03)	74	258	0.54 (0.36-0.81)
Tubal ligation						
No	891	904	1.0	525	871	1.0
Yes	90	227	0.50 (0.37-0.68)	100	271	0.60 (0.44-0.81)
DMPA use						
No	883	1009	1.0	555	1013	1.0
Yes	20	32	1.02 (0.56-1.86)	13	49	0.55 (0.29-1.07)
Family history of ovarian cancer						
No	735	837	1.0	442	854	1.0
Yes	56	24	2.82 (1.59-4.99)	34	22	3.27 (1.81-5.92)
Endometriosis						
No	891	1098	1.0	542	1089	1.0
Yes	98	58	1.92 (1.34-2.76)	80	73	1.89 (1.32-2.72)

Risk factors	Oral contraceptive use 5-9.99 years			Oral contraceptive use 10+ years		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI						
<18.5 kg/m2	9	23	1.07 (0.46-2.51)	9	22	2.32 (0.98-5.50)
18.5-24.99 kg/m2	176	523	1.0	118	580	1.0
25-29.99 kg/m2	91	219	1.12 (0.80-1.56)	72	215	1.63 (1.13-2.34)
30+ kg/m2	73	151	1.21 (0.84-1.74)	55	139	1.67 (1.11-2.52)
Height (m)						
<1.60	80	226	1.0	59	201	1.0
1.60-1.64	102	244	1.13 (0.77-1.64)	70	271	0.88 (0.57-1.34)
1.65-1.69	86	213	1.11 (0.75-1.66)	73	265	0.93 (0.61-1.43)
1.70-1.74	52	163	0.89 (0.57-1.40)	30	149	0.61 (0.36-1.03)
1.75+	34	72	1.35 (0.78-2.32)	23	71	1.01 (0.55-1.85)
Age at menarche						
<12 years	75	166	1.21 (0.86-1.70)	55	186	1.05 (0.72-1.53)
12-14 years	251	652	1.0	172	660	1.0
15+ years	25	97	0.68 (0.41-1.12)	25	109	0.94 (0.57-1.54)
Parity						
0	124	181	1.0	95	215	1.0
1	59	150	0.60 (0.35-1.05)	47	203	0.71 (0.39-1.30)
2	107	348	0.44 (0.25-0.75)	78	373	0.77 (0.43-1.39)
3+	64	240	0.33 (0.18-0.62)	36	167	0.92 (0.46-1.85)
Breastfeeding						
Never	191	331	1.0	140	362	1.0
<12 months	89	277	0.75 (0.50-1.13)	74	292	0.93 (0.58-1.49)
12-23 months	43	140	0.74 (0.45-1.23)	30	159	0.63 (0.36-1.12)
24+ months	27	142	0.46 (0.26-0.82)	11	120	0.32 (0.15-0.69)
Incomplete pregnancy						
0	218	539	1.0	149	563	1.0
1	81	211	1.01 (0.72-1.41)	72	223	1.42 (0.99-2.05)
2+	48	154	0.83 (0.55-1.26)	31	151	0.94 (0.58-1.55)
Age at last pregnancy						
<25 years or never being pregnant	119	200	1.0	96	221	1.0
25-29 years	80	210	1.09 (0.67-1.77)	40	169	0.63 (0.36-1.11)
30-34 years	91	295	1.06 (0.65-1.72)	67	262	0.78 (0.46-1.33)
35+ years	55	204	0.91 (0.53-1.58)	47	288	0.53 (0.30-0.95)
Tubal ligation						
No	291	729	1.0	222	779	1.0
Yes	63	167	0.91 (0.62-1.33)	34	151	0.71 (0.45-1.12)
DMPA use						
No	308	771	1.0	231	793	1.0
Yes	11	47	0.71 (0.34-1.51)	7	43	0.61 (0.26-1.45)
Family history of ovarian cancer						
No	262	711	1.0	215	807	1.0
Yes	17	23	1.84 (0.92-3.66)	12	15	3.35 (1.39-8.06)
Endometriosis						
No	307	853	1.0	225	892	1.0
Yes	45	62	1.75 (1.12-2.75)	30	64	2.04 (1.24-3.37)

* Numbers may not sum to total due to missing values.

** Pooled estimates from logistic regression models in the 50 imputed datasets, adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, and OCAC study.

Abbreviations: BMI: body mass index, CI: confidence interval; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; OR: odds ratio; PRS: polygenic risk score

Supplemental Table 3-13: Associations between risk factors and ovarian cancer risk among pre-menopausal women by strata of DMPA use

Risk factors	Never use DMPA			Ever use DMPA		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI						
<18.5 kg/m2	59	99	1.23 (0.88-1.73)	2	4	0.41 (0.01-13.13)
18.5-24.99 kg/m2	981	2034	1.0	22	87	1.0
25-29.99 kg/m2	476	844	1.13 (0.98-1.30)	14	37	1.38 (0.52-3.70)
30+ kg/m2	460	598	1.39 (1.19-1.62)	12	43	0.75 (0.25-2.23)
Height (m)						
<1.60	537	916	1.0	15	48	1.0
1.60-1.64	527	941	1.00 (0.86-1.18)	19	44	1.70 (0.59-4.94)
1.65-1.69	494	909	1.08 (0.91-1.27)	8	38	0.74 (0.20-2.76)
1.70-1.74	264	561	0.89 (0.73-1.08)	5	33	0.53 (0.12-2.30)
1.75+	155	258	1.10 (0.86-1.40)	4	8	1.15 (0.19-6.88)
Age at menarche						
<12 years	445	747	1.02 (0.88-1.18)	11	37	0.63 (0.22-1.79)
12-14 years	1341	2425	1.0	34	117	1.0
15+ years	186	409	0.77 (0.64-0.93)	6	15	0.92 (0.22-3.96)
Parity						
0	789	823	1.0	15	27	1.0
1	337	617	0.72 (0.58-0.91)	8	34	0.97 (0.20-4.79)
2	526	1220	0.62 (0.50-0.78)	14	60	0.63 (0.13-3.09)
3+	328	930	0.52 (0.40-0.68)	14	50	0.64 (0.12-3.35)
Breastfeeding						
Never	1155	1439	1.0	27	60	1.0
<12 months	474	1035	0.84 (0.71-1.01)	13	58	0.79 (0.23-2.66)
12-23 months	214	551	0.76 (0.61-0.94)	5	28	0.56 (0.12-2.63)
24+ months	134	557	0.45 (0.35-0.58)	6	25	0.67 (0.14-3.17)
Incomplete pregnancy						
0	1272	2086	1.0	20	85	1.0
1	425	874	1.02 (0.88-1.18)	20	38	2.49 (0.96-6.49)
2+	283	630	0.89 (0.75-1.06)	11	48	0.85 (0.27-2.65)
Age at last pregnancy						
<25 years or never pregnant	843	931	1.0	18	41	1.0
25-29 years	381	757	0.89 (0.73-1.09)	5	44	0.37 (0.07-1.92)
30-34 years	429	1002	0.89 (0.72-1.09)	19	51	1.03 (0.28-3.82)
35+ years	311	876	0.68 (0.54-0.85)	9	33	0.78 (0.17-3.55)
Tubal ligation						
No	1711	2861	1.0	45	134	1.0
Yes	259	723	0.64 (0.54-0.76)	6	37	0.49 (0.14-1.71)
COC use duration						
<1 year	883	1009	1.0	20	32	1.0
1-4.99 years	555	1013	0.69 (0.60-0.80)	13	49	0.47 (0.16-1.42)
5-9.99 years	308	771	0.50 (0.42-0.59)	11	47	0.32 (0.09-1.12)
10+ years	231	793	0.30 (0.25-0.36)	7	43	0.22 (0.06-0.84)
Family history of ovarian cancer						
No	1474	2714	1.0	41	123	1.0
Yes	99	65	2.61 (1.86-3.66)	3	3	3.48 (0.44-27.22)
Endometriosis						
No	1764	3366	1.0	47	159	1.0
Yes	212	218	1.87 (1.53-2.29)	4	10	2.51 (0.53-12.00)

* Numbers may not sum to total due to missing values.

** Pooled estimates from logistic regression models in the 50 imputed datasets, adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, and OCAC study.

Abbreviations: BMI: body mass index, CI: confidence interval; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; OR: odds ratio; PRS: polygenic risk score

Supplemental Table 3-14: Associations between risk factors and ovarian cancer risk among pre-menopausal women by strata of first-degree family history of ovarian cancer

Risk factors	No family history of ovarian cancer			With family history of ovarian cancer		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI						
<18.5 kg/m2	46	88	1.27 (0.91-1.79)	2	3	0.23 (0.02-2.68)
18.5-24.99 kg/m2	803	1799	1.0	59	38	1.0
25-29.99 kg/m2	414	759	1.15 (1.00-1.33)	26	27	0.67 (0.27-1.71)
30+ kg/m2	383	553	1.36 (1.16-1.59)	31	16	1.33 (0.46-3.87)
Height (m)						
<1.60	424	736	1.0	35	18	1.0
1.60-1.64	427	862	1.04 (0.89-1.22)	38	31	0.74 (0.28-1.98)
1.65-1.69	436	838	1.09 (0.93-1.29)	24	17	0.65 (0.22-1.95)
1.70-1.74	229	534	0.89 (0.73-1.08)	15	13	0.84 (0.24-2.95)
1.75+	136	238	1.11 (0.87-1.41)	10	5	1.42 (0.23-8.57)
Age at menarche						
<12 years	364	637	1.02 (0.88-1.17)	30	24	0.61 (0.25-1.51)
12-14 years	1134	2186	1.0	80	53	1.0
15+ years	149	378	0.78 (0.64-0.94)	11	7	0.73 (0.19-2.85)
Parity						
0	742	829	1.0	45	11	1.0
1	274	538	0.76 (0.61-0.95)	7	18	0.06 (0.01-0.36)
2	394	1058	0.64 (0.51-0.80)	46	36	0.31 (0.07-1.25)
3+	246	789	0.54 (0.42-0.71)	23	19	0.25 (0.05-1.31)
Breastfeeding						
Never	990	1280	1.0	69	33	1.0
<12 months	368	865	0.84 (0.70-1.00)	25	30	1.12 (0.38-3.29)
12-23 months	179	484	0.73 (0.59-0.91)	14	10	1.31 (0.33-5.15)
24+ months	115	507	0.45 (0.35-0.58)	10	7	1.00 (0.20-5.02)
Incomplete pregnancy						
0	1081	1928	1.0	79	40	1.0
1	322	703	1.05 (0.91-1.22)	33	19	1.09 (0.43-2.76)
2+	218	527	0.94 (0.79-1.12)	9	21	0.25 (0.08-0.82)
Age at last pregnancy						
<25 years or never pregnant	769	915	1.0	54	21	1.0
25-29 years	271	608	0.86 (0.70-1.06)	19	22	0.91 (0.26-3.22)
30-34 years	346	891	0.89 (0.72-1.08)	22	26	0.77 (0.22-2.70)
35+ years	244	768	0.65 (0.52-0.81)	23	15	1.84 (0.40-8.35)
Tubal ligation						
No	1467	2583	1.0	102	54	1.0
Yes	181	547	0.64 (0.54-0.77)	19	25	0.43 (0.15-1.25)
COC use duration						
<1 year	735	837	1.0	56	24	1.0
1-4.99 years	442	854	0.68 (0.58-0.78)	34	22	0.94 (0.34-2.60)
5-9.99 years	262	711	0.50 (0.43-0.59)	17	23	0.46 (0.15-1.39)
10+ years	215	807	0.30 (0.25-0.36)	12	15	0.33 (0.09-1.16)
DMPA use						
No	1474	2714	1.0	99	65	1.0
Yes	41	123	0.70 (0.49-1.00)	3	3	0.82 (0.09-7.54)
Endometriosis						
No	1461	3029	1.0	105	71	1.0
Yes	189	176	1.96 (1.60-2.40)	16	13	0.97 (0.32-2.90)

* Numbers may not sum to total due to missing values.

** Pooled estimates from logistic regression models in the 50 imputed datasets, adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, and OCAC study.

Abbreviations: BMI: body mass index, CI: confidence interval; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; OR: odds ratio; PRS: polygenic risk score

Supplemental Table 3-15: Associations between risk factors and ovarian cancer risk among pre-menopausal women by strata of endometriosis

Risk factors	No endometriosis			With endometriosis		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI						
<18.5 kg/m2	59	102	1.27 (0.89-1.80)	9	9	1.09 (0.36-3.33)
18.5-24.99 kg/m2	950	2207	1.0	139	150	1.0
25-29.99 kg/m2	470	936	1.11 (0.96-1.29)	65	57	1.40 (0.84-2.33)
30+ kg/m2	467	672	1.34 (1.14-1.57)	41	43	1.68 (0.94-2.99)
Height (m)						
<1.60	522	988	1.0	70	55	1.0
1.60-1.64	534	1061	1.03 (0.88-1.22)	63	67	1.03 (0.57-1.88)
1.65-1.69	500	974	1.12 (0.94-1.32)	59	77	0.71 (0.39-1.29)
1.70-1.74	261	626	0.87 (0.71-1.06)	38	37	0.98 (0.49-1.97)
1.75+	146	279	1.09 (0.84-1.40)	25	23	1.17 (0.52-2.59)
Age at menarche						
<12 years	433	793	1.01 (0.87-1.17)	62	62	1.06 (0.66-1.71)
12-14 years	1342	2655	1.0	164	175	1.0
15+ years	185	472	0.75 (0.61-0.91)	28	20	1.41 (0.71-2.82)
Parity						
0	762	871	1.0	120	70	1.0
1	323	672	0.70 (0.55-0.88)	49	60	1.07 (0.49-2.36)
2	534	1342	0.60 (0.48-0.76)	62	76	1.10 (0.49-2.46)
3+	349	1049	0.53 (0.40-0.69)	24	53	0.48 (0.18-1.30)
Breastfeeding						
Never	1123	1522	1.0	164	106	1.0
<12 months	482	1106	0.89 (0.74-1.06)	51	80	0.42 (0.21-0.83)
12-23 months	215	594	0.79 (0.63-0.98)	20	41	0.44 (0.19-1.03)
24+ months	134	620	0.44 (0.34-0.57)	18	25	0.72 (0.27-1.87)
Incomplete pregnancy						
0	1250	2280	1.0	159	126	1.0
1	420	912	1.09 (0.94-1.26)	52	64	0.67 (0.40-1.13)
2+	271	689	0.94 (0.79-1.12)	37	62	0.60 (0.34-1.08)
Age at last pregnancy						
<25 years or never being pregnant	822	1009	1.0	114	64	1.0
25-29 years	376	812	0.88 (0.72-1.09)	34	55	0.67 (0.32-1.38)
30-34 years	439	1118	0.89 (0.72-1.10)	51	65	0.94 (0.47-1.89)
35+ years	296	959	0.65 (0.52-0.82)	50	67	0.87 (0.41-1.86)
Tubal ligation						
No	1699	3083	1.0	227	199	1.0
Yes	259	761	0.65 (0.55-0.78)	27	52	0.44 (0.23-0.82)
COC use duration						
<1 year	891	1098	1.0	98	58	1.0
1-4.99 years	542	1089	0.67 (0.58-0.78)	80	73	0.84 (0.49-1.43)
5-9.99 years	307	853	0.49 (0.41-0.58)	45	62	0.47 (0.27-0.84)
10+ years	225	892	0.29 (0.24-0.35)	30	64	0.37 (0.20-0.69)
DMPA use						
No	1764	3366	1.0	212	218	1.0
Yes	47	159	0.69 (0.48-1.00)	4	10	0.78 (0.22-2.78)
Family history of ovarian cancer						
No	1461	3029	1.0	189	176	1.0
Yes	105	71	2.92 (2.04-4.18)	16	13	1.53 (0.62-3.80)

* Numbers may not sum to total due to missing values.

** Pooled estimates from logistic regression models in the 50 imputed datasets, adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, and OCAC study.

Abbreviations: BMI: body mass index, CI: confidence interval; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; OR: odds ratio; PRS: polygenic risk score

Supplemental Table 3-16: Associations between risk factors and ovarian cancer risk among pre-menopausal women by strata of the PRS

Risk factors	1st quartile PRS			2nd quartile PRS		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI						
<18.5 kg/m2	10	14	2.13 (0.83-5.44)	10	21	1.19 (0.47-3.01)
18.5-24.99 kg/m2	167	446	1.0	158	427	1.0
25-29.99 kg/m2	77	184	1.15 (0.80-1.67)	99	181	1.53 (1.07-2.18)
30+ kg/m2	70	132	1.44 (0.95-2.17)	114	136	2.42 (1.67-3.50)
Height (m)						
<1.60	95	209	1.0	120	190	1.0
1.60-1.64	83	187	1.13 (0.74-1.71)	93	207	0.81 (0.55-1.20)
1.65-1.69	84	193	1.28 (0.83-1.97)	88	206	0.77 (0.52-1.15)
1.70-1.74	44	139	0.88 (0.53-1.45)	52	106	0.98 (0.60-1.60)
1.75+	23	49	1.25 (0.65-2.41)	32	57	1.08 (0.59-1.98)
Age at menarche						
<12 years	72	161	0.95 (0.66-1.38)	94	172	1.01 (0.71-1.43)
12-14 years	234	505	1.0	250	511	1.0
15+ years	22	106	0.43 (0.25-0.75)	39	86	0.89 (0.55-1.42)
Parity						
0	121	169	1.0	151	160	1.0
1	66	159	0.66 (0.37-1.18)	65	131	0.82 (0.45-1.48)
2	96	251	0.74 (0.41-1.33)	108	271	0.75 (0.43-1.31)
3+	47	198	0.48 (0.24-0.96)	61	207	0.65 (0.33-1.26)
Breastfeeding						
Never	174	300	1.0	216	285	1.0
<12 months	88	226	0.95 (0.60-1.52)	100	221	0.90 (0.57-1.41)
12-23 months	40	120	0.94 (0.54-1.66)	39	113	0.82 (0.47-1.43)
24+ months	22	112	0.60 (0.31-1.15)	27	135	0.43 (0.23-0.80)
Incomplete pregnancy						
0	196	443	1.0	260	443	1.0
1	75	190	1.27 (0.87-1.85)	77	170	1.22 (0.84-1.78)
2+	52	133	1.29 (0.82-2.02)	43	147	0.77 (0.50-1.19)
Age at last pregnancy						
<25 years or never being pregnant	136	204	1.0	172	185	1.0
25-29 years	62	169	0.82 (0.49-1.36)	76	160	0.80 (0.49-1.31)
30-34 years	80	208	0.95 (0.58-1.57)	84	229	0.73 (0.44-1.21)
35+ years	47	187	0.54 (0.30-0.96)	43	188	0.38 (0.21-0.68)
Tubal ligation						
No	294	602	1.0	335	589	1.0
Yes	34	157	0.46 (0.29-0.74)	49	163	0.56 (0.37-0.87)
COC use duration						
<1 year	148	196	1.0	189	224	1.0
1-4.99 years	91	225	0.57 (0.39-0.84)	96	195	0.55 (0.38-0.79)
5-9.99 years	48	179	0.37 (0.24-0.58)	53	183	0.34 (0.22-0.52)
10+ years	44	176	0.29 (0.18-0.46)	46	166	0.30 (0.19-0.47)
DMPA use						
No	283	649	1.0	349	670	1.0
Yes	9	41	0.62 (0.28-1.41)	5	30	0.35 (0.11-1.09)
Family history of ovarian cancer						
No	261	625	1.0	302	625	1.0
Yes	19	13	3.25 (1.41-7.48)	16	20	1.27 (0.57-2.86)
Endometriosis						
No	286	727	1.0	340	716	1.0
Yes	41	49	2.04 (1.23-3.38)	44	51	2.01 (1.23-3.31)

Risk factors	3rd quartile PRS			4th quartile PRS		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI						
<18.5 kg/m2	4	12	0.58 (0.17-1.98)	12	19	1.02 (0.44-2.37)
18.5-24.99 kg/m2	208	402	1.0	242	387	1.0
25-29.99 kg/m2	104	182	1.07 (0.75-1.51)	124	178	1.03 (0.75-1.42)
30+ kg/m2	100	147	1.07 (0.74-1.54)	102	110	1.12 (0.77-1.63)
Height (m)						
<1.60	92	157	1.0	112	158	1.0
1.60-1.64	118	211	0.88 (0.59-1.32)	126	193	1.15 (0.78-1.68)
1.65-1.69	115	195	0.99 (0.65-1.50)	126	173	1.34 (0.91-1.98)
1.70-1.74	61	118	0.87 (0.53-1.41)	72	121	0.96 (0.62-1.49)
1.75+	32	64	0.63 (0.35-1.13)	48	50	1.92 (1.12-3.31)
Age at menarche						
<12 years	84	150	0.83 (0.58-1.20)	102	128	1.08 (0.77-1.51)
12-14 years	298	521	1.0	330	492	1.0
15+ years	38	72	0.77 (0.47-1.27)	51	75	0.98 (0.62-1.53)
Parity						
0	172	146	1.0	189	146	1.0
1	64	109	0.59 (0.34-1.03)	85	115	0.87 (0.51-1.48)
2	119	283	0.49 (0.28-0.83)	120	236	0.66 (0.39-1.10)
3+	65	208	0.27 (0.14-0.50)	90	199	0.62 (0.35-1.12)
Breastfeeding						
Never	247	262	1.0	283	252	1.0
<12 months	96	215	0.86 (0.55-1.33)	117	184	0.72 (0.47-1.09)
12-23 months	45	115	0.81 (0.48-1.38)	50	118	0.52 (0.32-0.87)
24+ months	30	130	0.55 (0.30-0.99)	32	127	0.30 (0.17-0.52)
Incomplete pregnancy						
0	267	432	1.0	309	413	1.0
1	86	178	0.97 (0.69-1.38)	96	151	1.07 (0.76-1.51)
2+	55	119	0.93 (0.60-1.43)	69	120	1.11 (0.74-1.65)
Age at last pregnancy						
<25 years or never pregnant	181	183	1.0	208	175	1.0
25-29 years	74	128	1.02 (0.63-1.67)	84	128	0.94 (0.58-1.51)
30-34 years	97	233	0.95 (0.58-1.55)	105	207	0.82 (0.51-1.31)
35+ years	58	195	0.61 (0.36-1.05)	77	181	0.64 (0.38-1.06)
Tubal ligation						
No	356	567	1.0	415	545	1.0
Yes	61	155	0.72 (0.48-1.07)	66	133	0.61 (0.41-0.91)
COC use duration						
<1 year	168	209	1.0	194	165	1.0
1-4.99 years	120	187	0.80 (0.56-1.14)	141	215	0.67 (0.48-0.94)
5-9.99 years	81	161	0.56 (0.38-0.83)	89	146	0.60 (0.41-0.88)
10+ years	49	187	0.29 (0.19-0.45)	59	169	0.30 (0.20-0.46)
DMPA use						
No	360	632	1.0	429	601	1.0
Yes	12	32	0.99 (0.47-2.09)	9	22	0.95 (0.40-2.27)
Family history of ovarian cancer						
No	337	592	1.0	387	565	1.0
Yes	23	15	3.50 (1.58-7.73)	24	18	2.20 (1.08-4.45)
Endometriosis						
No	360	707	1.0	433	661	1.0
Yes	57	39	2.86 (1.74-4.68)	51	34	2.20 (1.32-3.67)

* Numbers may not sum to total due to missing values.

** Pooled estimates from logistic regression models in the 50 imputed datasets, adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, OCAC study and genetic ancestry principal components.

Abbreviations: BMI: body mass index, CI: confidence interval; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; OR: odds ratio; PRS: polygenic risk score

Supplemental Table 3-17: P-values for pairwise interactions between risk factors among post-menopausal women

	BMI	Height	Age at menarche	Parity	Breastfeeding	Incomplete pregnancy	Age at last pregnancy	Tubal ligation	COC use duration	DMPA use	MHT use	Family history of ovarian	Endometriosis	PRS	Age at menopause
BMI		0.95	0.72	0.66	0.019	0.76	0.85	0.76	0.78	0.98	0.28	0.99	0.31	0.54	0.18
Height			0.10	0.43	0.60	0.30	0.10	0.66	0.63	0.99	0.55	0.89	0.086	0.90	0.64
Age at menarche				0.94	0.94	0.43	0.56	0.57	0.18	0.80	0.69	0.31	0.037	0.027	0.64
Parity					0.62*	0.53	0.29	0.33	0.21	0.73	0.038	0.78	0.28	0.10	0.27
Breastfeeding						0.67	0.064	0.91	0.28	0.98	0.10	0.34	0.76	0.23	0.23
Incomplete pregnancy							0.40	0.48	0.32	0.68	0.68	0.51	0.19	0.64	0.57
Age at last pregnancy								0.93	0.92	0.17	0.25	0.90	0.78	0.95	0.14
Tubal ligation									0.004	0.49	0.28	0.77	0.30	0.71	0.11
COC use duration										0.65	0.39	0.72	0.13	0.24	0.29
DMPA use											0.88	0.59	0.53	0.82	0.28
MHT use												0.56	0.95	0.35	0.87
Family history of ovarian cancer													0.48	0.47	0.94
Endometriosis														0.97	0.36

p-value from likelihood ratio tests in the 50 imputed datasets

* Interaction among parous women only

Abbreviations: BMI: body mass index, COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; MHT: menopausal hormone therapy; PRS: polygenic risk score.

Supplemental Table 3-18: Associations between risk factors and ovarian cancer risk among post-menopausal women by strata of BMI

Risk factors	BMI 18.5-24.99 kg/m2			BMI 25-29.99 kg/m2			BMI 30+ kg/m2		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
Height (m)									
<1.60	703	954	1.0	537	792	1.0	455	649	1.0
1.60-1.64	682	962	1.02 (0.88-1.18)	451	675	1.02 (0.86-1.21)	354	496	1.03 (0.85-1.25)
1.65-1.69	621	870	1.08 (0.92-1.26)	387	590	1.00 (0.84-1.20)	256	389	0.95 (0.77-1.18)
1.70-1.74	339	476	1.11 (0.92-1.34)	217	301	1.15 (0.92-1.44)	139	168	1.08 (0.82-1.43)
1.75+	115	180	0.99 (0.75-1.29)	68	108	0.98 (0.70-1.39)	57	75	1.06 (0.72-1.57)
Age at menarche									
<12 years	382	579	0.87 (0.75-1.02)	359	533	0.99 (0.84-1.16)	341	548	0.78 (0.66-0.93)
12-14 years	1700	2334	1.0	1085	1604	1.0	788	1038	1.0
15+ years	362	509	0.93 (0.80-1.09)	198	309	0.96 (0.78-1.18)	128	175	1.02 (0.78-1.32)
Parity									
0	500	489	1.0	287	283	1.0	225	232	1.0
1	339	418	1.05 (0.84-1.32)	207	289	0.88 (0.66-1.17)	165	192	1.06 (0.76-1.46)
2	721	1139	0.85 (0.69-1.05)	476	717	0.83 (0.64-1.08)	311	495	0.84 (0.63-1.13)
3+	899	1396	0.83 (0.66-1.04)	690	1176	0.69 (0.52-0.91)	558	858	0.83 (0.60-1.13)
Breastfeeding									
Never	1319	1489	1.0	841	1079	1.0	690	872	1.0
<12 months	705	1101	0.79 (0.68-0.91)	477	790	0.82 (0.70-0.98)	365	536	0.89 (0.73-1.07)
12-23 months	278	436	0.79 (0.65-0.95)	216	293	1.01 (0.80-1.26)	97	188	0.63 (0.47-0.85)
24+ months	148	325	0.54 (0.42-0.68)	119	234	0.72 (0.55-0.95)	103	141	0.87 (0.63-1.18)
Incomplete pregnancy									
0	1654	2193	1.0	1133	1600	1.0	845	1144	1.0
1	465	762	0.88 (0.77-1.01)	326	520	0.97 (0.82-1.15)	256	370	0.99 (0.82-1.20)
2+	300	447	0.96 (0.81-1.14)	180	314	0.85 (0.69-1.06)	146	245	0.79 (0.62-1.00)
Age at last pregnancy									
<25 years or never being pregnant	698	728	1.0	480	542	1.0	383	430	1.0
25-29 years	647	940	0.86 (0.72-1.04)	471	736	0.91 (0.74-1.12)	354	547	0.86 (0.68-1.10)
30-34 years	640	991	0.89 (0.73-1.08)	404	677	0.87 (0.70-1.09)	316	468	0.94 (0.73-1.21)
35+ years	454	752	0.87 (0.70-1.07)	287	494	0.91 (0.71-1.17)	202	320	0.87 (0.65-1.15)
Tubal ligation									
No	2096	2640	1.0	1371	1799	1.0	1010	1243	1.0
Yes	359	712	0.73 (0.63-0.85)	284	606	0.65 (0.55-0.77)	241	487	0.67 (0.55-0.82)
COC use duration									
<1 year	1460	1650	1.0	983	1240	1.0	762	849	1.0
1-4.99 years	465	736	0.72 (0.62-0.84)	317	547	0.72 (0.61-0.87)	258	425	0.67 (0.54-0.82)
5-9.99 years	284	534	0.60 (0.50-0.71)	196	330	0.70 (0.57-0.87)	137	264	0.57 (0.44-0.73)
10+ years	235	513	0.45 (0.38-0.55)	159	338	0.49 (0.39-0.62)	102	236	0.39 (0.30-0.51)
DMPA use									
No	2127	2993	1.0	1479	2185	1.0	1117	1566	1.0
Yes	15	24	1.06 (0.55-2.05)	10	15	0.98 (0.43-2.24)	8	15	0.94 (0.41-2.17)
MHT use									

Risk factors	BMI 18.5-24.99 kg/m2			BMI 25-29.99 kg/m2			BMI 30+ kg/m2		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
Never use	1258	1763	1.0	950	1335	1.0	813	1115	1.0
ET only	413	468	1.27 (1.08-1.50)	287	347	1.16 (0.96-1.41)	174	205	1.32 (1.04-1.69)
EPT only	583	904	0.97 (0.85-1.12)	290	583	0.70 (0.58-0.83)	177	352	0.73 (0.59-0.91)
Others	149	244	0.90 (0.72-1.13)	79	144	0.84 (0.62-1.13)	48	74	1.00 (0.68-1.48)
Family history of ovarian cancer									
No	1749	2582	1.0	1247	1877	1.0	952	1386	1.0
Yes	115	89	1.88 (1.35-2.61)	85	75	1.75 (1.24-2.48)	68	54	1.94 (1.30-2.91)
Endometriosis									
No	2217	3161	1.0	1493	2309	1.0	1140	1649	1.0
Yes	232	269	1.12 (0.92-1.36)	156	151	1.52 (1.19-1.95)	114	117	1.33 (0.99-1.77)

* Numbers may not sum to total due to missing values.

** Pooled estimates from logistic regression models in the 50 imputed datasets, adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, and OCAC study.

Abbreviations: BMI: body mass index, CI: confidence interval; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; EPT: estrogen plus progestin therapy; ET: estrogen therapy; MHT: menopausal hormone therapy; OR: odds ratio; PRS: polygenic risk score.

Supplemental Table 3-19: Associations between risk factors and ovarian cancer risk among post-menopausal women by strata of height

Risk factors	Height <1.60m			Height 1.60-1.64 m			Height 1.65-1.69 m		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI									
<18.5 kg/m2	32	24	1.47 (0.84-2.58)	24	33	0.89 (0.50-1.57)	27	38	1.03 (0.61-1.74)
18.5-24.99 kg/m2	703	954	1.0	682	962	1.0	621	870	1.0
25-29.99 kg/m2	537	792	0.93 (0.80-1.09)	451	675	0.96 (0.82-1.14)	387	590	0.88 (0.74-1.05)
30+ kg/m2	455	649	0.98 (0.82-1.16)	354	496	1.03 (0.86-1.24)	256	389	0.89 (0.73-1.09)
Age at menarche									
<12 years	405	587	0.95 (0.81-1.12)	308	479	0.91 (0.77-1.09)	223	375	0.80 (0.66-0.98)
12-14 years	1110	1509	1.0	1008	1434	1.0	924	1233	1.0
15+ years	233	310	0.91 (0.75-1.12)	210	243	1.23 (0.99-1.52)	149	262	0.79 (0.63-1.00)
Parity									
0	267	264	1.0	288	257	1.0	254	287	1.0
1	225	249	1.04 (0.78-1.39)	206	262	1.05 (0.78-1.41)	164	212	1.20 (0.88-1.64)
2	494	707	0.84 (0.64-1.10)	399	660	0.78 (0.59-1.03)	391	596	1.06 (0.80-1.40)
3+	776	1203	0.70 (0.53-0.93)	642	993	0.86 (0.64-1.16)	494	797	0.98 (0.73-1.32)
Breastfeeding									
Never	875	1108	1.0	831	983	1.0	715	829	1.0
<12 months	489	723	0.88 (0.74-1.04)	430	693	0.75 (0.63-0.90)	372	626	0.70 (0.58-0.85)
12-23 months	207	291	0.88 (0.70-1.11)	157	262	0.74 (0.57-0.95)	139	208	0.78 (0.59-1.02)
24+ months	161	242	0.79 (0.62-1.02)	99	186	0.66 (0.49-0.89)	67	165	0.48 (0.34-0.68)
Incomplete pregnancy									
0	1230	1596	1.0	1040	1421	1.0	851	1168	1.0
1	311	527	0.83 (0.70-0.98)	302	432	1.08 (0.91-1.29)	274	427	0.94 (0.78-1.13)
2+	206	279	1.05 (0.85-1.29)	172	293	0.87 (0.69-1.08)	154	267	0.83 (0.65-1.05)
Age at last pregnancy									
<25 years or never being pregnant	465	519	1.0	447	446	1.0	379	439	1.0
25-29 years	467	728	0.91 (0.73-1.13)	436	634	0.81 (0.64-1.02)	355	543	0.88 (0.69-1.11)
30-34 years	474	616	1.10 (0.88-1.38)	392	646	0.72 (0.57-0.92)	317	517	0.88 (0.69-1.14)
35+ years	325	543	0.88 (0.69-1.13)	236	430	0.68 (0.52-0.90)	232	371	0.99 (0.75-1.31)
Tubal ligation									
No	1450	1781	1.0	1272	1595	1.0	1097	1430	1.0
Yes	300	585	0.68 (0.57-0.81)	262	526	0.72 (0.60-0.86)	200	403	0.68 (0.56-0.84)
COC use duration									
<1 year	1159	1321	1.0	932	1085	1.0	723	851	1.0
1-4.99 years	300	514	0.71 (0.59-0.85)	292	477	0.74 (0.61-0.90)	269	446	0.72 (0.59-0.88)
5-9.99 years	162	284	0.69 (0.55-0.87)	173	313	0.62 (0.49-0.77)	176	307	0.65 (0.51-0.82)
10+ years	134	300	0.45 (0.36-0.57)	132	290	0.43 (0.34-0.55)	130	281	0.47 (0.37-0.61)
DMPA use									

Risk factors	Height <1.60m			Height 1.60-1.64 m			Height 1.65-1.69 m		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
No	1559	2146	1.0	1354	1915	1.0	1119	1653	1.0
Yes	9	13	1.07 (0.44-2.56)	8	17	0.87 (0.38-1.99)	10	13	1.24 (0.51-3.01)
MHT use									
Never use	1068	1370	1.0	837	1190	1.0	712	1020	1.0
ET only	281	324	1.23 (1.01-1.49)	246	284	1.27 (1.03-1.57)	205	260	1.12 (0.90-1.40)
EPT only	271	529	0.72 (0.60-0.86)	312	518	0.92 (0.77-1.11)	276	455	0.86 (0.71-1.04)
Others	90	159	0.74 (0.55-0.98)	83	126	1.00 (0.73-1.36)	59	119	0.84 (0.60-1.18)
Family history of ovarian cancer									
No	1212	1716	1.0	1134	1675	1.0	968	1501	1.0
Yes	85	72	1.63 (1.09-2.42)	81	61	1.89 (1.30-2.76)	60	52	1.97 (1.31-2.96)
Endometriosis									
No	1622	2253	1.0	1374	2025	1.0	1167	1746	1.0
Yes	127	158	1.10 (0.84-1.42)	151	142	1.48 (1.15-1.92)	132	136	1.40 (1.08-1.83)

Risk factors	Height 1.70-1.74 m			Height 1.75+ m		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI						
<18.5 kg/m2	23	18	1.76 (0.90-3.46)	8	11	0.85 (0.30-2.44)
18.5-24.99 kg/m2	339	476	1.0	115	180	1.0
25-29.99 kg/m2	217	301	1.01 (0.79-1.29)	68	108	0.99 (0.65-1.52)
30+ kg/m2	139	168	1.04 (0.77-1.39)	57	75	1.18 (0.73-1.91)
Age at menarche						
<12 years	127	179	0.80 (0.61-1.05)	39	56	0.97 (0.59-1.60)
12-14 years	511	651	1.0	162	252	1.0
15+ years	85	135	0.79 (0.57-1.09)	47	63	1.24 (0.76-2.00)
Parity						
0	188	153	1.0	70	70	1.0
1	95	139	0.72 (0.47-1.08)	38	45	1.17 (0.58-2.35)
2	209	301	0.75 (0.51-1.12)	65	127	0.75 (0.38-1.46)
3+	236	375	0.61 (0.40-0.93)	77	131	0.77 (0.38-1.55)
Breastfeeding						
Never	379	416	1.0	144	167	1.0
<12 months	225	320	1.01 (0.77-1.33)	63	108	0.73 (0.45-1.19)
12-23 months	75	120	0.88 (0.60-1.29)	29	52	0.71 (0.38-1.34)
24+ months	44	87	0.65 (0.41-1.04)	13	38	0.37 (0.17-0.81)
Incomplete pregnancy						
0	489	619	1.0	169	230	1.0
1	141	212	0.95 (0.73-1.23)	49	85	0.80 (0.51-1.27)
2+	83	126	0.85 (0.61-1.19)	30	54	0.72 (0.41-1.26)
Age at last pregnancy						
<25 years or never being pregnant	245	230	1.0	89	98	1.0

Risk factors	Height 1.70-1.74 m			Height 1.75+ m		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
25-29 years	194	259	0.93 (0.66-1.30)	53	93	0.79 (0.44-1.41)
30-34 years	154	288	0.75 (0.52-1.07)	59	106	0.89 (0.50-1.60)
35+ years	126	187	1.00 (0.69-1.46)	46	73	1.20 (0.64-2.27)
Tubal ligation						
No	623	713	1.0	203	277	1.0
Yes	104	227	0.62 (0.46-0.82)	47	90	0.83 (0.53-1.31)
COC use duration						
<1 year	400	394	1.0	119	158	1.0
1-4.99 years	158	213	0.63 (0.47-0.83)	55	85	0.85 (0.53-1.36)
5-9.99 years	83	188	0.39 (0.28-0.53)	44	60	0.91 (0.54-1.53)
10+ years	83	171	0.41 (0.29-0.57)	32	68	0.48 (0.28-0.84)
DMPA use						
No	619	831	1.0	210	314	1.0
Yes	7	9	1.14 (0.36-3.62)	1	3	0.48 (0.04-5.06)
MHT use						
Never use	392	503	1.0	142	209	1.0
ET only	124	130	1.32 (0.96-1.80)	32	44	1.38 (0.77-2.47)
EPT only	160	276	0.78 (0.60-1.01)	59	93	1.01 (0.64-1.59)
Others	39	44	1.21 (0.74-1.98)	14	24	0.82 (0.38-1.78)
Family history of ovarian cancer						
No	552	757	1.0	201	300	1.0
Yes	36	25	2.15 (1.21-3.82)	13	11	1.65 (0.66-4.13)
Endometriosis						
No	638	891	1.0	232	339	1.0
Yes	87	75	1.42 (1.00-2.04)	18	35	0.65 (0.34-1.26)

* Numbers may not sum to total due to missing values.

** Pooled estimates from logistic regression models in the 50 imputed datasets, adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, and OCAC study.

Abbreviations: BMI: body mass index, CI: confidence interval; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; EPT: estrogen plus progestin therapy; ET: estrogen therapy; MHT: menopausal hormone therapy; OR: odds ratio; PRS: polygenic risk score.

Supplemental Table 3-20: Associations between risk factors and ovarian cancer risk among post-menopausal women by strata of age at menarche

Risk factors	Age at menarche <12 years			Age at menarche 12-14 years			Age at menarche 15+ years		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI									
<18.5 kg/m2	11	12	1.08 (0.45-2.57)	79	88	1.10 (0.80-1.52)	24	19	1.39 (0.73-2.66)
18.5-24.99 kg/m2	382	579	1.0	1700	2334	1.0	362	509	1.0
25-29.99 kg/m2	359	533	1.04 (0.85-1.27)	1085	1604	0.91 (0.82-1.01)	198	309	0.91 (0.72-1.16)
30+ kg/m2	341	548	0.94 (0.77-1.16)	788	1038	1.01 (0.90-1.14)	128	175	1.03 (0.77-1.37)
Height (m)									
<1.60	405	587	1.0	1110	1509	1.0	233	310	1.0
1.60-1.64	308	479	0.94 (0.76-1.16)	1008	1434	1.00 (0.89-1.12)	210	243	1.21 (0.92-1.60)
1.65-1.69	223	375	0.88 (0.70-1.11)	924	1233	1.11 (0.98-1.26)	149	262	0.82 (0.61-1.10)
1.70-1.74	127	179	0.95 (0.72-1.27)	511	651	1.23 (1.06-1.43)	85	135	0.91 (0.64-1.31)
1.75+	39	56	0.94 (0.60-1.49)	162	252	0.96 (0.76-1.20)	47	63	1.17 (0.74-1.85)
Parity									
0	222	218	1.0	714	689	1.0	123	119	1.0
1	148	196	1.01 (0.73-1.41)	480	582	0.99 (0.82-1.20)	95	122	1.06 (0.69-1.63)
2	311	508	0.88 (0.64-1.19)	1050	1570	0.82 (0.69-0.98)	191	307	0.91 (0.61-1.37)
3+	422	759	0.75 (0.54-1.04)	1488	2252	0.75 (0.62-0.91)	322	467	0.96 (0.62-1.49)
Breastfeeding									
Never	602	790	1.0	1960	2276	1.0	371	425	1.0
<12 months	306	531	0.81 (0.66-0.99)	1077	1625	0.83 (0.74-0.93)	193	307	0.76 (0.58-0.99)
12-23 months	122	186	0.89 (0.66-1.19)	400	614	0.81 (0.69-0.95)	82	130	0.70 (0.48-1.00)
24+ months	61	131	0.71 (0.49-1.02)	251	455	0.65 (0.54-0.79)	76	129	0.57 (0.39-0.84)
Incomplete pregnancy									
0	748	1030	1.0	2539	3330	1.0	483	642	1.0
1	209	381	0.81 (0.66-1.00)	724	1071	0.97 (0.87-1.09)	145	227	0.94 (0.72-1.22)
2+	129	246	0.80 (0.62-1.03)	417	637	0.91 (0.79-1.05)	96	134	0.99 (0.72-1.35)
Age at last pregnancy									
<25 years or never being pregnant	369	391	1.0	1070	1141	1.0	178	191	1.0
25-29 years	294	531	0.73 (0.57-0.93)	1009	1447	0.92 (0.79-1.08)	200	276	0.85 (0.60-1.21)
30-34 years	261	454	0.78 (0.60-1.01)	950	1413	0.94 (0.80-1.10)	179	298	0.79 (0.55-1.13)
35+ years	168	297	0.78 (0.58-1.06)	637	1058	0.89 (0.74-1.06)	163	244	0.93 (0.63-1.35)
Tubal ligation									
No	906	1188	1.0	3123	3825	1.0	606	761	1.0
Yes	191	449	0.64 (0.52-0.79)	595	1142	0.71 (0.63-0.81)	124	234	0.65 (0.49-0.85)
COC use duration									
<1 year	624	818	1.0	2201	2427	1.0	494	547	1.0
1-4.99 years	245	392	0.87 (0.71-1.08)	720	1149	0.70 (0.62-0.78)	107	187	0.56 (0.41-0.75)
5-9.99 years	141	237	0.80 (0.62-1.04)	435	763	0.60 (0.52-0.69)	66	142	0.46 (0.33-0.66)

Risk factors	Age at menarche <12 years			Age at menarche 12-14 years			Age at menarche 15+ years		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
10+ years	90	230	0.44 (0.33-0.59)	359	737	0.46 (0.39-0.53)	61	134	0.40 (0.28-0.57)
DMPA use									
No	946	1457	1.0	3246	4450	1.0	652	928	1.0
Yes	8	15	0.86 (0.36-2.06)	24	35	1.12 (0.65-1.92)	4	5	1.45 (0.37-5.61)
MHT use									
Never use	624	949	1.0	2090	2749	1.0	430	566	1.0
ET only	192	219	1.36 (1.07-1.74)	590	677	1.22 (1.07-1.40)	106	146	0.99 (0.73-1.35)
EPT only	205	386	0.85 (0.68-1.05)	739	1257	0.83 (0.74-0.93)	128	222	0.82 (0.62-1.09)
Others	52	91	0.99 (0.68-1.44)	195	315	0.86 (0.71-1.05)	38	65	0.91 (0.58-1.41)
Family history of ovarian cancer									
No	817	1242	1.0	2740	3935	1.0	494	749	1.0
Yes	60	54	1.88 (1.27-2.80)	187	132	1.98 (1.51-2.59)	27	32	1.26 (0.70-2.28)
Endometriosis									
No	960	1545	1.0	3370	4716	1.0	688	957	1.0
Yes	137	131	1.71 (1.30-2.25)	337	357	1.21 (1.03-1.43)	41	55	0.96 (0.62-1.50)

* Numbers may not sum to total due to missing values.

** Pooled estimates from logistic regression models in the 50 imputed datasets, adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, and OCAC study.

Abbreviations: BMI: body mass index, CI: confidence interval; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; EPT: estrogen plus progestin therapy; ET: estrogen therapy; MHT: menopausal hormone therapy; OR: odds ratio; PRS: polygenic risk score.

Supplemental Table 3-21: Associations between risk factors and ovarian cancer risk among post-menopausal women by strata of parity

Risk factors	Nulliparous			Parity 1		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI						
<18.5 kg/m2	42	25	1.52 (0.88-2.61)	12	7	2.13 (0.79-5.73)
18.5-24.99 kg/m2	500	489	1.0	339	418	1.0
25-29.99 kg/m2	287	283	0.97 (0.78-1.20)	207	289	0.83 (0.65-1.07)
30+ kg/m2	225	232	0.98 (0.77-1.25)	165	192	0.95 (0.72-1.26)
Height (m)						
<1.60	267	264	1.0	225	249	1.0
1.60-1.64	288	257	1.20 (0.92-1.56)	206	262	0.90 (0.68-1.19)
1.65-1.69	254	287	1.02 (0.78-1.33)	164	212	0.88 (0.65-1.19)
1.70-1.74	188	153	1.48 (1.09-2.01)	95	139	0.81 (0.57-1.14)
1.75+	70	70	1.23 (0.82-1.84)	38	45	0.90 (0.54-1.50)
Age at menarche						
<12 years	222	218	0.96 (0.76-1.21)	148	196	0.86 (0.66-1.12)
12-14 years	714	689	1.0	480	582	1.0
15+ years	123	119	1.04 (0.78-1.40)	95	122	0.97 (0.71-1.34)
Breastfeeding						
Never				369	429	1.0
<12 months				302	396	0.93 (0.74-1.16)
12-23 months				40	45	0.98 (0.60-1.59)
24+ months				14	16	0.87 (0.38-1.95)
Incomplete pregnancy						
0	829	731	1.0	461	546	1.0
1	139	160	0.93 (0.63-1.39)	141	206	0.90 (0.69-1.17)
2+	91	131	0.64 (0.39-1.04)	118	142	0.96 (0.71-1.30)
Age at last pregnancy						
<25 years or never pregnant	884	804	1.0	229	275	1.0
25-29 years	38	74	0.65 (0.36-1.15)	193	234	1.07 (0.81-1.42)
30-34 years	51	57	1.19 (0.68-2.09)	161	193	1.03 (0.76-1.40)
35+ years	60	67	1.19 (0.68-2.09)	138	204	0.83 (0.60-1.14)
Tubal ligation						
No	1020	922	1.0	659	757	1.0
Yes	32	74	0.52 (0.33-0.82)	72	131	0.67 (0.48-0.94)
COC use duration						
<1 year	684	521	1.0	405	389	1.0
1-4.99 years	172	170	0.70 (0.53-0.92)	145	207	0.59 (0.44-0.78)
5-9.99 years	104	149	0.52 (0.38-0.71)	92	157	0.48 (0.35-0.67)
10+ years	103	193	0.37 (0.27-0.50)	84	150	0.41 (0.29-0.57)
DMPA use						
No	915	860	1.0	640	788	1.0
Yes	12	6	1.47 (0.54-4.01)	1	5	0.75 (0.14-3.95)
MHT use						
Never use	651	578	1.0	439	488	1.0
ET only	117	116	0.90 (0.66-1.23)	79	113	0.88 (0.62-1.24)
EPT only	216	276	0.79 (0.63-1.00)	158	236	0.83 (0.64-1.09)
Other	55	50	1.00 (0.66-1.52)	33	54	0.68 (0.42-1.10)
Family history of ovarian cancer						
No	926	907	1.0	548	717	1.0
Yes	46	26	2.01 (1.19-3.39)	34	25	1.61 (0.92-2.81)
Endometriosis						
No	890	909	1.0	636	821	1.0
Yes	174	118	1.45 (1.10-1.90)	93	84	1.54 (1.10-2.16)

Risk factors	Parity 2			Parity 3+		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI						
<18.5 kg/m2	25	34	1.12 (0.65-1.95)	35	58	0.89 (0.57-1.39)
18.5-24.99 kg/m2	721	1139	1.0	899	1396	1.0
25-29.99 kg/m2	476	717	1.01 (0.87-1.19)	690	1176	0.89 (0.78-1.01)
30+ kg/m2	311	495	0.99 (0.82-1.19)	558	858	0.98 (0.85-1.14)
Height (m)						
<1.60	494	707	1.0	776	1203	1.0
1.60-1.64	399	660	0.91 (0.76-1.09)	642	993	1.08 (0.93-1.24)
1.65-1.69	391	596	1.05 (0.87-1.27)	494	797	1.07 (0.92-1.25)
1.70-1.74	209	301	1.20 (0.95-1.51)	236	375	1.08 (0.88-1.32)
1.75+	65	127	0.87 (0.62-1.22)	77	131	0.99 (0.72-1.36)
Age at menarche						
<12 years	311	508	0.90 (0.76-1.07)	422	759	0.85 (0.74-0.98)
12-14 years	1050	1570	1.0	1488	2252	1.0
15+ years	191	307	0.90 (0.73-1.11)	322	467	0.98 (0.83-1.16)
Breastfeeding						
Never	683	918	1.0	834	1132	1.0
<12 months	579	908	0.84 (0.72-0.98)	704	1175	0.75 (0.65-0.86)
12-23 months	211	352	0.77 (0.62-0.96)	358	538	0.78 (0.65-0.93)
24+ months	75	143	0.70 (0.51-0.97)	300	562	0.61 (0.51-0.74)
Incomplete pregnancy						
0	1081	1572	1.0	1432	2202	1.0
1	292	518	0.85 (0.72-1.01)	509	803	1.00 (0.87-1.14)
2+	170	283	0.94 (0.76-1.17)	267	466	0.93 (0.78-1.10)
Age at last pregnancy						
<25 years or never pregnant	325	422	1.0	194	234	1.0
25-29 years	611	901	0.88 (0.73-1.06)	669	1058	0.82 (0.64-1.05)
30-34 years	400	666	0.86 (0.69-1.06)	789	1265	0.84 (0.65-1.07)
35+ years	212	403	0.81 (0.63-1.04)	561	933	0.85 (0.66-1.10)
Tubal ligation						
No	1244	1737	1.0	1740	2396	1.0
Yes	319	599	0.80 (0.67-0.94)	497	1033	0.67 (0.59-0.77)
COC use duration						
<1 year	821	956	1.0	1437	1953	1.0
1-4.99 years	337	613	0.66 (0.55-0.79)	420	746	0.79 (0.68-0.92)
5-9.99 years	243	410	0.70 (0.57-0.86)	204	437	0.63 (0.52-0.76)
10+ years	159	408	0.40 (0.32-0.51)	169	365	0.55 (0.45-0.68)
DMPA use						
No	1357	2087	1.0	1969	3142	1.0
Yes	14	22	1.11 (0.55-2.23)	9	22	0.78 (0.37-1.67)
MHT use						
Never use	840	1270	1.0	1237	1969	1.0
ET only	263	294	1.38 (1.13-1.69)	432	522	1.32 (1.13-1.55)
EPT only	322	636	0.81 (0.68-0.97)	383	726	0.88 (0.75-1.03)
Other	89	158	0.88 (0.66-1.18)	109	213	0.90 (0.70-1.16)
Family history of ovarian cancer						
No	1126	1879	1.0	1482	2465	1.0
Yes	77	73	1.61 (1.13-2.30)	120	98	2.06 (1.44-2.93)
Endometriosis						
No	1428	2233	1.0	2103	3313	1.0
Yes	127	161	1.22 (0.95-1.58)	121	184	1.09 (0.85-1.40)

* Numbers may not sum to total due to missing values.

** Pooled estimates from logistic regression models in the 50 imputed datasets, adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, and OCAC study.

Abbreviations: BMI: body mass index, CI: confidence interval; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; EPT: estrogen plus progestin therapy; ET: estrogen therapy; MHT: menopausal hormone therapy; OR: odds ratio; PRS: polygenic risk score.

Supplemental Table 3-22: Associations between risk factors and ovarian cancer risk among post-menopausal women by strata of breastfeeding duration

Risk factors	Never breastfed			Breastfed <12 months		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI						
<18.5 kg/m2	72	51	1.32 (0.90-1.92)	23	38	0.97 (0.57-1.68)
18.5-24.99 kg/m2	1319	1489	1.0	705	1101	1.0
25-29.99 kg/m2	841	1079	0.89 (0.78-1.00)	477	790	0.89 (0.76-1.04)
30+ kg/m2	690	872	0.94 (0.82-1.07)	365	536	1.04 (0.87-1.24)
Height (m)						
<1.60	875	1108	1.0	489	723	1.0
1.60-1.64	831	983	1.13 (0.99-1.30)	430	693	0.91 (0.76-1.08)
1.65-1.69	715	829	1.16 (1.00-1.34)	372	626	0.89 (0.74-1.08)
1.70-1.74	379	416	1.19 (0.99-1.42)	225	320	1.10 (0.88-1.37)
1.75+	144	167	1.09 (0.84-1.40)	63	108	0.88 (0.62-1.25)
Age at menarche						
<12 years	602	790	0.89 (0.78-1.01)	306	531	0.83 (0.70-0.99)
12-14 years	1960	2276	1.0	1077	1625	1.0
15+ years	371	425	1.00 (0.85-1.18)	193	307	0.95 (0.77-1.17)
Parity						
0	1071	1034	1.0			
1	369	429	0.97 (0.80-1.16)	302	396	1.0
2	683	918	0.87 (0.74-1.03)	579	908	0.79 (0.65-0.96)
3+	834	1132	0.83 (0.69-1.00)	704	1175	0.70 (0.58-0.86)
Incomplete pregnancy						
0	2121	2426	1.0	1018	1535	1.0
1	526	678	0.98 (0.85-1.12)	334	594	0.96 (0.81-1.12)
2+	278	391	0.82 (0.68-0.98)	199	346	0.97 (0.79-1.18)
Age at last pregnancy						
<25 or never being pregnant	1265	1247	1.0	296	385	1.0
25-29	688	1000	0.81 (0.68-0.95)	554	788	0.96 (0.79-1.18)
30-34	585	766	0.91 (0.76-1.09)	455	744	0.86 (0.69-1.06)
35+	375	467	0.95 (0.78-1.16)	279	561	0.72 (0.57-0.92)
Tubal ligation						
No	2562	2760	1.0	1261	1823	1.0
Yes	376	715	0.66 (0.57-0.76)	323	656	0.75 (0.63-0.88)
COC use duration						
<1 year	1836	1788	1.0	884	1131	1.0
1-4.99 years	517	723	0.68 (0.59-0.79)	324	585	0.65 (0.55-0.78)
5-9.99 years	317	486	0.62 (0.52-0.73)	214	385	0.63 (0.51-0.78)
10+ years	271	503	0.45 (0.38-0.54)	155	369	0.43 (0.34-0.54)
DMPA use						
No	2588	3115	1.0	1393	2260	1.0
Yes	17	23	0.93 (0.49-1.75)	11	17	1.06 (0.49-2.29)
MHT use						
Never use	1721	1999	1.0	815	1295	1.0
ET only	437	446	1.19 (1.02-1.39)	289	378	1.13 (0.93-1.37)
EPT only	574	821	0.85 (0.74-0.97)	333	590	0.86 (0.72-1.02)
Others	140	190	0.92 (0.73-1.17)	94	178	0.83 (0.63-1.10)
Family history of ovarian cancer						
No	2196	2677	1.0	1150	1882	1.0
Yes	133	108	1.61 (1.21-2.15)	85	57	2.27 (1.55-3.34)
Endometriosis						
No	2631	3232	1.0	1444	2307	1.0
Yes	311	266	1.33 (1.11-1.59)	130	162	1.24 (0.96-1.59)

Risk factors	Breastfed 12-23 months			Breastfed 24+ months		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI						
<18.5 kg/m2	10	13	1.10 (0.45-2.65)	9	18	0.99 (0.41-2.39)
18.5-24.99 kg/m2	278	436	1.0	148	325	1.0
25-29.99 kg/m2	216	293	1.11 (0.87-1.42)	119	234	1.21 (0.87-1.67)
30+ kg/m2	97	188	0.72 (0.53-0.99)	103	141	1.77 (1.22-2.55)
Height (m)						
<1.60	207	291	1.0	161	242	1.0
1.60-1.64	157	262	0.91 (0.68-1.22)	99	186	0.99 (0.69-1.43)
1.65-1.69	139	208	1.08 (0.79-1.47)	67	165	0.80 (0.53-1.19)
1.70-1.74	75	120	1.02 (0.70-1.49)	44	87	1.03 (0.64-1.65)
1.75+	29	52	1.07 (0.63-1.82)	13	38	0.74 (0.36-1.54)
Age at menarche						
<12 years	122	186	1.02 (0.77-1.36)	61	131	0.83 (0.57-1.21)
12-14 years	400	614	1.0	251	455	1.0
15+ years	82	130	0.92 (0.67-1.28)	76	129	0.95 (0.66-1.36)
Parity						
0						
1	40	45	1.0	14	16	1.0
2	211	352	0.62 (0.38-1.02)	75	143	0.61 (0.26-1.44)
3+	358	538	0.60 (0.37-0.98)	300	562	0.53 (0.23-1.23)
Incomplete pregnancy						
0	393	567	1.0	232	402	1.0
1	118	209	0.81 (0.61-1.06)	87	195	0.83 (0.60-1.14)
2+	91	154	0.86 (0.63-1.18)	66	122	0.93 (0.64-1.35)
Age at last pregnancy						
<25 or never being pregnant	49	65	1.0	19	14	1.0
25-29	185	272	0.97 (0.61-1.53)	80	145	0.49 (0.21-1.13)
30-34	219	356	0.96 (0.60-1.53)	135	258	0.49 (0.22-1.12)
35+	156	241	1.07 (0.66-1.73)	155	303	0.51 (0.23-1.16)
Tubal ligation						
No	485	678	1.0	307	523	1.0
Yes	124	257	0.70 (0.54-0.91)	81	198	0.71 (0.51-0.98)
COC use duration						
<1 year	333	426	1.0	251	378	1.0
1-4.99 years	133	213	0.88 (0.66-1.17)	89	163	0.95 (0.67-1.35)
5-9.99 years	82	155	0.73 (0.52-1.02)	24	99	0.39 (0.23-0.65)
10+ years	61	140	0.49 (0.34-0.71)	22	80	0.42 (0.24-0.73)
DMPA use						
No	537	837	1.0	343	648	1.0
Yes	4	8	1.41 (0.42-4.67)	3	7	1.02 (0.24-4.33)
MHT use						
Never use	334	503	1.0	253	436	1.0
ET only	111	101	1.55 (1.12-2.15)	50	70	1.58 (1.01-2.47)
EPT only	117	240	0.75 (0.56-1.00)	51	163	0.77 (0.52-1.15)
Others	27	69	0.58 (0.35-0.95)	25	38	1.61 (0.91-2.85)
Family history of ovarian cancer						
No	452	733	1.0	267	512	1.0
Yes	31	30	1.50 (0.88-2.56)	24	17	2.63 (1.20-5.75)
Endometriosis						
No	560	887	1.0	364	677	1.0
Yes	46	47	1.54 (0.98-2.41)	22	43	0.99 (0.56-1.77)

* Numbers may not sum to total due to missing values.

** Pooled estimates from logistic regression models in the 50 imputed datasets, adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, and OCAC study.

Abbreviations: BMI: body mass index, CI: confidence interval; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; EPT: estrogen plus progestin therapy; ET: estrogen therapy; MHT: menopausal hormone therapy; OR: odds ratio; PRS: polygenic risk score.

Supplemental Table 3-23: Associations between risk factors and ovarian cancer risk among post-menopausal women by strata of incomplete pregnancy

Risk factors	0 incomplete pregnancy			1 incomplete prengnacy			2+ incomlete pregnancies		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI									
<18.5 kg/m2	88	85	1.16 (0.85-1.60)	15	26	1.03 (0.53-1.97)	7	10	1.40 (0.55-3.57)
18.5-24.99 kg/m2	1654	2193	1.0	465	762	1.0	300	447	1.0
25-29.99 kg/m2	1133	1600	0.93 (0.83-1.03)	326	520	1.04 (0.86-1.25)	180	314	0.83 (0.65-1.06)
30+ kg/m2	845	1144	0.98 (0.87-1.10)	256	370	1.15 (0.93-1.42)	146	245	0.82 (0.63-1.08)
Height (m)									
<1.60	1230	1596	1.0	311	527	1.0	206	279	1.0
1.60-1.64	1040	1421	0.99 (0.88-1.11)	302	432	1.35 (1.09-1.68)	172	293	0.76 (0.58-1.00)
1.65-1.69	851	1168	1.01 (0.89-1.14)	274	427	1.27 (1.02-1.59)	154	267	0.77 (0.58-1.03)
1.70-1.74	489	619	1.09 (0.94-1.27)	141	212	1.45 (1.10-1.90)	83	126	0.91 (0.64-1.30)
1.75+	169	230	1.00 (0.79-1.25)	49	85	1.14 (0.76-1.71)	30	54	0.71 (0.43-1.18)
Age at menarche									
<12 years	748	1030	0.94 (0.84-1.05)	209	381	0.77 (0.63-0.95)	129	246	0.83 (0.64-1.07)
12-14 years	2539	3330	1.0	724	1071	1.0	417	637	1.0
15+ years	483	642	0.98 (0.85-1.13)	145	227	0.86 (0.67-1.09)	96	134	1.08 (0.80-1.46)
Parity									
0	829	731	1.0	139	160	1.0	91	131	1.0
1	461	546	1.01 (0.83-1.23)	141	206	0.91 (0.65-1.28)	118	142	1.31 (0.88-1.97)
2	1081	1572	0.87 (0.72-1.04)	292	518	0.76 (0.56-1.03)	170	283	1.01 (0.69-1.50)
3+	1432	2202	0.78 (0.64-0.96)	509	803	0.77 (0.57-1.06)	267	466	0.85 (0.57-1.27)
Breastfeeding									
Never	2121	2426	1.0	526	678	1.0	278	391	1.0
<12 months	1018	1535	0.82 (0.73-0.92)	334	594	0.76 (0.63-0.93)	199	346	0.83 (0.63-1.09)
12-23 months	393	567	0.86 (0.73-1.01)	118	209	0.70 (0.53-0.94)	91	154	0.82 (0.58-1.16)
24+ months	232	402	0.69 (0.57-0.84)	87	195	0.54 (0.40-0.74)	66	122	0.70 (0.47-1.05)
Age at last pregnancy									
<25 years or never being pregnant	1423	1434	1.0	153	222	1.0	45	65	1.0
25-29 years	1051	1534	0.85 (0.73-0.98)	289	452	1.00 (0.76-1.32)	151	254	1.01 (0.63-1.61)
30-34 years	843	1308	0.84 (0.71-0.98)	338	545	1.02 (0.77-1.34)	199	304	1.17 (0.73-1.87)
35+ years	452	755	0.79 (0.65-0.95)	278	452	1.03 (0.77-1.36)	229	385	1.20 (0.75-1.92)
Tubal ligation									
No	3210	3792	1.0	867	1227	1.0	523	778	1.0
Yes	571	1130	0.67 (0.60-0.76)	213	459	0.70 (0.57-0.85)	122	243	0.79 (0.60-1.03)
COC use duration									
<1 year	2359	2556	1.0	603	756	1.0	350	472	1.0
1-4.99 years	673	1065	0.69 (0.61-0.79)	248	393	0.78 (0.63-0.96)	142	253	0.72 (0.55-0.95)
5-9.99 years	423	681	0.64 (0.55-0.74)	120	298	0.53 (0.41-0.68)	84	163	0.70 (0.51-0.96)
10+ years	331	732	0.41 (0.35-0.48)	104	233	0.54 (0.41-0.71)	65	131	0.53 (0.38-0.76)
DMPA use									

Risk factors	0 incomplete pregnancy			1 incomplete prengnacy			2+ incomlete pregnancies		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
No	3340	4473	1.0	969	1512	1.0	566	891	1.0
Yes	20	37	0.88 (0.49-1.56)	9	9	1.39 (0.55-3.51)	7	9	1.25 (0.46-3.42)
MHT use									
Never use	2149	2785	1.0	614	919	1.0	383	570	1.0
ET only	604	669	1.23 (1.08-1.41)	166	221	1.27 (1.00-1.61)	99	129	1.19 (0.87-1.63)
EPT only	734	1208	0.83 (0.74-0.93)	221	401	0.95 (0.77-1.17)	105	238	0.69 (0.52-0.91)
Others	196	293	0.91 (0.74-1.11)	43	114	0.82 (0.57-1.17)	38	65	0.92 (0.60-1.41)
Family history of ovarian cancer									
No	2784	3848	1.0	775	1259	1.0	455	773	1.0
Yes	182	150	1.70 (1.30-2.23)	52	42	2.22 (1.44-3.43)	34	27	2.17 (1.25-3.78)
Endometriosis									
No	3431	4701	1.0	993	1557	1.0	573	945	1.0
Yes	346	327	1.38 (1.16-1.63)	84	126	1.00 (0.74-1.34)	70	76	1.41 (0.99-2.02)

* Numbers may not sum to total due to missing values.

** Pooled estimates from logistic regression models in the 50 imputed datasets, adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, and OCAC study.

Abbreviations: BMI: body mass index, CI: confidence interval; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; EPT: estrogen plus progestin therapy; ET: estrogen therapy; MHT: menopausal hormone therapy; OR: odds ratio; PRS: polygenic risk score.

Supplemental Table 3-24: Associations between risk factors and ovarian cancer risk among post-menopausal women by strata of age at last pregnancy

Risk factors	Age at last pregnancy <25 years			Age at last pregnancy 25-29 years		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI						
<18.5 kg/m2	12	8	2.42 (0.90-6.49)	23	27	0.99 (0.56-1.78)
18.5-24.99 kg/m2	318	393	1.0	647	940	1.0
25-29.99 kg/m2	265	336	0.98 (0.77-1.23)	471	736	0.96 (0.81-1.12)
30+ kg/m2	201	265	0.95 (0.73-1.23)	354	547	0.96 (0.80-1.15)
Height (m)						
<1.60	244	326	1.0	467	728	1.0
1.60-1.64	218	249	1.19 (0.91-1.55)	436	634	1.10 (0.92-1.31)
1.65-1.69	188	252	1.00 (0.76-1.31)	355	543	1.07 (0.88-1.29)
1.70-1.74	112	124	1.27 (0.91-1.76)	194	259	1.24 (0.98-1.57)
1.75+	37	52	0.91 (0.56-1.48)	53	93	0.91 (0.62-1.32)
Age at menarche						
<12 years	188	239	0.98 (0.78-1.24)	294	531	0.79 (0.67-0.94)
12-14 years	526	639	1.0	1009	1447	1.0
15+ years	85	121	0.85 (0.62-1.17)	200	276	1.00 (0.81-1.24)
Parity						
0	55	73	1.0	38	74	1.0
1	229	275	0.86 (0.53-1.37)	193	234	1.65 (1.03-2.66)
2	325	422	0.79 (0.49-1.27)	611	901	1.29 (0.82-2.03)
3+	194	234	0.76 (0.46-1.26)	669	1058	1.12 (0.71-1.77)
Breastfeeding						
Never	436	516	1.0	688	1000	1.0
<12 months	296	385	0.81 (0.65-1.02)	554	788	0.98 (0.83-1.15)
12-23 months	49	65	0.72 (0.47-1.12)	185	272	0.88 (0.69-1.11)
24+ months	19	14	1.15 (0.54-2.45)	80	145	0.69 (0.50-0.95)
Incomplete pregnancy						
0	594	703	1.0	1051	1534	1.0
1	153	222	0.75 (0.57-0.98)	289	452	0.98 (0.83-1.17)
2+	45	65	0.70 (0.46-1.06)	151	254	0.86 (0.69-1.09)
Tubal ligation						
No	643	713	1.0	1202	1614	1.0
Yes	160	272	0.73 (0.57-0.94)	309	601	0.74 (0.62-0.88)
COC use duration						
<1 year	438	435	1.0	854	1041	1.0
1-4.99 years	148	229	0.64 (0.49-0.85)	322	546	0.71 (0.59-0.86)
5-9.99 years	109	144	0.76 (0.56-1.04)	202	346	0.65 (0.53-0.81)
10+ years	103	193	0.50 (0.37-0.67)	128	323	0.43 (0.34-0.55)
DMPA use						
No	691	886	1.0	1343	1983	1.0
Yes	5	8	1.03 (0.34-3.06)	4	19	0.41 (0.14-1.19)
MHT use						
Never use	411	526	1.0	806	1131	1.0
ET only	159	175	1.10 (0.83-1.45)	278	345	1.15 (0.95-1.40)
EPT only	165	230	0.93 (0.71-1.21)	292	601	0.71 (0.59-0.85)
Others	41	56	0.97 (0.63-1.50)	87	144	0.91 (0.68-1.22)
Family history of ovarian cancer						
No	594	782	1.0	1082	1706	1.0
Yes	42	27	1.96 (1.15-3.34)	85	78	1.72 (1.20-2.46)
Endometriosis						
No	732	902	1.0	1382	2126	1.0
Yes	70	98	0.87 (0.61-1.23)	118	131	1.48 (1.13-1.94)

Risk factors	Age at last pregnancy 30-34 years			Age at last pregnancy 35+ years		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI						
<18.5 kg/m2	24	32	1.12 (0.64-1.96)	16	33	0.79 (0.42-1.49)
18.5-24.99 kg/m2	640	991	1.0	454	752	1.0
25-29.99 kg/m2	404	677	0.89 (0.75-1.05)	287	494	0.95 (0.78-1.16)
30+ kg/m2	316	468	0.99 (0.82-1.20)	202	320	1.05 (0.83-1.33)
Height (m)						
<1.60	474	616	1.0	325	543	1.0
1.60-1.64	392	646	0.82 (0.68-0.98)	236	430	0.98 (0.78-1.24)
1.65-1.69	317	517	0.87 (0.71-1.06)	232	371	1.20 (0.94-1.52)
1.70-1.74	154	288	0.80 (0.62-1.03)	126	187	1.41 (1.05-1.89)
1.75+	59	106	0.80 (0.56-1.15)	46	73	1.42 (0.93-2.19)
Age at menarche						
<12 years	261	454	0.84 (0.70-1.01)	168	297	0.88 (0.70-1.10)
12-14 years	950	1413	1.0	637	1058	1.0
15+ years	179	298	0.89 (0.72-1.10)	163	244	1.00 (0.79-1.28)
Parity						
0	51	57	1.0	60	67	1.0
1	161	193	1.01 (0.64-1.60)	138	204	0.98 (0.62-1.54)
2	400	666	0.75 (0.49-1.15)	212	403	0.85 (0.55-1.32)
3+	789	1265	0.69 (0.45-1.07)	561	933	0.86 (0.56-1.33)
Breastfeeding						
Never	585	766	1.0	375	467	1.0
<12 months	455	744	0.76 (0.64-0.90)	279	561	0.61 (0.49-0.76)
12-23 months	219	356	0.76 (0.61-0.95)	156	241	0.77 (0.58-1.01)
24+ months	135	258	0.59 (0.45-0.77)	155	303	0.56 (0.43-0.74)
Incomplete pregnancy						
0	843	1308	1.0	452	755	1.0
1	338	545	0.95 (0.80-1.13)	278	452	1.04 (0.85-1.27)
2+	199	304	0.92 (0.75-1.14)	229	385	1.03 (0.83-1.29)
Tubal ligation						
No	1135	1599	1.0	812	1203	1.0
Yes	263	530	0.71 (0.60-0.86)	159	375	0.65 (0.52-0.81)
COC use duration						
<1 year	833	1076	1.0	592	830	1.0
1-4.99 years	287	505	0.72 (0.59-0.86)	188	347	0.74 (0.59-0.94)
5-9.99 years	153	335	0.56 (0.45-0.71)	111	226	0.67 (0.51-0.89)
10+ years	123	258	0.49 (0.38-0.64)	75	199	0.43 (0.32-0.60)
DMPA use						
No	1228	1937	1.0	868	1420	1.0
Yes	12	16	1.23 (0.56-2.69)	4	8	1.07 (0.37-3.08)
MHT use						
Never use	780	1216	1.0	605	992	1.0
ET only	230	278	1.42 (1.15-1.76)	125	161	1.32 (1.00-1.73)
EPT only	273	508	0.89 (0.74-1.08)	178	329	0.95 (0.75-1.20)
Others	72	139	0.84 (0.61-1.15)	41	99	0.75 (0.50-1.11)
Family history of ovarian cancer						
No	982	1616	1.0	653	1172	1.0
Yes	64	64	1.77 (1.18-2.66)	45	37	1.97 (1.18-3.28)
Endometriosis						
No	1283	2038	1.0	890	1510	1.0
Yes	111	139	1.21 (0.92-1.59)	73	93	1.36 (0.96-1.91)

* Numbers may not sum to total due to missing values.

** Pooled estimates from logistic regression models in the 50 imputed datasets, adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, and OCAC study.

Abbreviations: BMI: body mass index, CI: confidence interval; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; EPT: estrogen plus progestin therapy; ET: estrogen therapy; MHT: menopausal hormone therapy; OR: odds ratio; PRS: polygenic risk score.

Supplemental Table 3-25: Associations between risk factors and ovarian cancer risk among post-menopausal women by strata of tubal ligation

Risk factors	No tubal ligation			With tubal ligation		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI						
<18.5 kg/m2	100	102	1.13 (0.84-1.51)	13	18	1.48 (0.69-3.15)
18.5-24.99 kg/m2	2096	2640	1.0	359	712	1.0
25-29.99 kg/m2	1371	1799	0.94 (0.86-1.04)	284	606	0.89 (0.73-1.09)
30+ kg/m2	1010	1243	1.00 (0.89-1.11)	241	487	0.98 (0.79-1.22)
Height (m)						
<1.60	1450	1781	1.0	300	585	1.0
1.60-1.64	1272	1595	1.00 (0.90-1.11)	262	526	1.08 (0.87-1.35)
1.65-1.69	1097	1430	1.02 (0.91-1.14)	200	403	1.05 (0.83-1.34)
1.70-1.74	623	713	1.15 (1.00-1.32)	104	227	1.00 (0.74-1.34)
1.75+	203	277	0.94 (0.76-1.15)	47	90	1.08 (0.72-1.63)
Age at menarche						
<12 years	906	1188	0.90 (0.81-1.00)	191	449	0.80 (0.65-0.98)
12-14 years	3123	3825	1.0	595	1142	1.0
15+ years	606	761	0.97 (0.86-1.10)	124	234	0.92 (0.71-1.19)
Parity						
0	1020	922	1.0	32	74	1.0
1	659	757	0.99 (0.84-1.17)	72	131	1.30 (0.76-2.21)
2	1244	1737	0.81 (0.70-0.95)	319	599	1.26 (0.78-2.04)
3+	1740	2396	0.77 (0.65-0.91)	497	1033	1.08 (0.66-1.77)
Breastfeeding						
Never	2562	2760	1.0	376	715	1.0
<12 months	1261	1823	0.82 (0.73-0.91)	323	656	0.82 (0.67-1.00)
12-23 months	485	678	0.83 (0.72-0.96)	124	257	0.75 (0.57-1.00)
24+ months	307	523	0.65 (0.55-0.77)	81	198	0.67 (0.49-0.93)
Incomplete pregnancy						
0	3210	3792	1.0	571	1130	1.0
1	867	1227	0.92 (0.82-1.02)	213	459	0.96 (0.78-1.17)
2+	523	778	0.86 (0.75-0.98)	122	243	1.01 (0.78-1.30)
Age at last pregnancy						
<25 years or never being pregnant	1434	1367	1.0	179	320	1.0
25-29 years	1202	1614	0.87 (0.76-1.00)	309	601	0.88 (0.68-1.15)
30-34 years	1135	1599	0.88 (0.76-1.02)	263	530	0.87 (0.66-1.15)
35+ years	812	1203	0.88 (0.75-1.03)	159	375	0.82 (0.60-1.12)
COC use duration						
<1 year	2927	3073	1.0	400	648	1.0
1-4.99 years	862	1153	0.77 (0.69-0.86)	210	531	0.58 (0.46-0.72)
5-9.99 years	457	761	0.58 (0.51-0.67)	186	369	0.74 (0.58-0.94)
10+ years	395	805	0.43 (0.38-0.50)	121	285	0.52 (0.39-0.68)
DMPA use						
No	4047	5183	1.0	816	1675	1.0
Yes	25	39	0.96 (0.57-1.62)	11	16	1.35 (0.61-2.95)
MHT use						
Never use	2679	3313	1.0	474	919	1.0
ET only	747	801	1.19 (1.06-1.35)	142	195	1.36 (1.05-1.77)
EPT only	873	1277	0.87 (0.78-0.97)	203	535	0.72 (0.58-0.89)
Other	234	343	0.92 (0.77-1.11)	53	132	0.75 (0.53-1.07)
Family history of ovarian cancer						
No	3383	4397	1.0	684	1407	1.0
Yes	218	155	1.81 (1.40-2.35)	57	58	1.97 (1.32-2.94)
Endometriosis						
No	4194	5397	1.0	846	1710	1.0
Yes	445	391	1.33 (1.14-1.54)	67	124	1.11 (0.80-1.53)

* Numbers may not sum to total due to missing values.

** Pooled estimates from logistic regression models in the 50 imputed datasets, adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, and OCAC study.

Abbreviations: BMI: body mass index, CI: confidence interval; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; EPT: estrogen plus progestin therapy; ET: estrogen therapy; MHT: menopausal hormone therapy; OR: odds ratio; PRS: polygenic risk score.

Supplemental Table 3-26: Associations between risk factors and ovarian cancer risk among post-menopausal women by strata of COC use duration

Risk factors	Oral contraceptive use <1 year			Oral contraceptive use 1-4.99 years		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI						
<18.5 kg/m2	69	61	1.09 (0.76-1.58)	22	21	1.64 (0.87-3.12)
18.5-24.99 kg/m2	1460	1650	1.0	465	736	1.0
25-29.99 kg/m2	983	1240	0.90 (0.80-1.01)	317	547	0.90 (0.74-1.09)
30+ kg/m2	762	849	1.01 (0.89-1.15)	258	425	0.96 (0.78-1.19)
Height (m)						
<1.60	1159	1321	1.0	300	514	1.0
1.60-1.64	932	1085	1.02 (0.90-1.16)	292	477	1.03 (0.83-1.28)
1.65-1.69	723	851	1.02 (0.89-1.18)	269	446	1.01 (0.80-1.26)
1.70-1.74	400	394	1.20 (1.01-1.42)	158	213	1.15 (0.88-1.52)
1.75+	119	158	0.83 (0.64-1.09)	55	85	1.03 (0.69-1.53)
Age at menarche						
<12 years	624	818	0.81 (0.72-0.92)	245	392	0.99 (0.81-1.21)
12-14 years	2201	2427	1.0	720	1149	1.0
15+ years	494	547	1.01 (0.88-1.17)	107	187	0.83 (0.64-1.09)
Parity						
0	684	521	1.0	172	170	1.0
1	405	389	0.95 (0.77-1.18)	145	207	0.87 (0.61-1.24)
2	821	956	0.80 (0.65-0.98)	337	613	0.69 (0.50-0.95)
3+	1437	1953	0.69 (0.56-0.85)	420	746	0.69 (0.49-0.98)
Breastfeeding						
Never	1836	1788	1.0	517	723	1.0
<12 months	884	1131	0.84 (0.74-0.96)	324	585	0.84 (0.69-1.04)
12-23 months	333	426	0.80 (0.67-0.96)	133	213	0.98 (0.74-1.30)
24+ months	251	378	0.65 (0.54-0.80)	89	163	0.95 (0.68-1.32)
Incomplete pregnancy						
0	2359	2556	1.0	673	1065	1.0
1	603	756	0.92 (0.81-1.05)	248	393	0.99 (0.81-1.20)
2+	350	472	0.85 (0.72-0.99)	142	253	0.86 (0.67-1.09)
Age at last pregnancy						
<25 years or never being pregnant	1015	845	1.0	265	329	1.0
25-29 years	854	1041	0.91 (0.77-1.08)	322	546	0.91 (0.71-1.18)
30-34 years	833	1076	0.93 (0.78-1.11)	287	505	0.90 (0.68-1.18)
35+ years	592	830	0.89 (0.74-1.09)	188	347	0.88 (0.65-1.19)
Tubal ligation						
No	2927	3073	1.0	862	1153	1.0
Yes	400	648	0.70 (0.61-0.81)	210	531	0.54 (0.44-0.66)
DMPA use						
No	2954	3412	1.0	928	1512	1.0
Yes	17	13	1.28 (0.61-2.64)	6	15	0.72 (0.29-1.82)
MHT use						
Never use	2047	2330	1.0	593	902	1.0
ET only	526	503	1.24 (1.07-1.44)	169	240	1.13 (0.88-1.44)
EPT only	520	698	0.82 (0.71-0.94)	228	458	0.79 (0.64-0.97)
Others	158	226	0.82 (0.66-1.03)	51	92	1.00 (0.69-1.45)
Family history of ovarian cancer						
No	2317	2703	1.0	817	1381	1.0
Yes	159	102	1.90 (1.37-2.62)	58	46	2.14 (1.39-3.27)
Endometriosis						
No	3073	3583	1.0	947	1573	1.0
Yes	258	225	1.18 (0.97-1.43)	118	156	1.12 (0.85-1.46)

Risk factors	Oral contraceptive use 5-9.99 years			Oral contraceptive use 10+ years		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI						
<18.5 kg/m2	14	20	1.16 (0.55-2.43)	8	22	0.77 (0.33-1.80)
18.5-24.99 kg/m2	284	534	1.0	235	513	1.0
25-29.99 kg/m2	196	330	1.06 (0.83-1.35)	159	338	0.98 (0.76-1.27)
30+ kg/m2	137	264	0.98 (0.75-1.30)	102	236	0.89 (0.66-1.20)
Height (m)						
<1.60	162	284	1.0	134	300	1.0
1.60-1.64	173	313	0.97 (0.73-1.29)	132	290	1.03 (0.75-1.40)
1.65-1.69	176	307	1.01 (0.76-1.35)	130	281	1.10 (0.80-1.50)
1.70-1.74	83	188	0.83 (0.59-1.17)	83	171	1.21 (0.84-1.74)
1.75+	44	60	1.30 (0.81-2.07)	32	68	1.12 (0.68-1.86)
Age at menarche						
<12 years	141	237	1.04 (0.81-1.35)	90	230	0.76 (0.57-1.02)
12-14 years	435	763	1.0	359	737	1.0
15+ years	66	142	0.83 (0.60-1.16)	61	134	0.88 (0.62-1.25)
Parity						
0	104	149	1.0	103	193	1.0
1	92	157	1.13 (0.74-1.73)	84	150	1.28 (0.84-1.95)
2	243	410	1.13 (0.77-1.67)	159	408	0.97 (0.65-1.44)
3+	204	437	0.99 (0.64-1.52)	169	365	1.22 (0.78-1.88)
Breastfeeding						
Never	317	486	1.0	271	503	1.0
<12 months	214	385	0.78 (0.60-1.01)	155	369	0.69 (0.52-0.92)
12-23 months	82	155	0.71 (0.50-1.01)	61	140	0.67 (0.45-1.00)
24+ months	24	99	0.33 (0.20-0.56)	22	80	0.47 (0.27-0.82)
Incomplete pregnancy						
0	423	681	1.0	331	732	1.0
1	120	298	0.76 (0.59-0.98)	104	233	1.10 (0.84-1.46)
2+	84	163	0.96 (0.70-1.31)	65	131	1.17 (0.82-1.68)
Age at last pregnancy						
<25 years or never being pregnant	167	237	1.0	174	320	1.0
25-29 years	202	346	0.88 (0.64-1.20)	128	323	0.67 (0.48-0.93)
30-34 years	153	335	0.77 (0.55-1.08)	123	258	0.87 (0.61-1.23)
35+ years	111	226	0.93 (0.64-1.35)	75	199	0.74 (0.50-1.11)
Tubal ligation						
No	457	761	1.0	395	805	1.0
Yes	186	369	0.89 (0.71-1.13)	121	285	0.81 (0.62-1.06)
DMPA use						
No	535	981	1.0	449	954	1.0
Yes	8	11	1.47 (0.58-3.71)	5	16	0.72 (0.26-2.05)
MHT use						
Never use	285	543	1.0	234	518	1.0
ET only	102	154	1.32 (0.96-1.82)	89	141	1.26 (0.90-1.78)
EPT only	193	346	1.03 (0.80-1.32)	132	367	0.71 (0.54-0.94)
Others	44	88	0.84 (0.56-1.27)	34	68	1.07 (0.68-1.69)
Family history of ovarian cancer						
No	505	928	1.0	420	931	1.0
Yes	36	37	1.75 (1.07-2.88)	23	36	1.46 (0.83-2.57)
Endometriosis						
No	564	1066	1.0	449	1030	1.0
Yes	74	84	1.47 (1.04-2.09)	65	80	1.81 (1.25-2.63)

* Numbers may not sum to total due to missing values.

** Pooled estimates from logistic regression models in the 50 imputed datasets, adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, and OCAC study.

Abbreviations: BMI: body mass index, CI: confidence interval; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; EPT: estrogen plus progestin therapy; ET: estrogen therapy; MHT: menopausal hormone therapy; OR: odds ratio; PRS: polygenic risk score.

Supplemental Table 3-27: Associations between risk factors and ovarian cancer risk among post-menopausal women who had never used DMPA

The sample size among women with DMPA use was too small to conduct the stratified analysis.

Risk factors	Never use DMPA		
	Case*	Control*	OR** (95% CI)
BMI			
<18.5 kg/m2	99	97	1.15 (0.88-1.51)
18.5-24.99 kg/m2	2127	2993	1.0
25-29.99 kg/m2	1479	2185	0.93 (0.86-1.02)
30+ kg/m2	1117	1566	0.99 (0.90-1.09)
Height (m)			
<1.60	1559	2146	1.0
1.60-1.64	1354	1915	1.02 (0.92-1.12)
1.65-1.69	1119	1653	1.02 (0.92-1.13)
1.70-1.74	619	831	1.13 (0.99-1.27)
1.75+	210	314	0.98 (0.82-1.18)
Age at menarche			
<12 years	946	1457	0.89 (0.81-0.97)
12-14 years	3246	4450	1.0
15+ years	652	928	0.96 (0.86-1.07)
Parity			
0	915	860	1.0
1	640	788	1.01 (0.86-1.18)
2	1357	2087	0.84 (0.73-0.97)
3+	1969	3142	0.78 (0.67-0.91)
Breastfeeding			
Never	2588	3115	1.0
<12 months	1393	2260	0.81 (0.74-0.89)
12-23 months	537	837	0.81 (0.71-0.93)
24+ months	343	648	0.65 (0.56-0.76)
Incomplete pregnancy			
0	3340	4473	1.0
1	969	1512	0.92 (0.84-1.01)
2+	566	891	0.89 (0.79-0.99)
Age at last pregnancy			
<25 years or never being pregnant	1406	1513	1.0
25-29 years	1343	1983	0.88 (0.78-1.00)
30-34 years	1228	1937	0.89 (0.78-1.01)
35+ years	868	1420	0.87 (0.76-1.01)
Tubal ligation			
No	4047	5183	1.0
Yes	816	1675	0.69 (0.63-0.76)
COC use duration			
<1 year	2954	3412	1.0
1-4.99 years	928	1512	0.72 (0.65-0.79)
5-9.99 years	535	981	0.62 (0.55-0.70)
10+ years	449	954	0.45 (0.40-0.51)
MHT use			
Never use	2780	3832	1.0
ET only	750	851	1.22 (1.09-1.36)
EPT only	942	1632	0.83 (0.76-0.92)
Others	249	444	0.89 (0.75-1.05)
Family history of ovarian cancer			
No	3490	5111	1.0
Yes	236	181	1.85 (1.47-2.32)
Endometriosis			
No	4435	6404	1.0
Yes	425	448	1.28 (1.12-1.46)

* Numbers may not sum to total due to missing values.

** Pooled estimates from logistic regression models in the 50 imputed datasets, adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, and OCAC study.

Abbreviations: BMI: body mass index, CI: confidence interval; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; EPT: estrogen plus progestin therapy; ET: estrogen therapy; MHT: menopausal hormone therapy; OR: odds ratio; PRS: polygenic risk score.

Supplemental Table 3-28: Associations between risk factors and ovarian cancer risk among post-menopausal women by strata of MHT use

Risk factors	Never use			ET use only		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI						
<18.5 kg/m2	70	64	1.40 (0.97-2.00)	12	19	0.75 (0.35-1.60)
18.5-24.99 kg/m2	1258	1763	1.0	413	468	1.0
25-29.99 kg/m2	950	1335	1.01 (0.90-1.13)	287	347	0.91 (0.73-1.13)
30+ kg/m2	813	1115	1.06 (0.93-1.20)	174	205	0.87 (0.67-1.15)
Height (m)						
<1.60	1068	1370	1.0	281	324	1.0
1.60-1.64	837	1190	0.93 (0.82-1.06)	246	284	1.10 (0.86-1.42)
1.65-1.69	712	1020	0.96 (0.84-1.10)	205	260	1.08 (0.83-1.41)
1.70-1.74	392	503	1.04 (0.88-1.22)	124	130	1.34 (0.97-1.84)
1.75+	142	209	0.86 (0.67-1.09)	32	44	1.10 (0.65-1.85)
Age at menarche						
<12 years	624	949	0.83 (0.74-0.94)	192	219	0.98 (0.77-1.24)
12-14 years	2090	2749	1.0	590	677	1.0
15+ years	430	566	0.98 (0.85-1.13)	106	146	0.82 (0.61-1.10)
Parity						
0	651	578	1.0	117	116	1.0
1	439	488	0.99 (0.81-1.21)	79	113	0.90 (0.58-1.40)
2	840	1270	0.75 (0.62-0.90)	263	294	1.21 (0.82-1.79)
3+	1237	1969	0.67 (0.55-0.82)	432	522	0.95 (0.64-1.41)
Breastfeeding						
Never	1721	1999	1.0	437	446	1.0
<12 months	815	1295	0.82 (0.73-0.94)	289	378	0.80 (0.63-1.01)
12-23 months	334	503	0.84 (0.71-1.00)	111	101	1.06 (0.75-1.48)
24+ months	253	436	0.68 (0.56-0.83)	50	70	0.70 (0.45-1.10)
Incomplete pregnancy						
0	2149	2785	1.0	604	669	1.0
1	614	919	0.95 (0.84-1.07)	166	221	0.89 (0.70-1.13)
2+	383	570	0.93 (0.80-1.08)	99	129	0.84 (0.62-1.13)
Age at last pregnancy						
<25 years or never being pregnant	920	931	1.0	254	258	1.0
25-29 years	806	1131	0.95 (0.80-1.13)	278	345	0.86 (0.65-1.15)
30-34 years	780	1216	0.90 (0.76-1.08)	230	278	0.98 (0.72-1.33)
35+ years	605	992	0.87 (0.72-1.05)	125	161	0.91 (0.63-1.30)
Tubal ligation						
No	2679	3313	1.0	747	801	1.0
Yes	474	919	0.71 (0.62-0.81)	142	195	0.77 (0.59-1.00)
COC use duration						
<1 year	2047	2330	1.0	526	503	1.0
1-4.99 years	593	902	0.71 (0.62-0.81)	169	240	0.70 (0.54-0.90)
5-9.99 years	285	543	0.54 (0.46-0.64)	102	154	0.67 (0.49-0.91)
10+ years	234	518	0.43 (0.36-0.51)	89	141	0.53 (0.38-0.73)
DMPA use						
No	2780	3832	1.0	750	851	1.0
Yes	17	28	0.95 (0.53-1.72)	6	5	1.45 (0.41-5.14)
Family history of ovarian cancer						
No	2278	3203	1.0	624	798	1.0
Yes	158	132	1.75 (1.32-2.32)	47	22	2.51 (1.46-4.30)
Endometriosis						
No	2895	4037	1.0	766	936	1.0
Yes	255	249	1.31 (1.08-1.58)	116	109	1.44 (1.07-1.95)

Risk factors	EPT use only			Other MHT use		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI						
<18.5 kg/m2	22	30	1.00 (0.56-1.81)	8	10	0.96 (0.35-2.66)
18.5-24.99 kg/m2	583	904	1.0	149	244	1.0
25-29.99 kg/m2	290	583	0.79 (0.66-0.95)	79	144	0.99 (0.68-1.45)
30+ kg/m2	177	352	0.82 (0.66-1.02)	48	74	1.11 (0.69-1.78)
Height (m)						
<1.60	271	529	1.0	90	159	1.0
1.60-1.64	312	518	1.18 (0.95-1.47)	83	126	1.21 (0.78-1.87)
1.65-1.69	276	455	1.18 (0.94-1.49)	59	119	1.04 (0.66-1.64)
1.70-1.74	160	276	1.21 (0.93-1.58)	39	44	1.50 (0.84-2.68)
1.75+	59	93	1.33 (0.91-1.94)	14	24	0.83 (0.37-1.87)
Age at menarche						
<12 years	205	386	0.90 (0.73-1.10)	52	91	1.00 (0.65-1.53)
12-14 years	739	1257	1.0	195	315	1.0
15+ years	128	222	1.03 (0.81-1.33)	38	65	1.18 (0.72-1.94)
Parity						
0	216	276	1.0	55	50	1.0
1	158	236	1.26 (0.91-1.74)	33	54	0.69 (0.34-1.39)
2	322	636	1.02 (0.76-1.38)	89	158	0.78 (0.41-1.50)
3+	383	726	1.12 (0.81-1.55)	109	213	0.76 (0.39-1.50)
Breastfeeding						
Never	574	821	1.0	140	190	1.0
<12 months	333	590	0.83 (0.68-1.01)	94	178	0.77 (0.51-1.17)
12-23 months	117	240	0.68 (0.51-0.90)	27	69	0.49 (0.27-0.90)
24+ months	51	163	0.44 (0.30-0.64)	25	38	1.08 (0.55-2.11)
Incomplete pregnancy						
0	734	1208	1.0	196	293	1.0
1	221	401	0.97 (0.79-1.18)	43	114	0.77 (0.51-1.18)
2+	105	238	0.76 (0.59-0.99)	38	65	1.04 (0.64-1.71)
Age at last pregnancy						
<25 years or never pregnant	328	426	1.0	81	91	1.0
25-29 years	292	601	0.68 (0.53-0.87)	87	144	0.90 (0.54-1.50)
30-34 years	273	508	0.79 (0.60-1.02)	72	139	0.75 (0.44-1.28)
35+ years	178	329	0.89 (0.66-1.20)	41	99	0.66 (0.36-1.24)
Tubal ligation						
No	873	1277	1.0	234	343	1.0
Yes	203	535	0.61 (0.50-0.75)	53	132	0.64 (0.42-0.96)
COC use duration						
<1 year	520	698	1.0	158	226	1.0
1-4.99 years	228	458	0.70 (0.57-0.86)	51	92	0.85 (0.53-1.35)
5-9.99 years	193	346	0.76 (0.61-0.96)	44	88	0.59 (0.36-0.97)
10+ years	132	367	0.42 (0.33-0.54)	34	68	0.53 (0.31-0.90)
DMPA use						
No	942	1632	1.0	249	444	1.0
Yes	10	17	1.22 (0.55-2.72)	1	4	0.58 (0.06-5.40)
Family history of ovarian cancer						
No	820	1474	1.0	215	367	1.0
Yes	43	53	1.69 (1.09-2.60)	17	11	2.72 (1.19-6.19)
Endometriosis						
No	976	1730	1.0	254	434	1.0
Yes	99	138	1.27 (0.96-1.69)	32	39	1.13 (0.64-2.01)

* Numbers may not sum to total due to missing values.

** Pooled estimates from logistic regression models in the 50 imputed datasets, adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, and OCAC study.

Abbreviations: BMI: body mass index, CI: confidence interval; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; EPT: estrogen plus progestin therapy; ET: estrogen therapy; MHT: menopausal hormone therapy; OR: odds ratio; PRS: polygenic risk score.

Supplemental Table 3-29: Associations between risk factors and ovarian cancer risk among post-menopausal women by strata of first-degree family history of ovarian cancer

Risk factors	No family history of ovarian cancer			With family history of ovarian cancer		
	Case *	Control *	OR** (95% CI)	Case *	Control *	OR** (95% CI)
BMI						
<18.5 kg/m2	82	87	1.16 (0.88-1.53)	5	3	0.85 (0.16-4.56)
18.5-24.99 kg/m2	1749	2582	1.0	115	89	1.0
25-29.99 kg/m2	1247	1877	0.94 (0.86-1.02)	85	75	0.86 (0.53-1.37)
30+ kg/m2	952	1386	0.99 (0.90-1.09)	68	54	0.98 (0.57-1.65)
Height (m)						
<1.60	1212	1716	1.0	85	72	1.0
1.60-1.64	1134	1675	1.01 (0.92-1.12)	81	61	1.18 (0.69-2.01)
1.65-1.69	968	1501	1.02 (0.92-1.14)	60	52	1.05 (0.58-1.89)
1.70-1.74	552	757	1.12 (0.99-1.28)	36	25	1.29 (0.62-2.70)
1.75+	201	300	0.98 (0.81-1.18)	13	11	0.95 (0.35-2.61)
Age at menarche						
<12 years	817	1242	0.89 (0.81-0.97)	60	54	0.73 (0.45-1.18)
12-14 years	2740	3935	1.0	187	132	1.0
15+ years	494	749	0.98 (0.87-1.10)	27	32	0.67 (0.36-1.27)
Parity						
0	926	907	1.0	46	26	1.0
1	548	717	1.01 (0.86-1.18)	34	25	1.13 (0.47-2.70)
2	1126	1879	0.84 (0.73-0.98)	77	73	0.98 (0.43-2.23)
3+	1482	2465	0.77 (0.66-0.90)	120	98	1.22 (0.51-2.91)
Breastfeeding						
Never	2196	2677	1.0	133	108	1.0
<12 months	1150	1882	0.80 (0.73-0.88)	85	57	1.09 (0.65-1.83)
12-23 months	452	733	0.82 (0.71-0.93)	31	30	0.73 (0.37-1.45)
24+ months	267	512	0.64 (0.55-0.75)	24	17	1.06 (0.46-2.46)
Incomplete pregnancy						
0	2784	3848	1.0	182	150	1.0
1	775	1259	0.92 (0.83-1.01)	52	42	1.19 (0.71-1.99)
2+	455	773	0.88 (0.78-0.99)	34	27	1.15 (0.60-2.20)
Age at last pregnancy						
<25 years or never being pregnant	1321	1440	1.0	82	42	1.0
25-29 years	1082	1706	0.88 (0.78-1.00)	85	78	0.59 (0.31-1.12)
30-34 years	982	1616	0.90 (0.79-1.03)	64	64	0.53 (0.26-1.08)
35+ years	653	1172	0.88 (0.76-1.02)	45	37	0.56 (0.25-1.22)
Tubal ligation						
No	3383	4397	1.0	218	155	1.0
Yes	684	1407	0.69 (0.63-0.76)	57	58	0.76 (0.46-1.28)
COC use duration						
<1 year	2317	2703	1.0	159	102	1.0
1-4.99 years	817	1381	0.72 (0.65-0.79)	58	46	0.62 (0.34-1.11)
5-9.99 years	505	928	0.63 (0.56-0.71)	36	37	0.47 (0.25-0.89)
10+ years	420	931	0.46 (0.40-0.52)	23	36	0.24 (0.12-0.50)
DMPA use						
No	3490	5111	1.0	236	181	1.0
Yes	31	41	1.08 (0.69-1.69)	2	3	0.69 (0.10-4.69)
MHT use						
Never use	2278	3203	1.0	158	132	1.0
ET only	624	798	1.21 (1.08-1.35)	47	22	1.53 (0.82-2.87)
EPT only	820	1474	0.84 (0.76-0.92)	43	53	0.72 (0.42-1.23)
Others	215	367	0.88 (0.74-1.04)	17	11	1.12 (0.47-2.67)
Endometriosis						

Risk factors	No family history of ovarian cancer			With family history of ovarian cancer		
	Case *	Control *	OR** (95% CI)	Case *	Control *	OR** (95% CI)
No	3646	5507	1.0	253	202	1.0
Yes	411	438	1.30 (1.14-1.49)	22	17	0.82 (0.39-1.76)

* Numbers may not sum to total due to missing values.

** Pooled estimates from logistic regression models in the 50 imputed datasets, adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, and OCAC study.

Abbreviations: BMI: body mass index, CI: confidence interval; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; EPT: estrogen plus progestin therapy; ET: estrogen therapy; MHT: menopausal hormone therapy; OR: odds ratio; PRS: polygenic risk score.

Supplemental Table 3-30: Associations between risk factors and ovarian cancer risk among post-menopausal women by strata of endometriosis

Risk factors	No endometriosis			With endometriosis		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI						
<18.5 kg/m2	107	116	1.15 (0.87-1.53)	7	8	0.85 (0.28-2.55)
18.5-24.99 kg/m2	2217	3161	1.0	232	269	1.0
25-29.99 kg/m2	1493	2309	0.91 (0.83-0.99)	156	151	1.31 (0.96-1.80)
30+ kg/m2	1140	1649	0.97 (0.88-1.07)	114	117	1.26 (0.88-1.80)
Height (m)						
<1.60	1622	2253	1.0	127	158	1.0
1.60-1.64	1374	2025	0.99 (0.89-1.09)	151	142	1.44 (1.00-2.09)
1.65-1.69	1167	1746	1.01 (0.90-1.12)	132	136	1.34 (0.92-1.95)
1.70-1.74	638	891	1.10 (0.97-1.25)	87	75	1.57 (1.01-2.43)
1.75+	232	339	1.02 (0.84-1.24)	18	35	0.69 (0.35-1.36)
Age at menarche						
<12 years	960	1545	0.85 (0.77-0.94)	137	131	1.20 (0.88-1.65)
12-14 years	3370	4716	1.0	337	357	1.0
15+ years	688	957	0.97 (0.86-1.08)	41	55	0.81 (0.50-1.30)
Parity						
0	890	909	1.0	174	118	1.0
1	636	821	1.03 (0.87-1.21)	93	84	0.92 (0.56-1.52)
2	1428	2233	0.88 (0.76-1.02)	127	161	0.67 (0.43-1.06)
3+	2103	3313	0.81 (0.69-0.95)	121	184	0.61 (0.37-1.02)
Breastfeeding						
Never	2631	3232	1.0	311	266	1.0
<12 months	1444	2307	0.82 (0.74-0.90)	130	162	0.75 (0.52-1.09)
12-23 months	560	887	0.81 (0.71-0.93)	46	47	0.94 (0.56-1.60)
24+ months	364	677	0.66 (0.57-0.78)	22	43	0.50 (0.26-0.97)
Incomplete pregnancy						
0	3431	4701	1.0	346	327	1.0
1	993	1557	0.96 (0.87-1.05)	84	126	0.64 (0.45-0.90)
2+	573	945	0.90 (0.80-1.02)	70	76	0.74 (0.49-1.11)
Age at last pregnancy						
<25 years or never being pregnant	1423	1550	1.0	202	175	1.0
25-29 years	1382	2126	0.83 (0.73-0.95)	118	131	1.30 (0.85-1.96)
30-34 years	1283	2038	0.85 (0.74-0.97)	111	139	1.25 (0.81-1.92)
35+ years	890	1510	0.83 (0.72-0.97)	73	93	1.25 (0.77-2.05)
Tubal ligation						
No	4194	5397	1.0	445	391	1.0
Yes	846	1710	0.70 (0.64-0.78)	67	124	0.59 (0.41-0.86)
COC use duration						
<1 year	3073	3583	1.0	258	225	1.0
1-4.99 years	947	1573	0.72 (0.65-0.80)	118	156	0.59 (0.42-0.83)
5-9.99 years	564	1066	0.61 (0.54-0.69)	74	84	0.66 (0.44-1.00)
10+ years	449	1030	0.43 (0.38-0.49)	65	80	0.58 (0.38-0.89)
DMPA use						
No	4435	6404	1.0	425	448	1.0
Yes	29	51	1.01 (0.63-1.62)	7	4	1.47 (0.41-5.24)
MHT use						
Never use	2895	4037	1.0	255	249	1.0
ET only	766	936	1.22 (1.09-1.37)	116	109	1.13 (0.78-1.64)
EPT only	976	1730	0.84 (0.76-0.92)	99	138	0.67 (0.47-0.96)
Others	254	434	0.90 (0.75-1.07)	32	39	0.64 (0.37-1.11)
Family history of ovarian cancer						
No	3646	5507	1.0	411	438	1.0
Yes	253	202	1.88 (1.48-2.38)	22	17	1.77 (0.88-3.57)

* Numbers may not sum to total due to missing values.

** Pooled estimates from logistic regression models in the 50 imputed datasets, adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, OCAC study.

Abbreviations: BMI: body mass index, CI: confidence interval; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; EPT: estrogen plus progestin therapy; ET: estrogen therapy; MHT: menopausal hormone therapy; OR: odds ratio; PRS: polygenic risk score.

Supplemental Table 3-31: Associations between risk factors and ovarian cancer risk among post-menopausal women by strata of the PRS

Risk factors	1st quartile PRS			2nd quartile PRS		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI						
<18.5 kg/m2	19	20	1.96 (0.97-3.97)	15	24	0.97 (0.48-1.95)
18.5-24.99 kg/m2	311	618	1.0	358	638	1.0
25-29.99 kg/m2	207	447	0.96 (0.76-1.21)	273	468	1.05 (0.85-1.30)
30+ kg/m2	184	351	1.08 (0.84-1.39)	210	317	1.19 (0.93-1.51)
Height (m)						
<1.60	237	433	1.0	289	462	1.0
1.60-1.64	206	386	0.99 (0.76-1.28)	236	388	0.98 (0.77-1.24)
1.65-1.69	163	346	0.90 (0.69-1.19)	191	360	0.92 (0.71-1.19)
1.70-1.74	86	188	0.97 (0.69-1.37)	116	152	1.32 (0.96-1.80)
1.75+	40	85	0.85 (0.54-1.34)	37	88	0.74 (0.48-1.16)
Age at menarche						
<12 years	156	301	1.02 (0.80-1.30)	167	329	0.73 (0.58-0.92)
12-14 years	465	951	1.0	586	917	1.0
15+ years	108	186	1.19 (0.89-1.59)	110	195	0.85 (0.65-1.12)
Parity						
0	149	171	1.0	171	202	1.0
1	77	160	0.63 (0.41-0.96)	125	176	0.94 (0.65-1.36)
2	221	425	0.68 (0.46-1.00)	228	441	0.76 (0.53-1.07)
3+	287	694	0.47 (0.31-0.71)	348	633	0.80 (0.56-1.15)
Breastfeeding						
Never	388	606	1.0	441	622	1.0
<12 months	221	491	0.80 (0.62-1.02)	258	459	0.87 (0.69-1.10)
12-23 months	81	170	0.81 (0.58-1.15)	103	196	0.78 (0.57-1.06)
24+ months	34	153	0.38 (0.24-0.59)	62	137	0.57 (0.39-0.84)
Incomplete pregnancy						
0	481	951	1.0	571	932	1.0
1	153	307	1.09 (0.86-1.39)	174	309	1.04 (0.83-1.31)
2+	82	175	1.04 (0.76-1.42)	110	187	1.01 (0.77-1.34)
Age at last pregnancy						
<25 years or never being pregnant	216	305	1.0	255	344	1.0
25-29 years	195	432	0.94 (0.69-1.29)	231	405	0.97 (0.73-1.29)
30-34 years	179	413	0.99 (0.71-1.39)	222	420	0.86 (0.64-1.16)
35+ years	130	290	1.07 (0.75-1.54)	150	276	0.90 (0.64-1.25)
Tubal ligation						
No	595	1066	1.0	718	1029	1.0
Yes	137	353	0.84 (0.65-1.09)	153	382	0.64 (0.51-0.80)
COC use duration						
<1 year	410	696	1.0	494	706	1.0
1-4.99 years	142	301	0.80 (0.61-1.05)	175	314	0.82 (0.64-1.04)
5-9.99 years	102	228	0.82 (0.61-1.11)	112	211	0.80 (0.60-1.06)
10+ years	76	220	0.53 (0.38-0.73)	90	219	0.54 (0.40-0.73)
DMPA use						
No	618	1275	1.00	750	1282	1.00
Yes	6	10	1.16 (0.38-3.53)	8	11	1.44 (0.51-4.09)
MHT use						
Never use	432	788	1.0	505	758	1.0
ET only	118	181	1.43 (1.06-1.91)	126	169	1.28 (0.97-1.70)
EPT only	129	362	0.71 (0.55-0.92)	162	392	0.67 (0.53-0.84)
Others	39	96	0.86 (0.57-1.30)	47	97	0.79 (0.53-1.16)
Family history of ovarian cancer						
No	569	1147	1.00	677	1141	1.00
Yes	39	38	1.92 (1.15-3.23)	41	39	1.79 (1.10-2.92)
Endometriosis						
No	657	1341	1.00	784	1340	1.00
Yes	76	105	1.30 (0.92-1.84)	81	107	1.23 (0.88-1.70)

Risk factors	3rd quartile PRS			4th quartile PRS		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI						
<18.5 kg/m2	20	26	0.93 (0.49-1.74)	27	22	1.14 (0.62-2.09)
18.5-24.99 kg/m2	436	641	1.0	629	641	1.0
25-29.99 kg/m2	312	430	1.04 (0.85-1.28)	446	509	0.86 (0.72-1.02)
30+ kg/m2	273	381	1.03 (0.83-1.28)	316	362	0.85 (0.70-1.05)
Height (m)						
<1.60	348	459	1.0	406	425	1.0
1.60-1.64	285	415	0.98 (0.79-1.23)	417	435	1.05 (0.86-1.29)
1.65-1.69	237	367	0.95 (0.75-1.21)	359	402	1.00 (0.80-1.24)
1.70-1.74	132	179	1.09 (0.81-1.45)	204	208	1.11 (0.86-1.44)
1.75+	51	63	1.27 (0.83-1.94)	61	68	0.92 (0.61-1.37)
Age at menarche						
<12 years	210	310	0.98 (0.79-1.21)	295	351	0.84 (0.69-1.02)
12-14 years	689	1000	1.0	978	973	1.0
15+ years	154	168	1.31 (1.02-1.69)	175	207	0.79 (0.62-1.00)
Parity						
0	174	201	1.0	252	186	1.0
1	151	155	1.58 (1.10-2.28)	204	184	1.08 (0.78-1.50)
2	304	448	1.08 (0.77-1.51)	399	488	0.79 (0.59-1.08)
3+	428	681	0.99 (0.70-1.42)	602	682	0.76 (0.55-1.05)
Breastfeeding						
Never	547	682	1.0	755	677	1.0
<12 months	305	453	0.88 (0.70-1.09)	422	506	0.79 (0.65-0.96)
12-23 months	112	182	0.82 (0.61-1.11)	152	175	0.83 (0.63-1.10)
24+ months	82	126	0.85 (0.60-1.21)	105	133	0.77 (0.55-1.06)
Incomplete pregnancy						
0	731	956	1.0	970	978	1.0
1	200	324	0.87 (0.70-1.07)	286	334	0.95 (0.78-1.16)
2+	110	190	0.82 (0.62-1.08)	177	200	1.02 (0.80-1.30)
Age at last pregnancy						
<25 years or never pregnant	307	318	1.0	413	345	1.0
25-29 years	301	434	0.75 (0.57-0.99)	412	458	0.89 (0.70-1.14)
30-34 years	262	411	0.75 (0.56-0.99)	364	421	0.92 (0.70-1.19)
35+ years	169	312	0.66 (0.48-0.92)	242	305	0.85 (0.63-1.14)
Tubal ligation						
No	855	1059	1.0	1194	1129	1.0
Yes	194	384	0.67 (0.54-0.84)	256	363	0.74 (0.61-0.91)
COC use duration						
<1 year	624	698	1.0	838	666	1.0
1-4.99 years	214	348	0.73 (0.58-0.91)	289	365	0.62 (0.51-0.76)
5-9.99 years	117	215	0.60 (0.46-0.80)	173	264	0.48 (0.37-0.61)
10+ years	100	218	0.46 (0.35-0.61)	146	239	0.38 (0.29-0.49)
DMPA use						
No	922	1315	1.00	1262	1345	1.00
Yes	6	9	1.26 (0.44-3.60)	7	12	0.87 (0.32-2.37)
MHT use						
Never use	586	836	1.0	776	811	1.0
ET only	173	190	1.34 (1.04-1.72)	239	238	1.09 (0.86-1.36)
EPT only	218	368	0.88 (0.71-1.10)	295	365	0.92 (0.75-1.12)
Others	49	73	1.01 (0.68-1.50)	76	91	0.90 (0.64-1.27)
Family history of ovarian cancer						
No	819	1187	1.00	1137	1283	1.00
Yes	50	48	1.51 (0.98-2.34)	79	39	2.44 (1.60-3.72)
Endometriosis						
No	959	1379	1.00	1324	1429	1.00
Yes	94	101	1.40 (1.02-1.91)	120	98	1.29 (0.96-1.74)

* Numbers may not sum to total due to missing values.

** Pooled estimates from logistic regression models in the 50 imputed datasets, adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, OCAC study, and genetic ancestry principal components.

Abbreviations: BMI: body mass index, CI: confidence interval; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; EPT: estrogen plus progestin therapy; ET: estrogen therapy; MHT: menopausal hormone therapy; OR: odds ratio; PRS: polygenic risk score.

Supplemental Table 3-32: Associations between risk factors and ovarian cancer risk among post-menopausal women by strata of age of menopause

Risk factors	Age at menopause <45 years			Age at menopause 45-49 years			Age at menopause 50-54 years		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
BMI									
<18.5 kg/m2	16	12	1.79 (0.77-4.15)	26	29	0.91 (0.51-1.62)	21	27	0.98 (0.53-1.80)
18.5-24.99 kg/m2	178	247	1.0	469	620	1.0	661	998	1.0
25-29.99 kg/m2	109	191	0.78 (0.55-1.10)	290	433	0.93 (0.75-1.15)	436	636	1.08 (0.91-1.28)
30+ kg/m2	81	142	0.96 (0.65-1.42)	205	304	0.91 (0.71-1.15)	327	500	1.01 (0.83-1.22)
Height (m)									
<1.60	126	193	1.0	312	452	1.0	486	728	1.0
1.60-1.64	87	166	0.87 (0.59-1.29)	251	377	0.98 (0.77-1.25)	404	615	0.96 (0.80-1.16)
1.65-1.69	100	136	1.26 (0.85-1.86)	245	330	1.10 (0.85-1.41)	329	487	1.02 (0.83-1.25)
1.70-1.74	50	61	1.22 (0.74-2.01)	135	162	1.34 (0.99-1.82)	190	250	1.13 (0.88-1.44)
1.75+	27	36	1.29 (0.69-2.42)	59	73	1.20 (0.78-1.82)	59	85	0.96 (0.66-1.41)
Age at menarche									
<12 years	82	156	0.78 (0.55-1.11)	199	310	0.86 (0.69-1.08)	261	442	0.82 (0.68-0.98)
12-14 years	256	365	1.0	672	897	1.0	1028	1461	1.0
15+ years	50	69	1.04 (0.67-1.64)	130	182	0.85 (0.65-1.12)	171	257	0.93 (0.74-1.17)
Parity									
0	104	114	1.0	257	202	1.0	285	289	1.0
1	65	77	1.01 (0.57-1.79)	142	169	0.84 (0.59-1.20)	193	230	1.14 (0.84-1.55)
2	79	165	0.54 (0.32-0.93)	276	422	0.72 (0.51-1.00)	417	686	0.96 (0.72-1.28)
3+	143	237	0.66 (0.38-1.18)	331	604	0.57 (0.40-0.81)	578	967	0.94 (0.70-1.28)
Breastfeeding									
Never	233	326	1.0	581	668	1.0	797	963	1.0
<12 months	95	163	1.01 (0.69-1.47)	255	409	0.80 (0.63-1.01)	384	670	0.73 (0.60-0.88)
12-23 months	38	51	1.39 (0.81-2.38)	83	164	0.63 (0.45-0.88)	173	296	0.72 (0.56-0.92)
24+ months	22	50	0.75 (0.40-1.43)	80	151	0.58 (0.41-0.82)	103	235	0.55 (0.42-0.74)
Incomplete pregnancy									
0	261	373	1.0	662	901	1.0	1032	1398	1.0
1	78	135	0.85 (0.58-1.23)	222	313	1.04 (0.83-1.30)	276	485	0.85 (0.71-1.02)
2+	52	84	0.89 (0.57-1.38)	122	183	0.90 (0.67-1.20)	165	289	0.85 (0.67-1.07)
Age at last pregnancy									
<25 years or never being pregnant	140	161	1.0	308	305	1.0	411	421	1.0
25-29 years	83	149	0.76 (0.47-1.21)	264	368	1.21 (0.90-1.62)	357	627	0.70 (0.55-0.90)
30-34 years	91	166	0.79 (0.49-1.27)	211	391	0.94 (0.69-1.28)	401	594	0.95 (0.73-1.23)
35+ years	72	117	0.83 (0.49-1.42)	215	324	1.15 (0.83-1.59)	284	520	0.78 (0.59-1.02)
Tubal ligation									
No	325	455	1.0	868	1039	1.0	1235	1648	1.0
Yes	64	134	0.96 (0.65-1.43)	138	355	0.54 (0.43-0.69)	233	515	0.65 (0.53-0.78)
COC use duration									
<1 year	261	295	1.0	612	699	1.0	908	1101	1.0

Risk factors	Age at menopause <45 years			Age at menopause 45-49 years			Age at menopause 50-54 years		
	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)	Case*	Control*	OR** (95% CI)
1-4.99 years	65	125	0.70 (0.47-1.05)	198	303	0.75 (0.59-0.96)	269	484	0.73 (0.60-0.88)
5-9.99 years	34	96	0.40 (0.25-0.65)	113	207	0.56 (0.42-0.75)	165	281	0.72 (0.57-0.91)
10+ years	31	74	0.44 (0.26-0.73)	82	186	0.41 (0.30-0.56)	127	300	0.43 (0.34-0.55)
DMPA use									
No	354	544	1.0	905	1273	1.0	1337	1999	1.0
Yes	1	9	0.29 (0.05-1.78)	12	13	1.13 (0.50-2.55)	10	9	1.87 (0.70-5.00)
MHT use									
Never use	275	417	1.0	705	888	1.0	994	1349	1.0
ET only	17	20	0.83 (0.34-2.06)	54	62	1.18 (0.72-1.93)	82	114	1.02 (0.70-1.49)
EPT only	64	105	1.13 (0.66-1.93)	193	334	0.60 (0.44-0.83)	312	536	0.74 (0.59-0.94)
Others	18	37	0.64 (0.31-1.32)	39	87	0.53 (0.33-0.85)	65	140	0.64 (0.45-0.90)
Family history of ovarian cancer									
No	278	443	1.0	701	982	1.0	1034	1603	1.0
Yes	23	20	1.89 (0.97-3.70)	57	40	1.78 (1.10-2.89)	65	57	1.90 (1.25-2.89)
Endometriosis									
No	361	554	1.0	924	1323	1.0	1373	2073	1.0
Yes	30	39	1.07 (0.60-1.89)	78	68	1.45 (1.00-2.11)	97	95	1.51 (1.10-2.06)

* Numbers may not sum to total due to missing values.

** Pooled estimates from logistic regression models in the 50 imputed datasets, adjusted for age at diagnosis for cases/reference age for controls, race/ethnicity, education level, OCAC study, and duration of hormonal therapy use.

Abbreviations: BMI: body mass index, CI: confidence interval; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; EPT: estrogen plus progestin therapy; ET: estrogen therapy; MHT: menopausal hormone therapy; OR: odds ratio; PRS: polygenic risk score.

Supplemental Table 3-33: Risk of developing ovarian cancer estimated for control women in the test set by country and race/ethnicity

Risk of developing ovarian cancer by age <50										
Country	**Race/ethnicity**	**Mean[a]**	**Sources and period**	**Number of control women in the test set**	**Number of observed profiles**	**Number of possible profiles**	**13-factor model[b]**		**Reduced model[c]**	
							Min	**Max**	**Min**	**Max**
US[d]	Non-Hispanic White	0.15%	SEER 13 (1992-2010)	652	625	2,350,080	0.02%	0.99%	0.03%	0.79%
US[d]	Hispanic White	0.12%	SEER 13 (1992-2010)	37	37	2,350,080	0.02%	0.48%	0.02%	0.40%
US[d]	Black	0.09%	SEER 13 (1992-2010)	12	12	2,350,080	0.03%	0.25%	0.03%	0.25%
US[d]	Asian	0.16%	SEER 13 (1992-2010)	35	35	2,350,080	0.04%	0.56%	0.04%	0.49%
Australia[e]	All races	0.15%	Australian Institute of Health and Welfare (2001-2005)	138	138	2,350,080	0.02%	0.99%	0.04%	0.75%
Germany[f]	All races	0.21%	International Agency for Research on Cancer Eurostat (1993-1998)	45	45	2,350,080	0.04%	1.36%	0.05%	1.14%
Risk of developing ovarian cancer between ages 50-84										
Country	**Race/ethnicity**	**Mean[a]**	**Sources and period**	**Number of control women in the test set**	**Number of observed profiles**	**Number of possible profiles**	**15-factor model**		**Reduced model[c]**	
							Min	**Max**	**Min**	**Max**
US[d]	Non-Hispanic White	0.98%	SEER 13 (1992-2010)	1,134	1,130	37,601,280	0.17%	4.10%	0.20%	3.29%
US[d]	Hispanic White	0.82%	SEER 13 (1992-2010)	17	17	37,601,280	0.17%	2.68%	0.23%	2.04%
US[d]	Black	0.59%	SEER 13 (1992-2010)	20	20	37,601,280	0.17%	1.23%	0.17%	1.25%
US[d]	Asian	0.65%	SEER 13 (1992-2010)	32	32	37,601,280	0.19%	2.75%	0.28%	2.16%
Australia[e]	All races	1.04%	Australian Institute of Health and Welfare (2001-2005)	265	265	37,601,280	0.26%	3.93%	0.29%	3.12%
Germany[f]	All races	1.23%	International Agency for Research on Cancer Eurostat (1993-1998)	18	18	37,601,280	0.45%	2.50%	0.82%	2.18%

[a] Generated by DevCan using public data.

[b] There were 13 factors instead of 15 for women aged <50 because menopausal hormone therapy use and age at menopause were not included in this age group.

[c] Risk calculated using a reduced model that included nine risk factors body mass index (BMI), height, tubal ligation, parity, combined oral contraceptive (COC) use duration, menopausal hormone therapy (MHT) use, family history of ovarian cancer, endometriosis, and the polygenic risk score (PRS), with the estimates from our model.

[d] Risk of developing invasive epithelial ovarian cancer.

[e] Risk of developing ovarian cancer overall.

Chapter 4. Epidemiologic Factors Associated with Having Macroscopic Residual Disease after Ovarian Cancer Primary Cytoreductive Surgery

Introduction

Ovarian cancer is the deadliest gynecologic cancer with about 20,000 new cases and more than 13,000 deaths in the US in 2022[1]. High-grade serous cancer is the most common histotype, comprising of ~70% of all ovarian cancers[125]; about 80% of high-grade serous cancer cases are diagnosed at an advanced stage[2]. Five-year survival rate for advanced stage high-grade serous cancer is very low (~32%)[124].

The single most important factor influencing survival for high-grade serous ovarian cancer patients is ovarian cancer surgical outcome, i.e., whether no macroscopic residual disease (R0) is achieved[63,389]. Studies have shown better progression-free survival and overall survival for patients with no macroscopic residual disease following primary cytoreductive surgery (PCS) compared to patients with any residual disease ($p<0.0001$)[62]. Similarly, a meta-analysis of more than 13,000 patients in 18 studies found that each 10% increase in the proportion of patients with no macroscopic residual disease was associated with a statistically significant 2.3 month increase in cohort median survival (95% CI 0.6-4.0, $p=0.011$)[63].

Factors known to affect residual disease following PCS include age and disease stage[64,65,69,70]. Significant efforts have been made to identify additional factors associated with presence of residual disease following PCS including epidemiologic factors[64-78,197-199], clinical

factors[64,65,67-72,74-76,198-210], serum biomarkers[64-67,69-76,198,199,201-204,206,210-219], protein expression[198,200,208,220-232], gene expression[229,233-246], computed tomography[64,66,67,69,72,75,202,204,205,209,212,214,215,247-254], positron emission tomography/computed tomography[67,201,255], magnetic resonance imaging[254], and laparoscopy[252,253,256,257].

We have previously shown that use of menopausal hormone therapy is associated with lower risk of having residual disease. Women who used menopausal hormone therapy for five or more years were associated with 29% lower odds of having residual disease compared to never users (odd ratio OR=0.71, 95% confidence interval CI 0.54-0.93)[79]. Other studies of epidemiologic factors suggested that having a family history of cancer[73], a personal history of endometriosis[73], or use of combined oral contraceptives (COCs)[76] were associated with a higher likelihood of achieving complete cytoreduction (R0) or optimal cytoreduction (residual disease <1cm). Conversely, post-menopausal status[76-78], higher parity[76,199], higher body mass index (BMI)[67,75,76], and ever smoking[76] were associated with a lower likelihood of achieving complete or optimal cytoreduction. However, these findings are difficult to interpret because there was no adjustment for potential confounders and there is heterogeneity in inclusion eligibility criteria and outcome definitions.

Some studies included all epithelial ovarian cancer patients, some restricted to invasive tumors only[71,76], and others restricted to advanced stage ovarian cancer patients only[70,71]. Residual disease has been defined differently across studies, including complete cytoreduction to microscopic residual disease (R0) versus any macroscopic residual disease[64,65,67], or optimal cytoreduction (residual disease ≤1 cm) versus suboptimal cytoreduction (residual disease >1

cm)[70,73]. There is evidence that factors associated with complete cytoreduction after PCS do not mirror factors associated with optimal cytoreduction[75].

To address these limitations, we conducted a pooled analysis on 2,169 participants in ten studies from the international Ovarian Cancer Association Consortium to comprehensively examine the association between 12 epidemiologic factors and the likelihood of having macroscopic residual disease after PCS for advanced stage high-grade serous ovarian cancer patients. We were able to adjust for important confounders and used a rigorous outcome measure (i.e., no macroscopic residual disease).

Methods

Study population

This analysis used data from ten studies that participated in OCAC (https://ocac.ccge.medschl.cam.ac.uk/). Studies that had information on residual disease following PCS and data on at least eight of the 12 exposures of interest (see below) were included. Two studies from Australia, one from Germany, one from Japan, and six from the US met these criteria (Table 4-1). People who were diagnosed with primary invasive epithelial fallopian tubal, peritoneal and ovarian cancers (hereafter referred to as ovarian cancer), had advanced stage high-grade serous cancers, underwent PCS, and had no prior cancer (except for non-melanoma skin cancer) were included in the analysis. Of the total of 2,569 individuals in the ten OCAC studies who underwent PCS and met the above eligibility criteria, 2,169 participants had information on residual disease and were included in the analysis. Women undergoing neoadjuvant chemotherapy (NACT; N=568) and those who were missing treatment sequence data (i.e., PCS versus NACT; N=1012) were excluded from this analysis. Patients whose

treatment sequence data were missing (N=1,012) were more likely to not have specific staging information (i.e., to be stage III not otherwise specified [NOS]) and more likely to have high school degree or higher compared to those whose data on treatment sequence were available (N=3,137) (Supplemental Table 4-1). As we adjusted for stage and education in the analysis (see below), it is unlikely that these differences between patients whose treatment sequence data were missing and available would bias the results. Figure 4-1 presents the flow chart of patients considered for this analysis. All studies obtained institutional review board approval and all participants provided written consent.

Variables

The outcome of interest was any versus no macroscopic residual disease after ovarian cancer PCS. The 12 exposures of interest included: first-degree family history of ovarian cancer (yes, no); personal history of endometriosis (yes, no); smoking (never, former, current); BMI (<18.5, 18.5-24.99, 25-29.99, 30+ kg/m^2); COC duration of use (<1, 1-4.99, 5-9.99, 10+ years); use of depot medroxyprogesterone acetate (DMPA; yes, no); menopausal hormone therapy use (never use, estrogen-only therapy [ET] use, combined estrogen-progestin therapy [EPT] use, other [use of both ET and EPT or type unknown]); menopausal status (pre- vs post-menopause); parity (nulliparous, parous); incomplete pregnancy (yes, no) breastfeeding (never, ever); and tubal ligation (yes, no). Results were similar when conducting analyses on finer categories of parity (0, 1, 2, 3+), incomplete pregnancy (0, 1, 2+), breastfeeding duration (never breastfed, breastfed <12, 12-23, 24+ months), and menopausal hormone therapy duration of use (never use, use for <5 years and 5+ years) separately for ET and EPT use. We considered other exposures but did not include them in the final analysis due to a high proportion of missingness (history of

polycystic ovary syndrome and pelvic inflammatory disease, alcohol consumption, environmental smoking, physical inactivity, use of talcum powder, non-steroidal anti-inflammatory drugs, aspirin, and acetaminophen).

Multiple imputation

Among the 2,169 participants who underwent PCS and had information on macroscopic residual disease, the proportion of missingness for the 12 exposures ranged from 5% for parity and menopausal status to 34% for breastfeeding. Multiple imputation was carried out using the *mice* package in R to generate 20 imputed datasets. All variables were initially included in the imputation models, including those that were not used in the analysis. Variables with 70% or more missingness were excluded from the imputation models. All variables were imputed, except for the outcome (residual disease). All studies were imputed together; OCAC study site (n=10) and country (Australia, Germany, Japan, US) were included as predictors in the imputation models. Results were pooled from 20 imputed datasets using Rubin's rule[390].

Statistical analyses

Logistic regression models were fit regressing macroscopic residual disease on the 12 exposures of interest listed above, adjusted for age at diagnosis (per five years); race/ethnicity (non-Hispanic White, Black, Asian, other); education level (<high school, high school, some college, college or above); year of diagnosis (continuous); Federation of Gynecology and Obstetrics (FIGO) stage (IIIA, IIIB, IIIC, III NOS, and IV); grade (moderately differentiated and poorly differentiated/undifferentiated); CA125 within one month of primary cytoreductive surgery (per 200 units); and OCAC study site. Models stratified on those covariates generated similar results.

Sensitivity analyses

We conducted a sensitivity analysis to assess the appropriateness of pooling the OCAC data. Meta-analysis results showed little evidence of heterogeneity in the associations between the exposures and having macroscopic residual disease across the OCAC studies: I^2=0.0% for 16 of the total 19 categories of the variables, except for family history of ovarian cancer (I^2=4.8%), COC use 10+ years (I^2=19.4%), and ET use (I^2=22.0%). P-values for heterogeneity were >0.05 for all categories. The fixed ORs were similar to the pooled analysis. Thus, the data were analyzed together as described above.

It is possible that type of treatment center (e.g., academic; large urban hospital; community hospital) may confound the association between residual disease and our exposures of interest. The reason is that surgical expertise and patient volume potentially affect residual disease. To address this potential concern, we conducted a sensitivity analysis in the OCAC studies that recruited patients from large treatment centers (i.e., AUS, HOP, LAX, MAC, MAY, NEC, OPL) where surgical expertise and patient volume is more homogeneous.

Comorbidity is a potential confounder as it is suggested to be associated with having residual disease after ovarian cancer PCS, possibly because patients with comorbidity are less likely to withstand an extensive surgery[199]. To address the potential confounding effect of comorbidity, we conducted a sensitivity analysis adjusting for Charlson comorbidity index[391] (0, 1, 2, and 3+) among participants in the two studies from Australia where this information was available.

Statistical significance was defined as $p \leq 0.05$ using a 2-sided test. Analyses were conducted using R version 4.0.3.

Results

Of the total 2,169 participants included in the analysis, 1,433 had macroscopic residual disease after PCS (66.1%; Table 4-1). The proportion of participants with macroscopic residual disease by OCAC study ranged from 43% to 78% (Table 4-1). Participants with and without macroscopic residual disease were similar in age (mean=60.9 and 59.6, respectively; Table 4-2). Data on age and FIGO stage were not missing for any participants; the proportion of missingness for race/ethnicity, education, and CA125 were 2%, 16%, and 34%, respectively (Table 4-2). All missing values were imputed. Based on the unimputed dataset, patients with macroscopic residual disease had a more advanced FIGO stage and a higher serum CA125 level compared to those who had no macroscopic residual disease (Table 4-2).

Age at diagnosis, FIGO stage, calendar year of diagnosis, and serum CA125 level were statistically significantly associated with the presence of macroscopic residual disease following PCS. A five-year increase in age was associated with 7% higher odds of having macroscopic residual disease (OR=1.07, 95% CI 1.00-1.15, p-value=0.039, Table 4-3). Compared to patients with FIGO stage IIIA and IIIB, those with stage IIIC and IV had higher odds of having macroscopic residual disease (OR=4.75, 95% CI 3.31-6.82, p-value<0.001 and OR=10.65, 95% CI 6.73-16.84, p-value<0.001, respectively). Patients who were diagnosed in later calendar years were less likely to have macroscopic residual disease (OR=0.93, 95% CI 0.89-0.96, p-value<0.001 for one calendar year increase; Table 4-3).

The exposures of interest that were statistically significantly associated with having macroscopic residual disease after PCS were ET use, parity, and breastfeeding. ET use was associated with 31% lower odds of having macroscopic residual disease after PCS compared to never use (OR=0.69, 95% CI 0.48-1.00, p-value=0.048; Table 4-4). EPT use was not associated with having residual disease (OR=1.00, 95% CI 0.75-1.35, p-value=0.97 versus never use). Parous women had 35% lower odds of having macroscopic residual disease compared to nulliparous women (OR=0.65, 95% CI 0.45-0.93, p=0.018), while women who had ever breastfed had 41% higher odds of having residual disease compared to those who had never breastfed (OR=1.41, 95% CI 1.03-1.92, p=0.032; Table 4-4).

Smoking was borderline associated with having residual disease after PCS. Compared to never smoking, ever smoking was associated with 38% higher odds while former smoking was associated with 21% lower odds of having macroscopic residual disease after PCS (OR=1.38, p=0.082, and OR=0.79, p=0.055; Table 4-4). None of the other exposures studied were associated with the presence of macroscopic residual disease (Table 4-4).

We conducted several sensitivity analyses including: restricting to the OCAC studies that recruited patients from large treatment centers (i.e., AUS, HOP, LAX, MAC, MAY, NEC, OPL) and adjusting for Charlson comorbidity score among participants in the two studies from Australia. Results from these sensitivity analyses were similar to the main analysis.

Discussion

We comprehensively examined the association between 12 epidemiologic factors and risk of having residual disease after PCS for ovarian cancer. People who had ever used menopausal estrogen therapy (ET) were statistically significantly more likely to achieve no macroscopic

residual disease after PCS compared to never users (p=0.048) as were parous women compared to nulliparous women (p=0.018). Conversely, women who had ever breastfed were statistically significantly more likely to have macroscopic residual disease after PCS compared to those who had never breastfed (p=0.032). Smoking was borderline associated with residual disease; current smokers were more likely to have macroscopic residual disease after PCS (p=0.082) while former smokers were less likely to have it compared to never smokers (p=0.055).

Previously, we used data from OCAC and found that people who used menopausal hormone therapy for 5+ years were more likely to achieve no macroscopic residual disease after ovarian cancer surgery[79]. We did not look at ET and EPT use separately in that study. In the current analysis, we did not find an association between EPT use and having macroscopic residual disease. The difference may be because the previous analysis did not restrict to women who underwent PCS (versus having NACT) and because of the differences in sample sizes.

The biological mechanism of the association between ET use and having macroscopic residual disease after PCS is unknown. A possible explanation is that estrogen makes the tumor less adhesive to nearby tissues and thus easier to resect. Another possibility is that inflammation may be associated with resectability[79]; estrogen at high concentrations promotes an anti-inflammatory environment and this milieu may make it possible to achieve no macroscopic residual disease. The observation that current smokers may be more likely to have macroscopic residual disease after PCS compared to never smokers could also be related to inflammation given that smoking leads to a pro-inflammatory environment. We also found that former smokers were less likely to have macroscopic residual disease after PCS compared to never smokers. This may be because people who quit smoking adopt healthier diets[392], which are associated with less

inflammation. However, the associations with smoking and having residual disease following PCS were not statistically significant.

We also found that parity was inversely associated with having macroscopic residual disease after PCS while breastfeeding is positively associated with having macroscopic residual disease. Similar to our results, two previous studies found that ovarian cancer patients who had residual disease (≥1cm) after PCS had more births than women who were optimally debulked (residual disease <1cm); however, the results from these two studies were not adjusted for confounders[76,199]. To our knowledge, no previous studies have examined the association between breastfeeding and risk of residual disease after PCS. Our findings of the opposite directions of the associations between parity and breastfeeding and risk of residual disease after PCS are unlikely to be explained by the residual confounding of socioeconomic status. We were able to adjust for education level, but not other measures of socioeconomic status such as income or occupation. However, further adjusted for socioeconomic status would make the associations for parity and breastfeeding even further away from null. Women of low socioeconomic status have higher fertility rates,[393] are less likely to breastfeed[394,395] and have poorer surgical outcomes[396,397] compared to those of high socioeconomic status. Our findings of statistically significantly associations for parity and breastfeeding but no associations for other hormonal factors (e.g., incomplete pregnancy and COC use) suggest that hormones do not universally affect risk of residual disease after PCS. It could be due to the differences in the levels of hormones corresponding to those factors or the influence of different hormones for different exposures (e.g. progesterone during pregnancy and prolactin during breastfeeding). More studies are needed to explore the roles of hormones in risk of residual disease after ovarian cancer PCS.

Strengths of the current study include the large sample size, the ability to adjust for confounders, and the use of a rigorous definition of residual disease (i.e. no macroscopic residual disease). However, we had limited information on comorbidities and surgical expertise. We were able to conduct a sensitivity analysis including Charlson comorbidity score in the model for the Australian studies where the information is available and found no evidence of confounding. We also restricted the analysis to the OCAC studies that recruited patients from large treatment centers where surgical expertise and patient volume are more likely to be equivalent and did not find different results. However, we cannot rule out residual confounding.

In conclusion, our study suggested that parity and ET use were associated with a lower likelihood of having macroscopic residual disease after ovarian cancer PCS, whereas breastfeeding was associated with a higher likelihood of having macroscopic residual disease. If our findings are replicated, these factors can be included in risk stratification models aiming to determine whether ovarian cancer patients should receive PCS or NACT followed by interval debulking surgery. Future studies on the mechanisms of these associations are warranted.

Table 4-1: Characteristics of studies included in Aim 2 analysis

Study Abbreviation	Study full name	Study Location	Year of diagnosis	Total of participants included in the main analysis	Macroscopic residual disease n (%)	No macroscopic residual disease n (%)
AUS[398]	Australian Ovarian Cancer Study	Australia	2001-2006	544	424 (77.9%)	120 (22.1%)
OPL[399]	Ovarian Cancer Prognosis and Lifestyle Study	Australia	2011-2015	245	148 (60.4%)	97 (39.6%)
BAV[400]	Bavarian Ovarian Cancer Study	Germany	2002-2009	80	49 (61.3%)	31 (38.8%)
JPN[401]	Hospital-based Research Program at Aichi Cancer Center	Japan	2001-2012	28	12 (42.9%)	16 (57.1%)
HAW[402]	Hawaii Ovarian Cancer Case-Control Study	Hawai'i, US	1994-2008	72	51 (70.8%)	21 (29.2%)
HOP[403]	Hormones and Ovarian Cancer Prediction	Western Pennsylvania, Northeast Ohio, Western New York, US	2003-2008	289	212 (73.4%)	77 (26.6%)
LAX	Women's Cancer Program at the Samuel Oschin Comprehensive Cancer Institute	California, US	1986-2012	134	64 (47.8%)	70 (52.2%)
MAC[404]	Mayo Clinic Case-Only Ovarian Cancer Study	Minnesota, US	1993-2018	82	40 (48.8%)	42 (51.2%)
MAY[405]	Mayo Clinic Ovarian Cancer Case Control Study	Minnesota, US	1999-2018	487	281 (57.7%)	206 (42.3%)
NEC[369]	New England Case Control Study	New Hampshire and Eastern Massachusetts, US	1992-2002	208	152 (73.1%)	56 (26.9%)
				2169	1433 (66.1%)	736 (33.9%)

Table 4-2: Characteristics of participants included in the main analysis based on the unimputed dataset

	Macroscopic residual disease (n=1433)	No macroscopic residual disease (n=736)	Total (N=2169)
Age at diagnosis			
Mean [SD]	60.9 [10.5]	59.6 [11.3]	60.4 [10.8]
Median [Min, Max]	61.0 [28.0, 91.0]	60.0 [25.0, 87.0]	61.0 [25.0, 91.0]
FIGO stage			
IIIA and IIIB	58 (33.7%)	114 (66.3%)	172
III (NOS)	146 (70.9%)	60 (29.1%)	206
IIIC	977 (66.1%)	501 (33.9%)	1478
IV	252 (80.5%)	61 (19.5%)	313
Grade			
Moderately differentiated	183 (68.3%)	85 (31.7%)	268
Poorly differentiated or undifferentiated	1250 (65.8%)	651 (34.2%)	1901
CA125			
Mean [SD]	2470 [6370]	1260 [6260]	2060 [6360]
Median [Min, Max]	904 [2.30, 86100]	420 [3.50, 134000]	692 [2.30, 134000]
Missing	484	246	730
Menopausal status			
Pre-menopause	262 (63.3%)	152 (36.7%)	414
Post-menopause	1111 (67.3%)	541 (32.7%)	1652
Missing	60	43	103
Race/ethnicity			
Non-Hispanic White	1308 (66.9%)	646 (33.1%)	1954
Black	13 (72.2%)	5 (27.8%)	18
Asian	46 (49.5%)	47 (50.5%)	93
Other	35 (57.4%)	26 (42.6%)	61
Missing	31	12	43
Education			
< high school	235 (71.4%)	94 (28.6%)	329
High school	344 (66.7%)	172 (33.3%)	516
Some college	326 (66.5%)	164 (33.5%)	490
College or above	315 (63.8%)	179 (36.2%)	494
Missing	213	127	340
Family history of ovarian cancer			
No	1126 (66.6%)	565 (33.4%)	1691
Yes	62 (55.4%)	50 (44.6%)	112
Missing	245	121	366
Endometriosis			
No	1121 (67.7%)	536 (32.3%)	1657
Yes	72 (60.5%)	47 (39.5%)	119
Missing	240	153	393
Smoking			
Never	714 (67.2%)	349 (32.8%)	1063
Current	181 (75.7%)	58 (24.3%)	239
Former	369 (62.0%)	226 (38.0%)	595
Missing	169	103	272
BMI (kg/m2)			
<18.5	28 (71.8%)	11 (28.2%)	39
18.5-24.99	551 (66.0%)	284 (34.0%)	835
25-29.99	432 (67.5%)	208 (32.5%)	640
30+	315 (64.9%)	170 (35.1%)	485
Missing	107	63	170
Parity			
Nulliparous	208 (68.0%)	98 (32.0%)	306
Parous	1152 (66.0%)	594 (34.0%)	1746
Missing	73	44	117

	Macroscopic residual disease (n=1433)	No macroscopic residual disease (n=736)	Total (N=2169)
Incomplete pregnancy			
No	898 (65.9%)	465 (34.1%)	1363
Yes	453 (67.0%)	223 (33.0%)	676
Missing	82	48	130
Breastfeeding			
Never	464 (67.1%)	227 (32.9%)	691
Ever	558 (72.5%)	212 (27.5%)	770
Missing	411	297	708
Tubal ligation			
No	840 (68.2%)	391 (31.8%)	1231
Yes	263 (67.8%)	125 (32.2%)	388
Missing	330	220	550
COC use (years)			
<1	640 (68.9%)	289 (31.1%)	929
1-4.99	274 (65.4%)	145 (34.6%)	419
5-9.99	178 (65.7%)	93 (34.3%)	271
10+	179 (66.8%)	89 (33.2%)	268
Missing	162	120	282
DMPA use			
Never	937 (71.8%)	368 (28.2%)	1305
Ever	93 (43.7%)	120 (56.3%)	213
Missing	403	248	651
Menopausal hormone use			
Never use	726 (66.9%)	360 (33.1%)	1086
ET use	122 (64.6%)	67 (35.4%)	189
EPT use	224 (67.9%)	106 (32.1%)	330
Other	66 (66.7%)	33 (33.3%)	99
Missing	295	170	465

Abbreviations: BMI: body mass index; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; EPT: estrogen plus progestin therapy; ET: estrogen therapy; FIGO: International Federation of Gynecology and Obstetrics; NOS, not otherwise specified; SD: standard deviation

Table 4-3: Association between clinical factors and having macroscopic residual disease after ovarian cancer primary cytoreductive surgery

	Macroscopic residual disease*	No macroscopic residual disease*	OR (95% CI)	p-value
Age at diagnosis				
Every 5 years	1433	736	1.07 (1.00-1.15)	0.039
Year at diagnosis				
Every calendar year	1433	736	0.93 (0.89-0.96)	<0.001
CA125				
Every 200 units	949	490	1.01 (1.00-1.01)	0.044
FIGO stage				
IIIA+IIIB	58	114	1.0	
III (NOS)	146	60	3.95 (1.65-9.43)	0.002
IIIC	977	501	4.75 (3.31-6.82)	<0.001
IV	252	61	10.65 (6.73-16.84)	<0.001
Grade				
Moderately differentiated	183	85	1.0	
Poorly differentiated or undifferentiated	1250	651	1.07 (0.78-1.46)	0.69

* The numbers may not sum to total due to missing values.

Abbreviations: CI: confidence interval; FIGO: International Federation of Gynecology and Obstetrics; NOS, not otherwise specified; OR: odds ratio

Table 4-4: Association between the exposures of interest and having macroscopic residual disease after ovarian cancer primary cytoreductive surgery

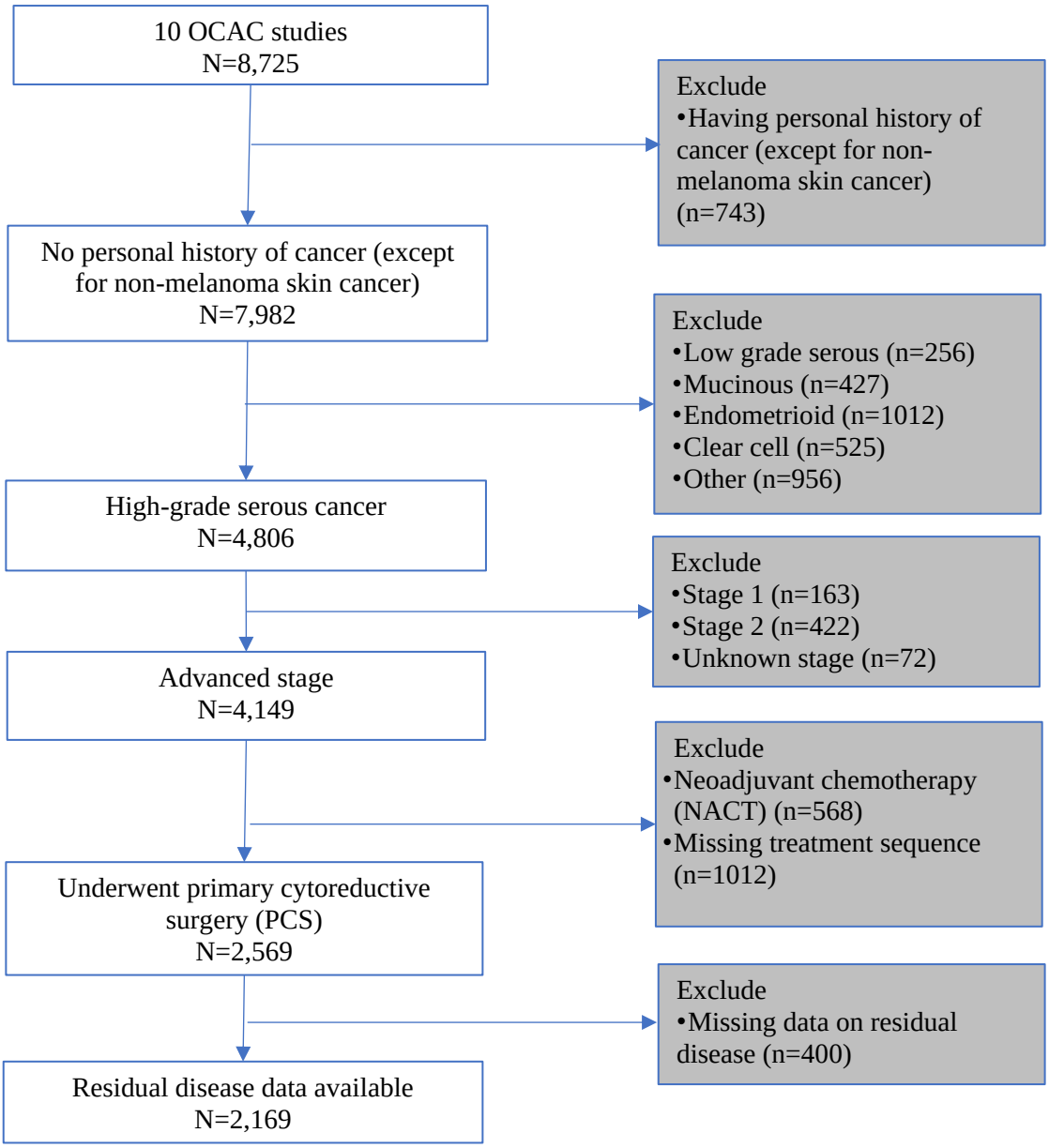
	Macroscopic residual disease*	No macroscopic residual disease*	OR** (95% CI)	p-value
Family history of ovarian cancer				
No	1126	565	1.0	
Yes	62	50	0.72 (0.48-1.09)	0.12
Endometriosis				
No	1121	536	1.0	
Yes	72	47	0.92 (0.60-1.43)	0.72
Smoking				
Never	714	349	1.0	
Current	181	58	1.38 (0.96-1.98)	0.082
Former	369	226	0.79 (0.63-1.00)	0.055
BMI (kg/m^2)				
<18.5	28	11	1.25 (0.57-2.74)	0.57
18.5-24.99	551	284	1.0	
25-29.99	432	208	1.02 (0.80-1.30)	0.89
30+	315	170	0.90 (0.69-1.17)	0.42
Parity				
Nulliparous	208	98	1.0	
Parous	1152	594	0.65 (0.45-0.93)	0.018
Incomplete pregnancy				
No	898	465	1.0	
Yes	453	223	1.09 (0.88-1.35)	0.44
Breastfeeding				
Never	464	227	1.0	
Ever	558	212	1.41 (1.03-1.92)	0.032
Tubal ligation				
No	840	391	1.0	
Yes	263	125	0.95 (0.72-1.25)	0.71
COC use (years)				
<1	640	289	1.0	
1-4.99	274	145	1.01 (0.76-1.35)	0.93
5-9.99	178	93	0.94 (0.68-1.30)	0.70
10+	179	89	0.98 (0.70-1.37)	0.92
DMPA use				
No	937	368	1.0	
Yes	93	120	0.77 (0.28-2.06)	0.59
Menopausal hormone therapy use				
Never	726	360	1.0	
ET use only	122	67	0.69 (0.48-1.00)	0.048
EPT use only	224	106	1.00 (0.75-1.35)	0.97
Other	66	33	0.93 (0.57-1.51)	0.77
Menopausal status				
Pre-menopausal	262	152	0.97 (0.69-1.36)	0.85
Post-menopausal	1111	541	1.0	

* Numbers may not sum to total due to missing values.

** Adjusted for age at diagnosis, race/ethnicity, education level, year of diagnosis, FIGO stage, grade, CA125, and OCAC study site.

Abbreviations: BMI: body mass index; CI: confidence interval; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; EPT: estrogen plus progestin therapy; ET: estrogen therapy; FIGO: International Federation of Gynecology and Obstetrics; OR: odds ratio

Figure 4-1: Flowchart of participants included in Aim 2 analysis



Supplemental Table 4-1: Comparison between individuals with and without data on treatment sequence

	Missing data on treatment sequence (N=1012)*	Data on treatment sequence available (N=3137)*
Age at diagnosis		
Mean [SD]	61.5 [11.4]	60.8 [10.8]
Median [Min, Max]	62.0 [23.0, 92.0]	61.0 [21.0, 91.0]
FIGO stage		
IIIA and IIIB	57 (6.1%)	192 (6.1%)
III (NOS)	245 (26.2%)	404 (12.9%)
IIIC	455 (48.7%)	1986 (63.3%)
IV	177 (19.0%)	555 (17.7%)
Grade		
Moderately differentiated	110 (10.9%)	391 (12.5%)
Poorly differentiated or undifferentiated	902 (89.1%)	2746 (87.5%)
CA125		
Mean [SD]	2110 [3500]	2260 [6330]
Median [Min, Max]	649 [11.0, 22100]	795 [2.30, 134000]
Year at diagnosis		
Mean [SD]	2010 [7.71]	2010 [4.76]
Median [Min, Max]	2010 [1990, 2020]	2010 [1990, 2020]
Race/ethnicity		
Non-Hispanic White	893 (89.7%)	2814 (91.4%)
Black	16 (1.6%)	24 (0.8%)
Asian	41 (4.1%)	141 (4.6%)
Other	45 (4.5%)	100 (3.3%)
Education		
< high school	91 (12.0%)	520 (19.2%)
High school	231 (30.4%)	716 (26.5%)
Some college	195 (25.6%)	741 (27.4%)
College or above	244 (32.1%)	726 (26.9%)

* Numbers may not sum to total due to missing values.

Abbreviations: FIGO: International Federation of Gynecology and Obstetrics; NOS, not otherwise specified; SD: standard deviation

Chapter 5. Rural-urban Disparities in Awareness of, Experience with and Attitudes toward Cervical Cancer Prevention among Women in Southern Vietnam: A Cross-sectional Study

Introduction

Cervical cancer is the most common gynecologic cancer among women worldwide, with more than 600,000 new cases and 340,000 deaths in 2020[84]. At least 80% of all cervical cancer cases and deaths occur in low- and middle-income countries[279]. In 2018, the incidence rate of cervical cancer in the countries with the lowest resources (Human Development Index <0.55) was three times higher than that in the richest countries (Human Development Index ≥0.8), at 26.7 and 9.6 per 100,000 women, respectively; the mortality rate was about seven times higher, at 20.0 and 3.0 per 100,000 women, respectively[279].

Vietnam is a middle-income country[345] where cervical cancer is the second most common and the deadliest gynecologic cancer, accounting for more than 4,000 new cases and about 2,200 deaths in 2020[84]. The incidence rate of cervical cancer in urban areas in Southern Vietnam was 1.5-4 times higher than that in Northern urban areas during 2004-2008, the most recent data available[85,86]. This is likely a consequence of Vietnam being separated into two nations during the Vietnam War in 1954-1975, and North Vietnam being socioeconomically isolated while South Vietnam being more exposed to Western culture. Additionally, during the war, South Vietnam was the battle field where millions of local and foreign soldiers were stationed,

facilitating the flourishment of sex services[347]. Although the North and South Vietnam have been reunited for almost 50 years, these sociocultural differences during the war may have had long-lasting effects that affect the risk factors for cervical cancer between the two regions.

The establishment of high-risk *Human Papillomavirus* (HPV) as the primary cause of cervical cancer as well as the long pre-cancer stage provide abundant opportunities for screening to detect the disease early[278]. The available cervical cancer screening methods in Vietnam include cytology (or Papanicolaou "Pap" test), visual inspection with acetic acid (VIA), and HPV testing on physician-collected or self-collected samples. These methods all rely on assessment of the cervix. However, only ~30% of at-risk Vietnamese women have ever had cervical cancer screening based on the most recent data available in 2015[89]. Reasons for such low uptake include the absence of a national cervical cancer screening program and low awareness of the disease[88,352,356-359]. Another barrier is that all cervical cancer screening methods, except HPV self-sampling, require women to visit healthcare providers. This is inconvenient for women living in remote areas and also presents a barrier for women who feel uncomfortable seeking gynecologic care.

HPV self-sampling has been proven to increase cervical cancer screening uptake[93,95,97,99] as it does not require women to visit healthcare professionals. Our previous studies found a high acceptability of HPV self-sampling among women in middle-income countries, including indigenous women in Guatemala[102,109] and women of different religious groups in Thailand[337]. HPV self-sampling was also highly accepted among women in an urban area in Northern Vietnam[118].

Although the incidence rate of cervical cancer in Southern Vietnam is higher than the national average, there has been limited research on cervical cancer in this geographic region. HPV self-sampling has great potential to improve cervical cancer screening uptake among women in Southern Vietnam, however no study has explored the acceptability of HPV self-sampling in this population. In addition, more than half of Southern Vietnamese people live in rural areas, where socioeconomic status, healthcare access and health outcomes are lower than urban areas[83], but no studies on cervical cancer prevention or screening have been conducted in Southern rural women to our knowledge. To address these gaps in knowledge and with an ultimate goal of reducing the cervical cancer burden in Southern Vietnam, we conducted a cross-sectional study to comprehensively evaluate the awareness of, experience with and attitudes toward cervical cancer prevention and screening in rural and urban areas in Southern Vietnam.

Methods

This study was approved by the University of Michigan Health Sciences and Behavioral Sciences Institutional Review Board (HUM00199150) and by the Ethics Committee in Biomedical Research at Ho Chi Minh City University of Medicine and Pharmacy (Decisions 446 and 480/HDDD-DHYD). All participants provided written informed consent.

Study design

In October and November 2021, we conducted a cross-sectional study of women residing in the rural district of Can Gio and the urban District 4, Ho Chi Minh City (Southern Vietnam). The inclusion criteria were women of Kinh ethnicity (accounting for more than 85% of the Vietnamese population[83]), aged 30-65 (ages recommended by the United States Preventive

Services Task Force to be screened with HPV testing[406]), and having no personal history of cervical cancer.

We worked with the district health center of the rural district of Can Gio with the goal of recruiting 200 rural women, including 30% aged 30-39, 30% aged 40-49, and 40% aged 50-65. The district health center assigned the two community health centers in Can Thanh and Long Hoa to invite 80 and 120 women in their communities, respectively. Each community health center then allocated an equal number of women to the neighborhoods in their community. For example, there are five neighborhoods in Can Thanh; population collaborators (i.e., neighborhood volunteers) in each neighborhood were allowed to invite 16 women, including 5 aged 30-39, 5 aged 40-49, and 6 aged 50-65, to achieve a total of 80 women. There are four neighborhoods in Long Hoa; population collaborators in each neighborhood were allocated to invite 30 women, including 9 aged 30-39, 9 aged 40-49, and 12 aged 50-65, to recruit a total of 120 women.

Similarly, we worked with the district health center of the urban District 4 with a goal of recruiting 200 urban women with the same age distribution described above. The district health center then allowed each of the two community health centers of Ward 14 and Ward 15 to invite 100 women in their community to participate. This number was then divided equally between three neighborhoods in Ward 14 (33 women each) and four neighborhoods in Ward 15 (25 women each).

Population collaborators sent invitation letters to women to come to the recruitment sites in their communities to participate in the study on the weekend or Monday to maximize the opportunity to participate. Some women received the invitation letters but did not come; we were

unable to know who these women were because we did not have the lists of invitees from the population collaborators. Some women heard of the study and came to participate without an invitation letter. We recruited all people coming to the recruitment sites if they met the eligibility criteria.

Female research staff obtained written informed consent from eligible participants. Participants were asked to answer a questionnaire in Vietnamese using a tablet. The questionnaire began with questions on demographics and awareness of HPV and cervical cancer. Participants then watched four short videos which had voiceover and subtitles in Vietnamese to describe four cervical cancer screening methods: Pap test, visual inspection with acetic acid (VIA), HPV testing with physician-collected samples, and HPV self-sampling. The women then answered questions about their experience with and attitudes toward each screening method.

Data analysis

The binary outcomes of interest (yes/no) included: awareness of HPV and cervical cancer (i.e., ever heard of HPV, HPV vaccine, and HPV testing; if knowing that HPV is a cause of cervical cancer); ever screened for cervical cancer; main reasons for not screening (i.e., no need/no reasons to screen; no awareness of the test; unaffordability; concerns of pain/unpleasant/embarrassment; travelling far; having a different test); willingness of trying HPV self-sampling (i.e., willing to self-collect, to have a kit mailed to home, to drop off the self-collected sample at a health center, to follow-up with doctors if the self-collected sample was abnormal); and concerns of HPV self-sampling (i.e., self-sampling improperly; fear of pain; embarrassment; fear of the test revealing cancer; fear of other people thinking that they had cancer; fear of people thinking negatively about their sexual life; need family's approval for self-

sampling; religious belief affecting screening decision). To ask participants if they would like to take each screening method, we used a Likert-scaled question with five options: strongly dislike (score=1), dislike (score=2), neutral (score=3), like (score=4), and strongly like (score=5); we coded those outcomes as continuous variables.

To examine if there were rural-urban disparities in the outcomes, we fit logistic and linear regression models for the binary or continuous outcomes, respectively, regressing on area (urban versus rural), adjusting for demographic and socioeconomic factors. The demographic and socioeconomic factors included age (continuous), religion (no religion, Buddhism, other), education (primary school or lower, secondary school, high school, more than high school), monthly household income (<5, 5-9.99, 10-19.99, 20+ million Vietnam Dong), marital status (never married, married, other [including separated, divorced and widowed]), having a friend or family member with cervical cancer (yes, no), having national health insurance (yes, no) or a private health insurance (yes, no). To explore which factors were associated with awareness of, experience with and attitudes toward cervical cancer prevention, we fit models for the rural and urban women separately, regressing the outcomes on the demographic and socioeconomic factors mentioned above.

Among the outcomes, proportion of missingness ranged from 0 (for ever heard of HPV, HPV vaccine or HPV testing) to 8.3% (for the question "I would be willing to go to the nearest health center to drop off the sample for an HPV test"). People with missing values of an outcome were not included in the models for that outcome. Most demographic and socioeconomic factors did not have any missing values, except for household income (proportion of missingness=0.5%)

and having a private health insurance (proportion of missingness=1.0%); a missingness category was created for these variables in the models.

Statistical significance was defined as $p \leq 0.05$ using two-sided tests. Data were analyzed using R version 4.0.3.

Results

A total of 203 rural and 205 urban women came to participate in the study. Of them, ten women were excluded because they were younger than the age limit (n=3) or had a history of cervical cancer (n=7), thus a total of 196 women in the rural area and 202 in the urban area were enrolled. The average age of participants in the rural and urban areas was similar (mean=47.4 and 47.5 years in rural and urban areas, respectively; Table 5-1). Compared to women in the rural area, those living in the urban area had a higher education level and a higher household income; fewer urban women were married (Table 5-1). There was a similarly high proportion of women with a national health insurance in both regions (84.7% in rural; 87.6% in urban) and a similarly low proportion of people with a private health insurance (7.7% in rural; 9.4% in urban; Table 5-1).

Awareness of HPV and cervical cancer

Only about a third of participants had ever heard of HPV (34.2% in rural, 37.6% in urban) or knew that HPV is a cause of cervical cancer (29.6% in rural, 35.1% in urban; Supplemental Table 5-1), and an even lower proportion had ever heard of the HPV vaccine (18.4% in rural; 29.2% in urban) or had ever heard of HPV testing (17.3% in rural; 28.7% in urban; Supplemental Table 5-1). There were no statistically significant differences in these

awareness outcomes between rural and urban women after adjusting for demographic and socioeconomic factors (Supplemental Table 5-1). In both areas, older age, higher education level, higher household income and having a friend or a family member with cervical cancer were associated a higher level of awareness (Supplemental Table 5-2).

Cervical cancer screening uptake

About half of the participants reported ever being screened for cervical cancer (49.1% in rural; 51.8% in urban; Supplemental Table 5-1). Some women reported being screened by more than one method. The most common screening method reported was Pap test (39.9% in rural; 45.5% in urban), followed by HPV testing on physician-collected samples (11.4% in rural; 13.0% in urban) and VIA (8.4% in rural; 8.7% in urban). The least common method reported was HPV self-sampling (1.0% in rural; 0.0% in urban). There were no statistically significant differences in reporting cervical cancer screening between the two areas after adjusting for demographic and socioeconomic factors (Supplemental Table 5-1). In both areas, women who reported ever being screened for cervical cancer were more likely to have a higher household income and national health insurance compared to those who reported never being screened (Supplemental Table 5-3).

Barriers to cervical cancer screening

For each of the four screening methods, we asked the participants who reported never taking that method the main reasons for not using it; women could select more than one reason. In both areas, “do not need it/no reasons to use it” was the most common reason for not taking Pap test (49.5% in rural; 54.1% in urban), VIA (48.8% in rural; 52.8% in urban), and HPV testing on physician-collected samples (49.0% in rural; 52.1% in urban; Supplemental Table 5-

4). The second most common reason was “do not know about the test”, with about 30-40% of participants choosing this option (Supplemental Table 5-4). Conversely, lack of knowledge of the test was the most common reason for not using HPV self-sampling in both areas (65.1% in rural; 78.9% in urban; Supplemental Table 5-4).

Overall, there were no differences in the reasons for not taking Pap test, VIA and HPV testing on physician-collected samples between participants in the two areas after adjusting for demographic and socioeconomic factors (Supplemental Table 5-4). For HPV self-sampling, urban women were statistically significantly more likely than rural women to indicate that lack of knowledge of the test was their main reason for not taking it (OR=2.54, 95% CI 1.46-4.40), but less likely to indicate that pain, discomfort, or embarrassment was the main reason for never taking HPV self-sampling, after adjusting for demographic and socioeconomic factors (OR=0.35, 95% 0.15-0.82; Supplemental Table 5-4).

Attitudes toward HPV self-sampling and other cervical cancer screening methods

We used a Likert-scaled question to ask participants if they would like to take each screening method. The most preferred method was Pap test (the proportion of women who indicated that they would like or strongly like taking it was 84.2% in rural; 82.2% in urban), followed by HPV testing on physician-collected samples (83.2% in rural; 81.7% in urban), and VIA (78.1% in rural; 79.2% in urban; Table 5-2). HPV self-sampling was the least favorite screening method, with only 40.3% women in the rural area and 53.5% in the urban area indicating that they would like or strongly like to use it (Table 5-2). Compared to rural women, urban women were statistically significantly less likely to indicate that they would like to take Pap test (mean Likert-scaled score difference= -0.29, 95% CI -0.51 to -0.06) and HPV testing on

physician-collected samples (mean difference= -0.23, 95% CI -0.46 to -0.01), but were more likely to indicate that they would like to take HPV self-sampling, after adjusting for demographic and socioeconomic factors (mean difference= 0.49, 95% CI 0.18 to 0.79; Table 5-2).

Compared to rural women, urban women were statistically significantly more likely to show a willingness to self-collect an HPV sample at home (42.2% in rural; 56.2% in urban; OR=2.02, 95% CI 1.26-3.23) and to have a self-sampling kit mailed to their houses (34.7% in rural; 48.1% in urban; OR=2.06, 95% CI 1.29-3.31), after adjusting for demographic and socioeconomic factors (Table 5-3). The majority of participants indicated that they were willing to drop off the self-collected samples at the nearest health center (65.6% in rural; 74.6% in urban) and to follow-up with doctors if their self-collected samples were abnormal (90.3% in rural; 88.1% in urban). None of these differences between the two areas were statistically significant after adjusting for demographic and socioeconomic factors (Table 5-3). In the urban area, age was the only factor suggestively associated with a willingness to self-collect an HPV sample, with younger people being more willing (OR=0.84, 95% CI 0.70-1.00 for every 5 years of age); this association was not observed among rural women (OR=0.99, 95% CI 0.83-1.19 for every 5 years of age; Supplementary Table 5-5).

The most common concerns regarding HPV self-sampling included: concern of self-sampling incorrectly (82.5% in rural; 73.4% in urban), fear of pain (59.0% in rural; 63.8% in urban) and fear of the test revealing cancer (47.1% in rural; 59.9% in urban; Table 5-3). Compared to rural women, urban women were less likely to have the concern of self-sampling improperly (OR=0.49, 95% CI 0.28-0.88), to need family approval for their self-sampling (OR=0.42, 95% CI 0.22-0.79), and to be embarrassed of self-sampling (OR=0.34, 95% CI 0.14-

0.78) after adjusting for demographic and socioeconomic factors. However, urban women were more likely to have the fear of the test revealing that they had cancer (OR=1.78, 95% CI 1.11-2.86; Table 5-3).

Discussion

This study is the first to comprehensively evaluate cervical cancer prevention and screening among women in Southern Vietnam. In both rural and urban areas, we found a similarly low awareness of HPV and cervical cancer. However, about half of women in both areas reported ever being screened for cervical cancer. There was a high acceptance of cervical cancer screening overall. Nearly 50% of the participants reported wanting to use HPV self-sampling. Urban women were more willing to try self-collecting, particularly younger women. Rural women were more likely to have the concern of self-sampling incorrectly while urban women were more likely to have the fear of the test revealing that they had cancer.

Our finding that women in Southern Vietnam had low awareness of HPV and cervical cancer is consistent with the literature. The six previous studies in Southern Vietnam conducted among adults, parents, and pre-teen/teenagers found a lack of knowledge of HPV and cervical cancer[88,352,356-359]. The most recent population survey conducted in 2010-2011 in Ho Chi Minh City (n=850) and Can Tho (n=1,100), the two largest urban areas in Southern Vietnam, found a slightly higher level of awareness than our study findings[88]. They found that about half of the women had ever heard of HPV and the HPV vaccine[88], while in our study only a third of women or fewer were aware. The difference is possibly due to the differences in age range, i.e., 18-65 in their study and 30-65 in our study. The previous study did not report information in finer age groups for comparison to our findings.

The observation that about 50% of women had ever screened for cervical cancer in our study, while still low, is higher than expected given that only a third of women were aware of HPV and its relationship with cervical cancer. A possible explanation is that women may think of cervical cancer screening as a part of a general gynecologic examination. Thus, when they visit the doctor for a gynecologic examination, they let the doctors perform any tests related to gynecologic issues, including cervical cancer screening. This is aligned with results from a study in medical and pharmaceutical claims of more than 2.3 million in the United States, which showed that among women who underwent a gynecologic examination, 76% had a cervical cancer screening in the same year; whereas among women who did not have a gynecologic examination in a given year, only 4% had a cervical cancer screening in that year[407]. Focus groups or in-depth interviews should be conducted to understand the perception of cervical cancer screening among women in Southern Vietnam.

Women reported high acceptance of cervical cancer screening but low screening uptake. Besides low awareness, lack of access to gynecologic healthcare is also a barrier to cervical cancer screening. This is supported by our finding that in both areas, women with higher income were more likely to report ever being screened for cervical cancer. There is no national cervical cancer screening program, and screening is not affordable for most women. Therefore, it is important to increase health literacy and gynecologic health access in order to improve cervical cancer screening uptake.

We found a moderate acceptability of HPV self-sampling in both areas. This is lower to several studies which found that HPV self-sampling is highly accepted by women in multiple settings. A meta-analysis of 37 studies from 24 countries across North America, South America,

Europe, Africa, and Asia estimated that 97% of more than 18,000 women found self-sampling to be acceptable (95% CI 95-98%)[341]. The difference might be because participants in those studies tried self-sampling before providing their views on this screening method, while participants in our study watched the video about HPV self-sampling but did not try it. Future studies should assess the acceptability and feasibility of HPV self-sampling in Southern Vietnam after letting women try self-collecting a sample.

Strengths of this study included measures to minimize information bias, including the utilization of tablets to deliver the questionnaire instead of an interview to ensure the privacy of their answers; having female research staff to make women feel comfortable; and giving participants plenty of time to recall past events. A limitation of this study is that we did not have access to population rosters, and thus we were unable to know if participants were different from non-participants in these two areas. We tried to maximize the chance of participation by recruiting on the weekends and Mondays. In addition, we compared the education levels of our study sample and the general population in Ho Chi Minh City[83]. We found that while our rural study sample had similar education levels to the general rural population, our urban study sample had lower education levels compared to the general urban population in Ho Chi Minh City. Therefore, the findings in the urban area in our study may not be generalizable to urban populations with different education levels.

Public health implications

We found high acceptability of cervical cancer screening but low levels of screening and low awareness of the disease among women in Southern Vietnam. The findings highlight the importance of improving health literacy and gynecologic healthcare access to reduce cervical

cancer burden in Southern Vietnam. We also found differential acceptability and concerns regarding HPV self-sampling between women in rural and urban areas. Tailored health educational programs for rural and urban areas are warranted to increase cervical cancer screening uptake. Future studies should include actual HPV self-sampling and other rural and urban areas in Vietnam to achieve broader generalizability.

Table 5-1: Participants' characteristics in rural and urban areas, Southern Vietnam, 2021

	Rural (n=196)		Urban (n=202)	
Age				
Mean [standard deviation]	47.4 [9.50]		47.5 [9.72]	
Median [Min, Max]	47.0 [30.0, 65.0]		46.0 [30.0, 65.0]	
Religion				
None	74	(37.8%)	45	(22.3%)
Buddhist	103	(52.6%)	118	(58.4%)
Christian	14	(7.1%)	1	(0.5%)
Catholic	4	(2.0%)	36	(17.8%)
Caodaiist	1	(0.5%)	1	(0.5%)
Muslim	0	(0.0%)	1	(0.5%)
Education level				
Primary school or lower	75	(38.3%)	35	(17.3%)
Secondary school	76	(38.8%)	78	(38.6%)
High school	30	(15.3%)	61	(30.2%)
More than high school	15	(7.7%)	28	(13.9%)
Household monthly income (million Vietnam Dong)				
<5	68	(34.7%)	25	(12.4%)
5-9.99	73	(37.2%)	69	(34.2%)
10-19.99	47	(24.0%)	71	(35.1%)
20+	8	(4.1%)	35	(17.3%)
Don’t know	0	(0.0%)	2	(1.0%)
Marital status				
Never married	2	(1.0%)	23	(11.4%)
Married	159	(81.1%)	144	(71.3%)
Other	35	(17.9%)	35	(17.3%)
Having friends or family members with cervical cancer				
No	170	(86.7%)	153	(75.7%)
Yes	26	(13.3%)	49	(24.3%)
Having national health insurance				
No	30	(15.3%)	25	(12.4%)
Yes	166	(84.7%)	177	(87.6%)
Having private health insurance				
No	179	(91.3%)	181	(89.6%)
Yes	15	(7.7%)	19	(9.4%)
Don’t know	2	(1.0%)	2	(1.0%)

Table 5-2: Preference of screening methods among women in rural and urban areas, Southern Vietnam, 2021

I would like to take…	Likert score	Rural (n=196)		Urban (n=202)		Mean Likert score difference (95% CI)*	p-value
Pap test						-0.29 (-0.51 to -0.06)	0.014
Strongly dislike	1	1	(0.5%)	9	(4.5%)		
Dislike	2	24	(12.2%)	18	(8.9%)		
Neutral	3	6	(3.1%)	9	(4.5%)		
Like	4	87	(44.4%)	109	(54.0%)		
Strongly like	5	78	(39.8%)	57	(28.2%)		
Visual inspection with acetic acid (VIA)						-0.17 (-0.41 to 0.06)	0.15
Strongly dislike	1	2	(1.02%)	9	(4.5%)		
Dislike	2	33	(16.8%)	19	(9.4%)		
Neutral	3	8	(4.1%)	14	(6.9%)		
Like	4	88	(44.9%)	106	(52.5%)		
Strongly like	5	65	(33.2%)	54	(26.7%)		
HPV testing on physician-collected samples						-0.23 (-0.46 to -0.01)	0.045
Strongly dislike	1	1	(0.5%)	10	(5.0%)		
Dislike	2	24	(12.2%)	16	(7.9%)		
Neutral	3	8	(4.1%)	11	(5.5%)		
Like	4	97	(49.5%)	106	(52.5%)		
Strongly like	5	66	(33.7%)	59	(29.2%)		
HPV self-sampling						0.49 (0.18 to 0.79)	0.002
Strongly dislike	1	31	(15.8%)	19	(9.4%)		
Dislike	2	79	(40.3%)	59	(29.2%)		
Neutral	3	7	(3.6%)	16	(7.9%)		
Like	4	45	(23.0%)	73	(36.1%)		
Strongly like	5	34	(17.3%)	35	(17.3%)		

* Mean Likert score difference and 95% confidence interval from linear regression models regressing on area (urban vs rural), adjusted for age, religion, education level, household income, marital status, having a friend or family member with cervical cancer, having a national health insurance, having a private health insurance

Abbreviations: CI, confidence interval; HPV, *Human papillomavirus;* VIA, visual inspection with acetic acid

Table 5-3: Willingness and concerns of HPV self-sampling among women in rural and urban areas, Southern Vietnam, 2021

	Rural (n=196)*		Urban (n=202)*		OR** (95%CI)	p-value
Willingness of self-sampling						
I would be willing to collect an HPV sample at home.						
No	111	(57.8%)	85	(43.8%)		
Yes	81	(42.2%)	109	(56.2%)	2.02 (1.26-3.23)	0.003
I would be willing to have an HPV self-sampling device mailed to my home to take an HPV sample.						
No	124	(65.3%)	98	(51.9%)		
Yes	66	(34.7%)	91	(48.1%)	2.06 (1.29-3.31)	0.003
I would be willing to go to the nearest health center to drop off the sample for an HPV test.						
No	62	(34.4%)	47	(25.4%)		
Yes	118	(65.6%)	138	(74.6%)	1.48 (0.88-2.48)	0.14
I would be willing to go to a clinic for an exam and Pap test if the sample I collected was abnormal.						
No	18	(9.68%)	23	(11.9%)		
Yes	168	(90.3%)	170	(88.1%)	0.68 (0.32-1.43)	0.31
Concerns of HPV self-sampling						
I am worried that I would not collect the sample properly.						
No	33	(17.5%)	53	(26.6%)		
Yes	156	(82.5%)	146	(73.4%)	0.49 (0.28-0.88)	0.016
I am afraid that collecting the sample myself will be painful.						
No	73	(41.0%)	72	(36.2%)		
Yes	105	(59.0%)	127	(63.8%)	1.08 (0.67-1.76)	0.74
I am afraid that HPV testing will show that I have cervical cancer.						
No	101	(52.9%)	79	(40.1%)		
Yes	90	(47.1%)	118	(59.9%)	1.78 (1.11-2.86)	0.017
I am afraid that HPV testing will make other people think that I have cervical cancer.						
No	148	(76.7%)	162	(82.2%)		
Yes	45	(23.3%)	35	(17.8%)	1.09 (0.62-1.92)	0.76
I would need my family's approval to collect the sample.						
No	146	(76.4%)	174	(87.9%)		
Yes	45	(23.6%)	24	(12.1%)	0.42 (0.22-0.79)	0.007
I am afraid that HPV testing will make others think negative things about my sexual life.						
No	162	(84.8%)	173	(87.4%)		
Yes	29	(15.2%)	25	(12.6%)	1.20 (0.63-2.30)	0.58
I would be embarrassed to collect a sample at home.						
No	167	(89.8%)	188	(94.5%)		
Yes	19	(10.2%)	11	(5.53%)	0.34 (0.14-0.78)	0.011

	Rural (n=196)*		Urban (n=202)*		OR** (95%CI)	p-value
My religious/spiritual belief would affect my decision to be screened.						
No	185	(98.9%)	194	(99.5%)		
Yes	2	(1.1%)	1	(0.5%)	0.43 (0.14-1.35)	0.15

* Numbers may not sum to the total due to missing values.

** Odds ratio and 95% confidence interval from logistic regression model regressing on area (urban vs rural), adjusted for age, religion, education level, household income, marital status, having a friend or family member with cervical cancer, having a national health insurance, having a private health insurance.

Abbreviations: CI, confidence interval; HPV, *Human papillomavirus*; OR, odds ratio

Supplemental Table 5-1: Awareness of HPV and cervical cancer and reporting screening among women in rural and urban areas, Southern Vietnam, 2021

	Rural (n=196)*		Urban (n=202)*		OR** (95%CI)	p-value
Awareness of HPV and cervical cancer						
Ever heard of HPV						
No	129	(65.8%)	126	(62.4%)		
Yes	67	(34.2%)	76	(37.6%)	0.73 (0.43-1.23)	0.23
Know that HPV causes cervical cancer						
No	138	(70.4%)	131	(64.9%)		
Yes	58	(29.6%)	71	(35.1%)	0.79 (0.46-1.38)	0.41
Ever heard of HPV vaccine						
No	160	(81.6%)	143	(70.8%)		
Yes	36	(18.4%)	59	(29.2%)	1.21 (0.67-2.18)	0.53
Ever heard of HPV testing						
No	162	(82.7%)	144	(71.3%)		
Yes	34	(17.3%)	58	(28.7%)	1.17 (0.64-2.14)	0.60
Report of cervical cancer screening uptake						
Ever screen						
No	88	(50.9%)	95	(48.2%)		
Yes	85	(49.1%)	102	(51.8%)	0.71 (0.43-1.17)	0.18
Ever take Pap test						
No	104	(60.1%)	109	(54.5%)		
Yes	69	(39.9%)	91	(45.5%)	0.74 (0.45-1.21)	0.23
Ever take visual inspection with acetic acid (VIA)						
No	163	(91.6%)	178	(91.3%)		
Yes	15	(8.4%)	17	(8.7%)	0.63 (0.32-1.23)	0.18
Ever take HPV testing on physician-collected samples						
No	156	(88.6%)	168	(87.0%)		
Yes	20	(11.4%)	25	(13.0%)	0.66 (0.36-1.22)	0.18
Ever HPV self-sampling						
No	193	(99.0%)	199	(100%)		
Yes	2	(1.0%)	0	(0.0%)	Not applicable	

* Numbers may not sum to the total due to missing values.

** Odds ratio and 95% confidence interval from logistic regression model regressing on area (urban vs rural), adjusted for age, religion, education level, household income, marital status, having a friend or family member with cervical cancer, having a national health insurance, having a private health insurance.

Abbreviations: CI, confidence interval; HPV, *Human papillomavirus*; OR, odds ratio; VIA, visual inspection with acetic acid

Supplemental Table 5-2: Factors associated with awareness of HPV and cervical cancer in rural and urban areas, Southern Vietnam, 2021

	Rural				Urban			
	Yes	**No**	**OR (95% CI)**	**p-value**	**Yes**	**No**	**OR (95% CI)**	**p-value**
Ever heard of HPV								
Age								
Every 5 years			1.29 (1.05-1.58)	0.017			1.19 (0.98-1.44)	0.083
Religion								
No religion	30	44	1.0		23	22	1.0	
Buddhism	29	74	0.93 (0.42-2.09)	0.86	43	75	0.91 (0.37-2.24)	0.84
Others	8	11	1.95 (0.58-6.61)	0.28	10	29	0.47 (0.15-1.44)	0.19
Education level								
Primary school or lower	21	54	1.0		6	29	1.0	
Secondary school	19	57	0.64 (0.29-1.45)	0.29	22	56	2.04 (0.68-6.13)	0.20
High school	16	14	2.94 (1.04-8.29)	0.041	25	36	3.70 (1.20-11.43)	0.023
More than high school	11	4	11.75 (2.54-54.37)	0.002	23	5	31.56 (6.18-161.31)	<0.001
Household monthly income (million Vietnam Dong)								
<5	15	53	1.0		7	18	1.0	
5-9.99	31	42	3.26 (1.39-7.63)	0.007	21	48	0.85 (0.27-2.70)	0.78
10-19.99	16	31	1.34 (0.46-3.89)	0.59	28	43	1.05 (0.32-3.39)	0.94
20+	5	3	5.76 (0.87-38.10)	0.069	20	15	2.06 (0.55-7.76)	0.28
Don’t know	0	0			0	2	NA	
Marital status								
Never married	1	1	0.26 (0.01-4.95)	0.37	10	13	1.43 (0.47-4.33)	0.53
Married	55	104	1.0		58	86	1.0	
Separated/ Divorced/ Widowed	11	24	0.58 (0.23-1.50)	0.26	8	27	0.66 (0.24-1.78)	0.41
Friends or family members with cervical cancer								
No	55	115	1.0		53	100	1.0	
Yes	12	14	2.13 (0.78-5.80)	0.14	23	26	1.85 (0.86-3.95)	0.11
National health insurance								
No	8	22	0.90 (0.33-2.41)	0.83	6	19	0.75 (0.25-2.27)	0.61
Yes	59	107	1.0		70	107	1.0	
Private health insurance								
No	59	120	1.0		68	113	1.0	
Yes	7	8	1.89 (0.55-6.54)	0.31	8	11	0.47 (0.13-1.67)	0.24
Don’t know	1	1	17.20 (0.75-395.30)	0.075	0	2	NA	
Know that HPV causes cervical cancer								
Age								
Every 5 years			1.18 (0.95-1.47)	0.14			1.16 (0.95-1.41)	0.14
Religion								
No religion	29	45	1.0		23	22	1.0	

	Rural				Urban			
	Yes	**No**	**OR (95% CI)**	**p-value**	**Yes**	**No**	**OR (95% CI)**	**p-value**
Buddhism	23	80	0.79 (0.33-1.89)	0.60	38	80	0.70 (0.28-1.77)	0.46
Others	6	13	1.45 (0.39-5.41)	0.58	10	29	0.46 (0.15-1.42)	0.18
Education level								
Primary school or lower	12	63	1.0		5	30	1.0	
Secondary school	19	57	1.25 (0.51-3.05)	0.63	21	57	2.46 (0.76-7.97)	0.13
High school	16	14	5.37 (1.73-16.61)	0.004	22	39	3.71 (1.11-12.41)	0.033
More than high school	11	4	16.42 (3.36-80.34)	0.001	23	5	37.72 (6.97-204.05)	<0.001
Household monthly income (million Vietnam Dong)								
<5	9	59	1.0		7	18	1.0	
5-9.99	28	45	3.98 (1.49-10.63)	0.006	18	51	0.58 (0.18-1.90)	0.37
10-19.99	16	31	1.52 (0.47-4.92)	0.49	27	44	0.82 (0.25-2.72)	0.75
20+	5	3	7.68 (1.07-55.25)	0.043	19	16	1.58 (0.41-6.07)	0.50
Don’t know	0	0			0	2	NA	
Marital status								
Never married	1	1	0.22 (0.01-4.32)	0.32	9	14	1.15 (0.36-3.66)	0.81
Married	50	109	1.0		55	89	1.0	
Separated/Divorced/ Widowed	7	28	0.42 (0.14-1.26)	0.12	7	28	0.55 (0.19-1.58)	0.27
Friends or family members with cervical cancer								
No	46	124	1.0		49	104	1.0	
Yes	12	14	2.78 (0.99-7.80)	0.052	22	27	1.94 (0.89-4.23)	0.094
National health insurance								
No	4	26	0.43 (0.12-1.55)	0.20	4	21	0.46 (0.13-1.61)	0.22
Yes	54	112	1.0		67	110	1.0	
Private health insurance								
No	51	128	1.0		64	117	1.0	
Yes	6	9	2.37 (0.60-9.40)	0.22	7	12	0.40 (0.10-1.52)	0.18
Don’t know	1	1	14.15 (0.56-358.12)	0.11	0	2	NA	
				Ever heard of HPV vaccine				
Age								
Every 5 years			1.13 (0.89-1.43)	0.31			1.08 (0.88-1.33)	0.45
Religion								
No religion	17	57	1.0		19	26	1.0	
Buddhism	17	86	1.02 (0.39-2.68)	0.97	33	85	1.11 (0.42-2.90)	0.83
Others	2	17	0.48 (0.08-2.76)	0.41	7	32	0.53 (0.16-1.78)	0.31
Education level								
Primary school or lower	9	66	1.0		2	33	1.0	
Secondary school	11	65	1.03 (0.37-2.88)	0.95	13	65	2.97 (0.60-14.69)	0.18
High school	9	21	3.55 (1.05-11.96)	0.041	23	38	9.09 (1.87-44.33)	0.006
More than high school	7	8	11.51 (2.32-57.09)	0.003	21	7	46.18 (6.82-312.75)	<0.001
Household monthly income (million Vietnam Dong)								
<5	9	59	1.0		3	22	1.0	
5-9.99	17	56	1.76 (0.64-4.85)	0.28	16	53	1.65 (0.38-7.28)	0.51

	Rural				Urban			
	Yes	**No**	**OR (95% CI)**	**p-value**	**Yes**	**No**	**OR (95% CI)**	**p-value**
10-19.99	8	39	0.59 (0.16-2.22)	0.44	23	48	2.14 (0.48-9.53)	0.32
20+	2	6	0.80 (0.10-6.52)	0.84	17	18	3.42 (0.69-16.82)	0.13
Don't know	0	0			0	2	NA	
Marital status								
Never married	1	1	0.88 (0.04-17.24)	0.93	8	15	1.56 (0.46-5.23)	0.47
Married	28	131	1.0		45	99	1.0	
Separated/Divorced/ Widowed	7	28	1.18 (0.41-3.38)	0.76	6	29	0.80 (0.26-2.46)	0.69
Friends or family members with cervical cancer								
No	28	142	1.0		42	111	1.0	
Yes	8	18	2.62 (0.88-7.82)	0.084	17	32	1.64 (0.72-3.72)	0.24
National health insurance								
No	3	27	0.52 (0.13-2.05)	0.35	5	20	0.86 (0.25-2.92)	0.81
Yes	33	133	1.0		54	123	1.0	
Private health insurance								
No	31	148	1.0		51	130	1.0	
Yes	4	11	1.68 (0.42-6.78)	0.46	8	11	0.73 (0.21-2.57)	0.63
Don't know	1	1	15.51 (0.66-361.71)	0.088	0	2	NA	

Abbreviations: CI, confidence interval; HPV, *Human papillomavirus*; OR, odds ratio

Supplemental Table 5-3: Factors associated with reporting ever being screened for cervical cancer among women in rural and urban areas, Southern Vietnam, 2021

	Reporting ever being screened for cervical cancer							
	Rural				Urban			
	Yes	No	OR (95% CI)	p-value	Yes	No	OR (95% CI)	p-value
Age								
Every 5 years			1.09 (0.89-1.34)	0.42			1.31 (1.07-1.61)	0.008
Religion								
No religion	35	33	1.0		26	19	1.0	
Buddhism	42	48	0.78 (0.36-1.73)	0.55	58	58	0.89 (0.35-2.26)	0.80
Others	8	7	0.68 (0.18-2.61)	0.57	18	18	0.90 (0.29-2.72)	0.85
Education level								
Primary school or lower	28	37	1.0		9	26	1.0	
Secondary school	31	35	0.92 (0.42-2.01)	0.83	39	35	4.37 (1.53-12.47)	0.006
High school	18	9	2.45 (0.80-7.49)	0.12	32	28	4.62 (1.53-13.97)	0.007
More than high school	8	7	1.32 (0.32-5.36)	0.70	22	6	24.39 (4.49-132.40)	<0.001
Household monthly income (million Vietnam Dong)								
<5	23	36	1.0		9	16	1.0	
5-9.99	37	26	2.35 (1.01-5.48)	0.047	29	38	0.78 (0.25-2.43)	0.67
10-19.99	20	24	1.29 (0.46-3.61)	0.63	39	30	1.07 (0.33-3.46)	0.91
20+	5	2	3.35 (0.50-22.38)	0.21	25	9	3.71 (0.89-15.48)	0.072
Don’t know	0	0	NA		0	2	NA	
Marital status								
Never married	0	2	NA		3	19	0.07 (0.02-0.33)	0.001
Married	65	75	1.0		83	58	1.0	
Separated/Divorced/ Widowed	20	11	2.53 (0.95-6.74)	0.062	16	18	0.72 (0.29-1.81)	0.49
Friends or family members with cervical cancer								
No	71	79	1.0		74	76	1.0	
Yes	14	9	1.94 (0.68-5.54)	0.22	28	19	1.18 (0.52-2.67)	0.69
National health insurance								
No	8	20	0.24 (0.08-0.69)	0.008	6	19	0.26 (0.08-0.85)	0.026
Yes	77	68	1.0		96	76	1.0	
Private health insurance								
No	74	84	1.0		90	87	1.0	
Yes	10	3	5.07 (1.06-24.18)	0.042	12	6	1.08 (0.30-3.85)	0.90
Don’t know	1	1	1.28 (0.06-26.53)	0.87	0	2	NA	

Abbreviations: OR, odds ratio; CI, confidence interval.

Supplemental Table 5-4: Main reasons for never taking a screening method (among the women who reported never taking that method) in rural and urban areas, Southern Vietnam, 2021

	Pap test			
	Rural n=104*	**Urban n=109***	**OR** (95%CI)**	**p-value**
No reasons/ No need the test				
False	52 (50.5%)	50 (45.9%)		
True	51 (49.5%)	59 (54.1%)	1.32 (0.68-2.55)	0.41
Do not know about the test				
False	71 (68.9%)	79 (72.5%)		
True	32 (31.1%)	30 (27.5%)	0.89 (0.43-1.84)	0.75
Too expensive/no insurance/cost				
False	91 (88.3%)	99 (90.8%)		
True	12 (11.7%)	10 (9.2%)	0.98 (0.34-2.81)	0.97
Too painful, unpleasant, embarrassing				
False	94 (91.3%)	98 (89.9%)		
True	9 (8.7%)	11 (10.1%)	1.37 (0.45-4.18)	0.58
Have to travel far to take this test				
False	94 (91.3%)	107 (98.2%)		
True	9 (8.7%)	2 (1.8%)	0.43 (0.08-2.43)	0.34
Have taken a different screening test				
False	97 (94.2%)	101 (92.7%)		
True	6 (5.8%)	8 (7.3%)	0.58 (0.12-2.89)	0.51
	Visual inspection with acetic acid (VIA)			
	Rural n=163*	**Urban n=178***	**OR** (95%CI)**	**p-value**
No reasons/ No need the test				
False	83 (51.2%)	84 (47.2%)		
True	79 (48.8%)	94 (52.8%)	1.41 (0.83-2.40)	0.21
Do not know about the test				
False	93 (57.4%)	101 (56.4%)		
True	69 (42.6%)	78 (43.6%)	1.19 (0.72-1.97)	0.49
Too expensive/no insurance/cost				
False	146 (90.1%)	168 (94.4%)		
True	16 (9.9%)	10 (5.6%)	0.86 (0.33-2.23)	0.75
Too painful, unpleasant, embarrassing				
False	152 (93.8%)	167 (93.8%)		
True	10 (6.2%)	11 (6.2%)	0.63 (0.21-1.89)	0.41
Have to travel far to take this test				
False	0 (0.0%)	0 (0.0%)		
True	0 (0.0%)	0 (0.0%)	NA	
Have taken a different screening test				
False	129 (79.6%)	138 (77.5%)		
True	33 (20.4%)	40 (22.5%)	0.90 (0.48-1.67)	0.73
	HPV testing on physician-collected samples			
	Rural n=156*	**Urban n=168***	**OR** (95%CI)**	**p-value**
No reasons/ No need the test				
False	78 (51.0%)	80 (47.9%)		
True	75 (49.0%)	87 (52.1%)	1.32 (0.77-2.26)	0.31
Do not know about the test				
False	89 (58.2%)	95 (56.5%)		
True	64 (41.8%)	73 (43.5%)	1.12 (0.67-1.89)	0.66
Too expensive/no insurance/cost				
False	136 (88.9%)	153 (91.6%)		
True	17 (11.1%)	14 (8.4%)	1.03 (0.44-2.46)	0.94
Too painful, unpleasant, embarrassing				
False	141 (92.2%)	154 (92.2%)		
True	12 (7.8%)	13 (7.8%)	0.68 (0.25-1.90)	0.47

Have to travel far to take this test				
False	144 (94.1%)	166 (99.4%)		
True	9 (5.9%)	1 (0.6%)	0.09 (0.01-0.81)	0.032
Have taken a different screening test				
False	129 (84.3%)	131 (78.4%)		
True	24 (15.7%)	36 (21.6%)	1.30 (0.66-2.57)	0.45
		HPV self-sampling		
	Rural n=193*	**Urban n=199***	**OR** (95%CI)**	**p-value**
No reasons/ No need the test				
False	122 (63.5%)	121 (61.1%)		
True	70 (36.5%)	77 (38.9%)	1.27 (0.78-2.07)	0.35
Do not know about the test				
False	67 (34.9%)	42 (21.1%)		
True	125 (65.1%)	157 (78.9%)	2.54 (1.46-4.40)	0.001
Too expensive/no insurance/cost				
False	181 (94.3%)	193 (97.5%)		
True	11 (5.7%)	5 (2.5%)	0.47 (0.14-1.65)	0.24
Too painful, unpleasant, embarrassing				
False	166 (86.5%)	186 (93.9%)		
True	26 (13.5%)	12 (6.06%)	0.35 (0.15-0.82)	0.016
Have to travel far to take this test				
False	0 (0.0%)	0 (0.0%)		
True	0 (0.0%)	0 (0.0%)	NA	
Have taken a different screening test				
False	166 (86.5%)	165 (83.3%)		
True	26 (13.5%)	33 (16.7%)	1.09 (0.56-2.11)	0.80

* Numbers may not sum to the total due to missing values.

** Odds ratio and 95% confidence interval from logistic regression model regressing on area (urban vs rural), adjusted for age, religion, education level, household income, marital status, having a friend or family member with cervical cancer, having a national health insurance, having a private health insurance.

Abbreviations: CI, confidence interval; HPV, *Human papillomavirus;* OR, odds ratio; VIA, visual inspection with acetic acid

Supplemental Table 5-5: Factors associated with willingness to self-collect an HPV sample among women in rural and urban areas, Southern Vietnam, 2021

	I would be willing to collect an HPV sample at home.							
	Rural				Urban			
	Yes	No	OR (95% CI)	p-value	Yes	No	OR (95% CI)	p-value
Age								
Every 5 years			0.99 (0.83-1.19)	0.94			0.84 (0.70-1.00)	0.051
Religion								
No religion	38	36	1.0		20	21	1.0	
Buddhism	34	65	0.45 (0.22-0.92)	0.029	65	49	1.64 (0.73-3.67)	0.23
Others	9	10	0.98 (0.32-2.99)	0.97	24	15	1.98 (0.75-5.24)	0.17
Education level								
Primary school or lower	32	40	1.0		19	15	1.0	
Secondary school	31	44	0.90 (0.44-1.84)	0.78	42	34	1.00 (0.41-2.46)	1.00
High school	11	19	0.52 (0.19-1.42)	0.20	32	28	0.90 (0.35-2.33)	0.83
More than high school	7	8	0.91 (0.23-3.52)	0.89	16	8	1.20 (0.32-4.53)	0.78
Household monthly income (million Vietnam Dong)								
<5	26	41	1.0		14	11	1.0	
5-9.99	31	40	1.24 (0.59-2.64)	0.57	42	24	1.18 (0.43-3.21)	0.75
10-19.99	21	25	1.27 (0.51-3.16)	0.61	34	34	0.67 (0.24-1.90)	0.45
20+	3	5	1.19 (0.22-6.53)	0.84	18	15	0.86 (0.26-2.87)	0.81
Don’t know	0	0			1	1	1.39 (0.07-28.92)	0.83
Marital status								
Never married	0	2	NA		13	8	1.24 (0.43-3.53)	0.69
Married	69	87	1.0		79	60	1.0	
Separated/Divorced/Widowed	12	22	0.64 (0.27-1.53)	0.32	17	17	0.76 (0.32-1.81)	0.54
Friends or family members with cervical cancer								
No	72	95	1.0		90	59	1.0	
Yes	9	16	0.89 (0.35-2.30)	0.81	19	26	0.56 (0.27-1.16)	0.12
National health insurance								
No	17	12	2.29 (0.96-5.48)	0.062	14	11	0.75 (0.29-1.93)	0.56
Yes	64	99	1.0		95	74	1.0	
Private health insurance								
No	73	102	1.0		98	77	1.0	
Yes	7	8	1.31 (0.41-4.17)	0.65	11	7	1.51 (0.49-4.62)	0.47
Don’t know	1	1	1.15 (0.06-22.91)	0.93	0	1	NA	

Abbreviations: CI, confidence interval; HPV, *Human papillomavirus*; OR, odds ratio

Chapter 6. Conclusion

6.1. Summary of the dissertation

6.1.1. Aim 1: A comprehensive assessment of interactions for ovarian cancer risk factors and the development and internal validation for a risk stratification model

Ovarian cancer is the deadliest gynecologic cancer[2]. Screening for ovarian cancer has been proved exclusive[3]. Primary prevention is important given that many prevention strategies are available[4,5], and that there are several well-established risk/preventive factors for ovarian cancer[15,16,19,21,23-40,139]. Although the lifetime risk of ovarian cancer in the general population is just ~1.3%, some women have a much higher than average risk of developing ovarian cancer, even for those who do not have a first-degree family history of the disease or are unknown to carry a ovarian cancer pathogenic variant[41]. Several risk stratification models have been developed to identify women with higher-than-average risk for primary prevention[41-50]. The online CanRisk tool (https://canrisk.org/) is the only model that has been approved for use by clinicians in the European Economic Area[51]. However, limitations of CanRisk as well as other previous models are that they were developed based on a limited number of risk factors and they did not account for interactions between risk factors and menopausal status or age as well as pairwise interactions between the risk factors.

Aim 1 of this dissertation developed a risk stratification model that was based on 15 well-established risk factors for ovarian cancer (including 14 environmental factors and a polygenic

risk score [PRS]) and that accounted for the interactions. The 14 environmental factors included: body mass index (BMI), height, age at menarche, parity, breastfeeding, incomplete pregnancy, age at last pregnancy, tubal ligation, age at menopause, combined oral contraceptive (COC) use duration, depot medroxyprogesterone acetate (DMPA) use, menopausal hormone therapy (MHT) use, first-degree family history of ovarian cancer, and endometriosis. The PRS included 36 genome-wide significant ovarian cancer common genetic variants[374]. We used a dataset of about 8,000 ovarian cancer cases and about 12,000 control women from nine studies participating in the international Ovarian Cancer Association Consortium (OCAC). Our sample size is the largest in the literature of interactions of ovarian cancer risk factors as well as the literature of the development of risk stratification models for the disease.

We first comprehensively assessed the interactions between the risk factors and menopausal status and age using three methods of assessing interactions (i.e., likelihood ratio tests, comparing odds ratios, and checking biological plausibility). We found that menopausal status rather than age modifies the association of some risk factors for ovarian cancer, including family history of the disease and endometriosis. We then checked the interactions between the risk factors and age as well as pairwise interactions between the risk factors stratified by menopausal status using the same methods above, but we found no evidence of such interactions.

Based on the findings of this work, we developed a multiplicative risk stratification model for ovarian cancer stratified by age 50 (as proxy for menopausal status because the results were similar) which included all 15 risk factors, but no pairwise exposure interactions. We compared our 15-factor model with a reduced model that included nine factors (i.e., BMI, height, tubal ligation, parity, COC use duration, MHT use, family history of ovarian cancer,

endometriosis and the PRS). These are the nine common factors that are included in the CanRisk model. Our 15-factor model more finely stratifies women into risk profiles compared to the reduced model. Additionally, in the internal validation in the test set which was comprised of 20% of the dataset, our 15-factor model showed similar discrimination ability to the reduced model, but better calibration.

Our findings regarding interactions of the risk factors and menopausal status contribute to the understanding of ovarian cancer biology. In addition, our newly developed risk stratification model has potential to be applied in ovarian cancer prevention practice to identify individuals with higher-than-average risk who may be candidates for many primary prevention strategies.

6.1.2. Aim 2: Epidemiologic factors associated with having macroscopic residual disease after ovarian cancer primary cytoreductive surgery

The likelihood that a patient achieves no macroscopic residual disease after ovarian cancer primary cytoreductive surgery (PCS) is important to decide the sequence of primary treatment. Patients with a low likelihood of achieving no macroscopic residual disease after PCS may be better served by having neoadjuvant chemotherapy (NACT) followed by interval debulking surgery and then additional chemotherapy[61]. Several efforts have been made to identify epidemiologic factors associated with having residual disease after PCS. However, findings of previous studies are difficult to interpret due to the lack of adjustment for confounders, the heterogeneity of the inclusion criteria and variable outcome definitions for the amount of residual disease (i.e., no macroscopic residual disease vs residual disease <1cm).

To address the limitations in the literature, we conducted a comprehensive study to determine the association between epidemiologic factors and risk of having residual disease after

ovarian cancer PCS. We used data from 2,169 advanced stage high-grade serous ovarian cancer patients who underwent PCS from ten studies participating in OCAC to examine the association between 12 epidemiologic factors and having residual disease. The 12 exposures of interest included: first-degree family history of ovarian cancer, personal history of endometriosis, smoking, BMI, COC duration of use, DMPA use, MHT use, menopausal status, parity, incomplete pregnancy, breastfeeding, and tubal ligation. We were able to adjust for important confounders and we used a rigorous definition of residual disease (i.e., no macroscopic residual disease).

We found that parity and menopausal estrogen therapy (ET) use were statistically significantly associated with a higher likelihood of achieving no macroscopic residual disease following PCS, while breastfeeding was statistically significantly associated with a higher likelihood of having residual disease after PCS. The other epidemiologic factors we studied were not associated with residual disease after PCS. It should be noted that in our data, we did observe the known associations between having macroscopic residual disease and clinical factors including age at diagnosis and disease stage.

This study has tremendous potential to contribute to precision medicine. If replicated, these novel factors associated with residual disease after PCS could be included in a risk stratification model to determine whether patients should have PCS or if they have a low likelihood of achieving no macroscopic residual disease after PCS and should therefore have NACT followed by interval debulking surgery and additional chemotherapy.

6.1.3. Aim 3: Rural-urban disparities in the awareness of, attitudes toward, and experience with cervical cancer screening and prevention among women in Southern Vietnam

Cervical cancer is the second most common and the deadliest gynecologic cancer in Vietnam[84]; the incidence in Southern Vietnam is higher than the national average[85,86]. The uptake of cervical cancer screening is very low in Vietnam[89]. The reasons include the lack of a national cervical cancer screening program and low public awareness of cervical cancer prevention and screening. HPV self-sampling has been proven to be effective in improving cervical cancer screening uptake due to its ability to reach the hard-to-reach populations. However, no study has been conducted to explore the acceptability of HPV self-sampling among women in Southern Vietnam. Notably, while more than half of Southern Vietnamese people live in rural areas[83] where socioeconomic status, healthcare access and health outcomes are poorer than urban areas[83,363], no study on cervical cancer prevention or screening has been conducted in Southern rural women. To address these gaps in knowledge and consider approaches to reduce cervical cancer burden in Southern Vietnam, we conducted a cross-sectional study to comprehensively assess the awareness of, attitudes toward and experience with cervical cancer prevention and screening among women in rural and urban areas in Southern Vietnam.

In October and November 2021, we recruited women who lived in a rural area (n=196) and an urban area (n=202) in Southern Vietnam. Participants were asked to answer a questionnaire including watching four short videos describing the screening methods. We found that women in both rural and urban areas lacked awareness of HPV and cervical cancer. However, about half of the participants had screened for cervical cancer. We found a high

acceptance to physician-based screening methods, but a moderate acceptance to HPV self-sampling. Our study found that women in the urban area, particularly young women, were more willing to try HPV self-sampling compared to rural women. Women in the rural area were more likely to have the concern of self-sampling incorrectly, while women in the urban area were more likely to fear that HPV testing would reveal that they had cancer.

Our study is the first to explore the awareness of, attitudes toward and experience with cervical cancer screening in women in rural areas in Southern Vietnam, who have not been included in previous studies. We also updated these data for women in Southern urban areas and compared them to rural results. Additionally, this is the first study to examine the acceptability of HPV self-sampling among women in Southern Vietnam. Our findings not only fill in the gaps in the literature, but also support the development of policies and interventions aimed at reducing the burden of cervical cancer in Southern Vietnam.

6.2. Public health relevance

This dissertation contributes to all three levels of prevention for gynecologic cancers. First, Aim 1 has great potential in improving ovarian cancer primary prevention. Our newly developed risk stratification model overcomes the limitations to the previous models by incorporating 15 well-established risk/preventive factors as well as accounting for their interactions. Additionally, compared to a reduced model including the nine common factors used in the online CanRisk tool, our 15-factor model showed better calibration and more finely stratifies women into risk profiles with a wider range of risk estimates. Therefore, our newly developed model can better identify women with higher-than-average risk for whom primary prevention should be considered.

Second, Aim 1 is the most comprehensive analysis of interactions between the 15 well-established risk factors for ovarian cancer and menopausal status and age as well as pairwise interactions between the risk factors. The strengths of the analysis included the largest sample size of more than 20,000 participants as well as the use of different methods to identify interactions. Our study is the first to identify that menopausal status rather than age modifies the associations between ovarian cancer risk and first-degree family history of the disease and personal history of endometriosis. Our findings of no interactions between the risk factors and age and no pairwise interactions between the risk factors stratified by menopausal status clarify inconsistencies in the literature and show that multiplicative models fit the data by menopausal status. The study findings are important to ovarian cancer primary prevention because they contribute to the understanding of ovarian cancer biology and support the development of new risk stratification models.

Third, Aim 2 of the dissertation is important to ovarian cancer tertiary prevention. Aim 2 overcomes the limitations of previous studies by using the largest sample size and being able to control for confounding. Our study suggested that parity, breastfeeding and ET use were associated with having residual disease after ovarian cancer PCS. This is of particular interest because the likelihood of achieving no macroscopic residual disease after PCS is important for treatment selection. If our results are replicated, these factors could be included in risk stratification models to help determine whether ovarian cancer patients should have PCS or NACT followed by interval debulking surgery and additional chemotherapy for primary treatment. In addition, residual disease is the strongest single prognostic factor for ovarian cancer, and understanding the factors associated with residual disease will help identify interventions to improve survival. For example, if inflammation plays a role in achieving no

macroscopic residual disease after PCS, interventions addressing inflammation-related factors may benefit surgical outcomes and ultimately survival for ovarian cancer patients.

Fourth, Aim 3 has tremendous potential to improve cervical cancer prevention and screening in Southern Vietnam. Aim 3 is the first study to compare the awareness of, attitudes toward and experience with cervical screening between women in rural and urban areas in Southern Vietnam. Therefore, our study provided important information for the development of policies and strategies to improve cervical cancer screening uptake in both rural and urban areas in Southern Vietnam. Our study findings highlight the needs of improving health literacy and gynecologic healthcare access for women in order to reduce the cervical cancer burden in Southern Vietnam.

Finally, Aim 3 is the first study to explore the acceptability of HPV self-sampling for cervical cancer among women in Southern Vietnam. HPV self-sampling has been proven to be effective in improving cervical cancer screening uptake in several settings. Our findings of different levels of willingness and concerns regarding HPV self-sampling between rural versus urban women suggest the development of tailored health promotion programs to promote HPV self-sampling in the two areas.

6.3. Recommendations for future studies

This dissertation opens up some directions for future studies. First, future studies should validate our ovarian cancer risk stratification model in independent populations and follow-up with women to see if the tool helps them reduce their risk. The next step is to develop a user-friendly online ovarian cancer risk calculator.

Second, future studies should investigate additional factors associated with having residual disease after ovarian cancer PCS. Potential factors to include in future studies include common genetic variants, large-scale somatic gene expression array data and genome-wide DNA copy number change information. Ultimately, a comprehensive risk stratification model should be developed to guide whether ovarian cancer patients should have PCS or NACT followed by interval debulking surgery.

Finally, future studies should explore the feasibility of HPV self-sampling for cervical cancer screening in Southern Vietnam. Aim 3 of this dissertation found that only 50% of women in Southern Vietnam would like to try HPV self-sampling, which is much lower than the acceptability found in previous studies in other settings. The inconsistency could be because we did not allow women to try HPV self-sampling like in previous studies. Therefore, future studies should let women try HPV self-sampling before asking for their views. Longitudinal studies should also be conducted to examine the effects of HPV self-sampling on cervical cancer screening uptake in rural and urban areas in Southern Vietnam. Future studies should also examine the associations between women's social network and their hesitancy to engage in cervical cancer screening.

My PhD dissertation has provided me with skills and experience in conducting epidemiologic studies to assist with prevention, screening, and treatment for cancer, particularly ovarian and cervical cancers. Most importantly, the dissertation has tremendous potential to contribute to the understanding of cancer biology as well as to the development of cancer prevention strategies.

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