Identifying opportunities for improving epithelial ovarian cancer survival using novel approaches for exploring the role of ovulation and hormone-related conditions

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Ovarian cancer is the most lethal gynecologic cancer. Epithelial ovarian cancer (EOC) accounts for more than 90% of ovarian cancers. Although the etiology of EOC remains unknown, the established protective effects of parity and oral contraceptive use suggest that ovulation plays a role. However, ovulation alone cannot explain the magnitude of the protective effects from these exposures. Hormones, including androgen, estrogen, and progesterone, may play a role in ovarian carcinogenesis and affect survival outcomes via hormone receptors. The overall objective of this dissertation is to assess the role of lifetime ovulatory years (LOYs) in EOC development and identify risk factors related to the survival of patients with ovarian tumors defined by hormone receptor status.

First, we evaluated the association of LOYs, calculated by 15 different algorithms, with EOC risk. We further evaluated the individual components in LOYs with EOC risk overall and by histotype. Our findings show the heterogeneity of the histotype-specific associations with LOYs and with the individual components of LOYs, suggesting that carcinogenesis mechanisms may differ by the individual components in LOYs and by histotype. Second, we demonstrated that EOC patients with tumor types defined by hormone receptor status and stratified by histotype have varying risk and prognostic profiles. These data suggest potential biological mechanisms underlying the association of hormonally-linked risk factors and EOC risk. Furthermore, outcomes need to be studied by histotype and by tumor hormone receptor status. Third, we built a prediction

model for EOC survival using machine learning techniques and conducted feature identification using nine immunohistochemistry biomarkers and clinical variables. Our prediction model indicates that CD8+ tumor-infiltrating lymphocytes, androgen receptor, progesterone receptor and p16 play critical roles in predicting EOC survival.

The implication of these findings allows us to better understand the role of LOYs and hormone receptors in ovarian cancer carcinogenesis and survival. Furthermore, the results provide a foundation for targeting risk factors related to survival and hormone receptors by histotype in treatment and provide potential opportunities to extend survival in EOC patients.

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Preface

The dissertation is submitted for the degree of Ph.D. at Epidemiology Department, Graduate School of Public Health, University of Pittsburgh. I would like to thank my mentors, family, and friends for their help, support, and inspiration during my doctoral program in the Epidemiology Department at the University of Pittsburgh.

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1.0 Introduction

1.1 Epidemiology of ovarian cancer and main histotypes

Ovarian cancer is the leading cause of gynecologic cancer death in women in the United States. According to the American Cancer Society, about 21,410 women will be diagnosed of ovarian cancer and 13,770 women will die from ovarian cancer in 2021.[1] Although the 5-year relative survival increased from 33.37% in 1975 to 52.58% in 2017,[2] because of the low survival rate, the mortality trend of ovary cancer is close to the incidence of ovary cancer.[3]

Ovarian cancer survival is profoundly affected by stage, which describes how the cancer has spread. There are two widely used systems for staging ovarian cancer, the International Federation of Gynecology and Obstetrics (FIGO) system and the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system. The two systems use three factors to stage cancer (the extent of the tumor, the spread to nearby lymph nodes, and the spread to distant sites) and can be translated from one to the other.[4,5] A higher number indicates more advanced disease. The Surveillance, Epidemiology, and End Results registry (SEER) program of the National Cancer Institute (NCI) uses a simplified approach to stage ovarian cancer as localized (roughly Stage I disease), regional (encompassing Stage II and III disease), and distant (Stage IV disease).[6] With no early screening test to detect ovarian cancer, 58% of ovarian cancers are diagnosed at distant stage (Stage IV). Based on data from SEER 2010-2016, the 5-year relative survival rate is only 48.6%.[2] It ranged from 30.2% for ovarian cancer at distant stage (Stage IV) to 92.6% for ovarian cancer at localized stage (roughly Stage I).[2]

The 5-year survival rate not only varies by stage but also by histotypes of ovarian cancer. Epithelial ovary cancer (EOC) accounts for nearly 90% of malignant ovarian cancer.[7] The most common histotypes of EOC include high-grade and low-grade serous (60%), endometrioid (10%), clear cell (6%), and mucinous (6%).[7] Tumor grade describes how cancer cells look different from normal cells. It is defined as well-differentiated (Grade 1), moderately differentiated (Grade 2), poorly differentiated (Grade 3), and undifferentiated (Grade 4).[8] However, serous cancer (SC) is unique. Tumor grade is contained in name of the two different histotypes. Serous tumors show a papillary structure, and the cells do not contain intracytoplasmic mucin, but low-grade and high-grade serous carcinomas develop through different carcinogenic pathways.[9,10] A widely accepted classification of EOC as type I and type II tumors is based on clinicopathologic and molecular evidence.[11] Type I tumors, which tend to grow locally and metastasize late, include endometrioid cancer (EC), clear cell cancer (CCC), low-grade serous cancer (LGSC), and mucinous cancer (MC). Type II tumors are highly aggressive, such as high-grade serous cancer (HGSC) (**Figure 1.1**). Among cases at distant stage (Stage IV disease), the 5-year overall survival ranges from 13.9% for MC to 54.2% for LGSC.[12]

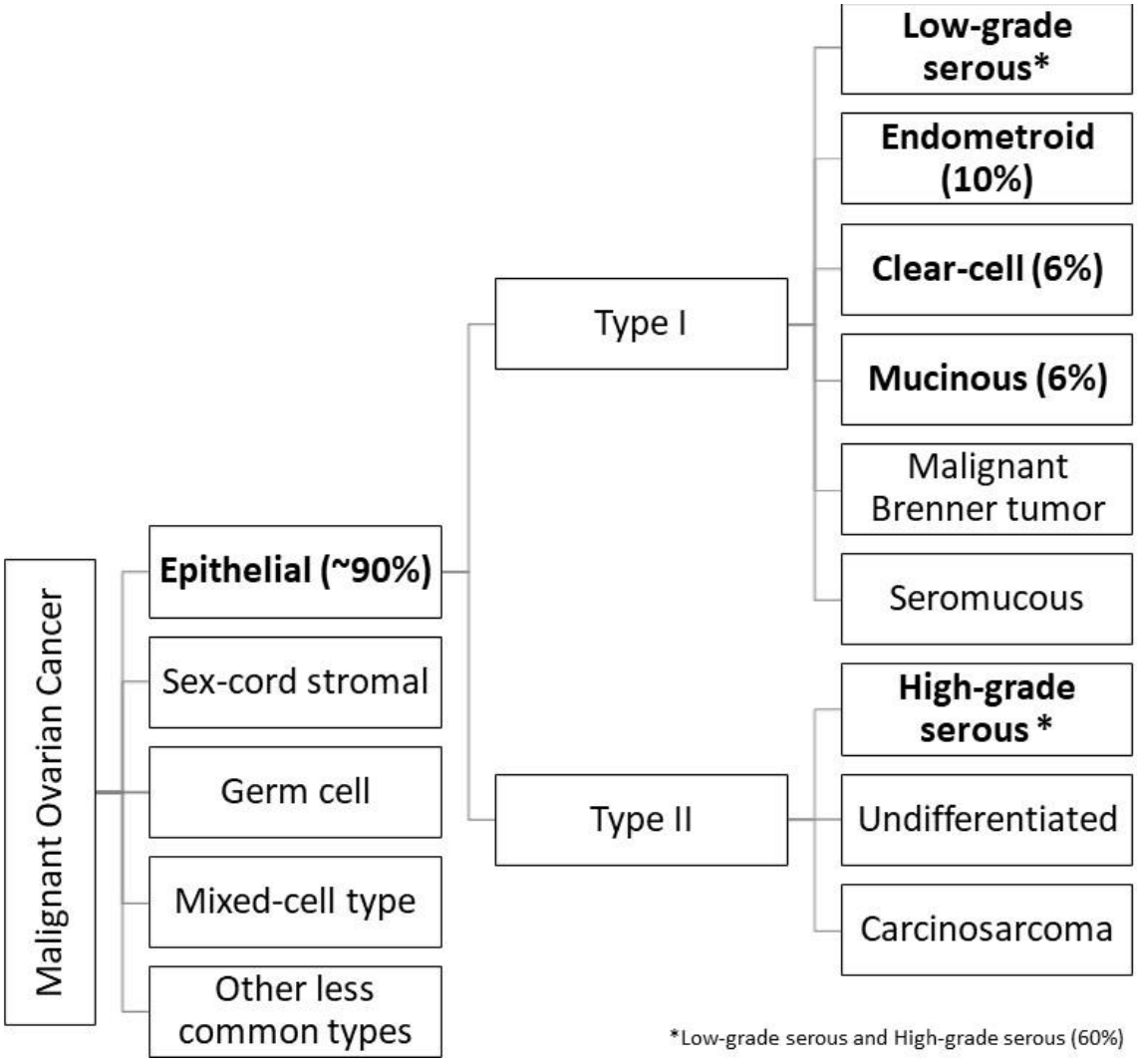


Figure 1-1 Classification of malignant ovarian cancer

1.2 Risk Factors for epithelial ovarian cancer and by histotypes

Increasing evidence indicated that risk factors for EOC vary by histotypes. Therefore, it is necessary to identify risk factors for EOC by histotypes. Risk factors for the overall risk of EOC and by histotypes have been well studied by the Ovarian Cancer Association Consortium (OCAC) and the Ovarian Cancer Cohort Consortium (OC3). The OCAC is originally a forum of investigators of case-control studies of ovarian cancer. There have been 81 worldwide studies, including case-control studies, case-only studies, cohort studies, and nested case-control studies, participating in OCAC since 2005. The OC3 is an international consortium of over 20 cohort studies to study the etiologic heterogeneity of ovarian cancer. It is under the National Cancer Institute's cohort consortium. There are numerous large cohort studies participating in OC3, such as the European Prospective Investigation into Cancer and Nutrition (EPIC) study, NIH-AARP Diet and Health Study, Nurses' Health Study, Women's Healthy Study, and Singapore Chinese Health Study. In addition to the OCAC and OC3, there is a large population-based prospective study, the Million Women Study, investigating risk factors for ovarian cancer in women in middle and old age.[13] Through 2018, more than 1.3 million UK women with an average 20 years follow-up have participated in the study.[14] **Table 1-1** presents the findings on risk factors by histotypes from OCAC and OC3. The associations between the risk factors and EOC evaluated by Mendelian randomization studies, systematic reviews and meta-analyses, the Million Women Study, and any individual study in OCAC or OC3 are summarized in the text. If no such association has been estimated by the types of studies listed above, the results from an individual study are summarized in the text. Some potential risk factors not estimated by OCAC or OC3 studies are only summarized in the text.

The associations between risk factors and EOC by histotypes appear inconsistent for several reasons. First, the classifications of histotypes, especially of serous cancer (SC) vary across studies. For example, the analysis pooling 39 studies in OCAC included invasive and unknown invasive SC[15], while the study in OC3 included only invasive SC when estimating the association between height and risk of HGSC and LGSC.[16] Second, the discrepancies in the associations between risk factors and EOC by histotypes can be due to the heterogeneity across studies, including study design, sample sizes, the various targeted populations, and sampling methods. For example, higher age at menopause was associated with an increased risk of most histotypes except HGSC and CCC in OC3,[16] while the NIH-AARP Diet and Health Study found no association between age at menopause and any histotype.[17] The US Nurses' Health Study (1976-2006) (NHS) and Nurses' Health Study II (1989-2005) (NHS II) found a significantly positive association between age at menopause and EC risk only.[18] The OC3 pooling 19 cohort and case-control studies had a total of 5584 EOC cases.[16] The NIH-AARP Diet and Health Study included 849 cases among 169,391 women aged 50-71 in California, Florida, Louisiana, New Jersey, North Carolina and Pennsylvania.[17] The NHS and NHS II included 924 EOC cases among 221,866 nurses aged 25-55.[18] The inconsistent results on the association between age at menopause and EOC risk by histotype could be due to the populations and sample sizes in the three studies.

Table 1-1 Risk Factors associated with overall risk of ovarian cancer and by histotypes from OCAC and OC3[a]

Factors		Study and comparison[b]	Overall	Type II	Type I			
				High-grade serous	Low-grade serous	Endometrioid	Clear Cell	Mucinous
Demographic	BMI	OCAC Olsen, 2013[19] per 5 kg/m^2	**1.06 (1.01, 1.11)**	0.98 (0.94, 1.02)		**1.17 (1.11, 1.23)**	1.06 (0.96, 1.17)	**1.19 (1.06, 1.32)**
		OC3[16] per 5 kg/m^2	1.01 (0.98, 1.04)	0.97 (0.93, 1.01)		1.07 (0.99, 1.16)	1.04 (0.92, 1.17)	1.08 (0.93, 1.20)
	Height	OCAC (MR) Dixon-Suen, 2018[15] per 5 cm increase	**1.06 (1.01, 1.11)**	1.05 (0.99, 1.11)	**1.15 (1.01, 1.30)**	1.05 (0.95, 1.16)	**1.20 (1.04, 1.38)**	1.08 (0.96, 1.21)
		OC3[16] per 0.5 m increase	**1.06 (1.04, 1.08)**	**1.06 (1.03, 1.09)**		**1.06 (1.00, 1.13)**	1.08 (0.98, 1.19)	1.08 (0.96, 1.20)
Reproductive and hormonal	Age at menarche	OC3[16] per 1-year	0.99 (0.97, 1.00)	0.99 (0.97, 1.02)		1.00 (0.94, 4.05)	**0.92 (0.85, 0.99)**	1.00 (0.93, 1.07)
	Age at menopause	OC3[16] per 5-year	**1.06 (1.02, 1.10)**	**1.05 (1.01, 1.10)**		1.00 (0.94, 1.05)	**1.37 (1.15, 1.64)**	0.95 (0.81, 1.11)
	Menstrual cycle length	OCAC Harris, 2018[20] >35 days vs. <=35 days	**0.70 (0.58, 0.84)**	**0.62 (0.48, 0.80)**	**0.48 (0.25, 0.92)**	0.75 (0.54, 1.06)	0.70 (0.43, 1.13)	**0.38 (0.19, 0.76)**
	Menstrual pain	OCAC Babic, 2018[21] severe vs. no	**1.17 (1.00, 1.38)**	1.13 (0.97, 1.31)	1.12 (0.90, 1.39)	1.24 (0.99, 1.54)	**1.48 (1.10, 1.99)**	1.18 (0.63, 2.19)
	Parity	OCAC Lee, 2021[22] >=3 complete pregnancies vs. 0	**0.51 (0.47, 0.57)**	**0.70 (0.62, 0.79)**	**0.45 (0.31, 0.66)**	**0.50 (0.37, 0.67)**	**0.39 (0.28, 0.52)**	**0.71 (0.59, 0.84)**
		OC3[16] per 1 child increase	**0.90 (0.89, 0.92)**	**0.93 (0.92, 0.95)**		**0.78 (0.74, 0.83)**	**0.68 (0.61, 0.76)**	**0.91 (0.84, 0.99)**
	Incomplete pregnancy	OCAC Lee, 2021[22] >=2 vs 0	**0.85 (0.74, 0.87)**	0.96 (0.84, 1.03)	**0.68 (0.49, 0.95)**	**0.71 (0.59, 0.84)**	**0.39 (0.28, 0.53)**	0.77 (0.59, 1.00)

	Offspring sex	OCAC Modugno, 2020[23] 3 more boys vs. none	0.93 (0.75, 1.16)	0.86 (0.65, 1.13)	-	0.54 (0.29, 1.02)	0.75 (0.34, 1.67)	**2.31** **(1.24, 4.29)**
	Breastfeeding	OCAC Babic, 2020[24] ever vs. never	**0.76** **(0.71, 0.80)**	**0.75** **(0.70, 0.81)**	0.78 (0.61, 1.01)	**0.73** **(0.64, 0.84)**	**0.78** **(0.64, 0.96)**	0.93 (0.76, 1.14)
		OC3[16] per 1 year	0.96 (0.89, 1.03)	0.94 (0.86, 1.03)		0.85 (0.69, 1.05)	1.03 (0.81, 1.33)	0.88 (0.63, 1.23)
	Oral contraceptive use	OC3[16] per 5-year increase	**0.87** **(0.84, 0.90)**	**0.85** **(0.81, 0.89)**		**0.86** **(0.77, 0.95)**	**0.86** **(0.74, 1.00)**	1.54 (0.93, 1.19)
	Lifetime ovulatory years	OC3[25] per 5-year increase	**1.08** **(1.05, 1.12)**	-		-	-	-
	Estrogen-only therapy	OCAC Lee, 2016[26] 10+ years vs. never	**1.54** **(1.18, 2.01)**	**1.79** **(1.31, 2.43)**		**3.58** **(1.74, 7.36)**	-	-
	Estrogen-progestin combined therapy	OCAC Lee, 2020[27] Ever postmenopausal use vs. never	**0.85** **(0.72, 1.0)**	0.98 (0.80, 1.20)		0.86 (0.57, 1.3)	0.68 (0.40, 1.2)	**0.40** **(0.18, 0.91)**
	Hormone replacement therapy	OC3[16] per 5-year increase	**1.06** **(1.02, 1.10)**	**1.21** **(1.17, 1.25)**		**1.25** **(1.15, 1.36)**	**0.69** **(0.52, 0.92)**	1.09 (0.94, 1.25)
	Polycystic ovary syndrome	OCAC Harris, 2018[20]	0.87 (0.65, 1.15)	0.88 (0.62, 1.26)	1.07 (0.43, 2.66)	1.03 (0.63, 1.67)	0.77 (0.34, 1.78)	0.61 (0.22, 1.66)
	Tubal ligation	OCAC Sieh, 2013[28]	**0.81** **(0.74, 0.89)**	**0.80** **(0.73, 0.89)**	0.89 (0.65, 1.22)	**0.48** **(0.40, 0.59)**	**0.52** **(0.40, 0.67)**	**0.68** **(0.52, 0.89)**
		OC3[16]	**0.82** **(0.73, 0.93)**	0.91 (0.79, 1.06)		**0.60** **(0.41, 0.88)**	**0.35** **(0.18, 0.69)**	1.01 (0.60, 1.71)
	Hysterectomy	OC3[16]	0.96 (0.89, 1.03)	1.03 (0.94, 1.13)		0.84 (0.66, 1.07)	**0.57** **(0.36, 0.88)**	0.72 (0.51, 1.02)

Gynecologic	Genital powder use (Talc use)	OCAC Terry, 2013[29]	**1.24 (1.15, 1.33)**	**1.24 (1.13, 1.35)**		**1.20 (1.03, 1.40)**	**1.26 (1.04, 1.52)**	1.06 (0.82, 1.36)
	Pelvic inflammatory disease	OCAC Rasmussen, 2016[30]	0.99 (0.83, 1.19)	0.89 (0.74, 1.08)	1.48 (0.92, 2.38)	1.15 (0.83, 1.60)	1.05 (0.65, 1.70)	0.84 (0.56, 1.25)
	Endometriosis	OCAC Pearce, 2012[31]	**1.46 (1.31, 1.63)**	1.13 (0.97, 1.32)	**2.11 (1.39, 3.20)**	**2.04 (1.67, 2.48)**	**3.05 (2.43, 3.84)**	1.02 (0.69, 1.50)
		OC3[16]	**1.35 (1.07, 1.71)**	1.03 (0.74, 1.46)		**2.32 (1.36, 3.95)**	**2.87 (1.53, 5.39)**	1.62 (0.58, 4.51)
	Family history of ovarian cancer	OC3[16]	**1.48 (1.26, 1.75)**	**1.61 (1.32, 1.97)**		0.97 (0.52, 1.82)	0.96 (0.36, 2.57)	1.33 (0.59, 3.00)
	Family history of breast cancer	OC3[16]	**1.09 (1.00, 1.19)**	**1.13 (1.02, 1.26)**		**1.47 (1.15, 1.87)**	0.75 (0.46, 1.22)	0.73 (0.47, 1.13)
Lifestyle	Physical inactivity	OCAC Cannioto, 2016[32]	**1.32 (1.12, 1.56)**	**1.30 (1.08, 1.53)**	**1.33 (1.01, 1.76)**	1.26 (0.98, 1.63)	**1.40 (1.11, 1.74)**	**1.50 (1.17, 2.10)**
	Alcohol	OCAC Kelemen, 2013[33] >3 drinks vs. none	0.92 (0.76, 1.10)	0.96 (0.77, 1.20)	1.12 (0.55, 2.29)	**0.49 (0.27, 0.91)**	0.82 (0.50, 1.34)	0.98 (0.52, 1.82)
	Smoking	OCAC Faber, 2013[34] current vs. never	0.89 (0.76, 1.04)	0.92 (0.76, 1.10)		0.84 (0.69, 1.02)	**0.74 (0.56, 0.98)**	**1.31 (1.03, 1.65)**
		OC3[16] ever vs. never	0.99 (0.94, 1.05)	0.99 (0.92, 1.06)		0.93 (0.79, 1.09)	0.95 (0.74, 1.21)	**1.27 (1.01, 1.59)**

BMI, body mass index.

[a] Numbers are reported as effect estimate (95% confidence intervals).

[b] If the comparison is yes vs. no, the comparison is not indicated in the table.

1.2.1 Demographic factors

Body Mass Index (BMI) and Obesity

Obesity is a risk factor for many cancer types;[35,36] however, its association with EOC risk is inconsistent. OCAC found a positive association between body mass index (BMI) per kg/m^2 increase and EOC risk,[19] while OC3 reported no association (**Table 1-1**).[16] A systematic review pooling 28 studies with odds ratios (ORs), risk ratios (RRs), or incidence ratios (IRs) reported a positive but small association between obesity and risk of ovarian cancer (pooled RR 1.30, 95% CI 1.12-1.50).[37] Pooling case-control studies produced a stronger association (pooled RR 1.49, 95%CI 1.29-1.54) than polling cohort studies (pooled RR 1.12, 95% CI 0.95-1.32).[37] A meta-analysis pooling 26 observational studies also indicated a positive association between BMI and EOC risk (pooled RR 1.07 and 1.28, 95% CI 1.02-1.12 and 1.16-1.41 comparing overweight and obesity with normal weight, respectively).[38] The most recent systematic review in 2017, including 43 studies with more than 3 million participants, concluded that there is inconsistent evidence of an association between obesity and the overall risk of ovarian cancer because 26 out of 43 studies reported no significant association between higher BMI and ovarian cancer risk, and three studies revealed a negative association between BMI and ovarian cancer risk.[39]

The associations of higher BMI and EOC risk by histotypes were estimated by OCAC pooling 15 studies.[19] Higher BMI was associated with increased risks of invasive EC (OR 1.17, 95% CI 1.11-1.23) and MC (OR 1.19, 95% CI 1.06-1.32).[19] OC3 did not find any significant association between BMI and EOC risk by histotype (**Table 1-1**).[16] A Mendelian randomization study pooling 39 studies in OCAC reported a null association between higher BMI and HGSC risk (pooled OR 1.29 per 5 units BMI, 95% CI 1.03-1.91), but a significant association between higher

BMI and LGSC risk (pooled OR 1.93 per 5 units BMI, 95% CI 1.33-2.81).[40] An individual participant meta-analysis including 25,157 women with ovarian cancer found an increased risk of invasive MC with increasing BMI (RR 1.15 with standard error (SE) 0.032 per 5 kg/m^2 increase in BMI), but no other histotype-specific associations with BMI.[41]

Overall, BMI might not be associated with the overall risk of EOC but could be associated with risks of some histotypes, such as EC and MC.

Height

Height is positively associated with the overall risk of EOC, but the mechanism is unclear. A Mendelian randomization study pooling 39 OCAC studies indicated that height was associated with an increased risk of invasive ovarian cancer (OR 1.06 per 5 cm increase in height, 95% CI 1.01-1.11).[15] OC3 found the same association between height and EOC risk (RR 1.06 per 0.5m increase in height, 95% CI 1.04-1.08) (**Table 1-1**).[16] A study pooling 47 studies showed the same association (RR 1.07 per 5cm increase in height, 95% CI 1.05- 1.09).[41] A pooled analysis from 12 prospective cohort studies indicated that women with height >=1.70 meters had a 1.38 times higher risk of EOC compared with those with height <1.60 meters (95% CI 1.16-1.65).[42] The Million Women Study also reported per 10 cm increase in height was positively associated with a risk of ovarian cancer (RR 1.17, 95% CI 1.11-1.23).[43]

Height might be associated with SC risk. OCAC indicated that per 5 cm increase in height was associated with increased risks of invasive and borderline LGSC (OR 1.15, 95% CI 1.01-1.30), and invasive CCC (OR 1.20, 95% CI 1.04-1.38).[15] OC3 found that the association between height and SC risk was significant when treating height as a continuous variable (RR 1.06 per 0.5m increase in height, 95% CI 1.03-1.09) (**Table 1-1**), but the significance disappeared when categorizing height into <1.60 meters, 1.60 to 1.65 meters, 1.65 to 1.70 meters, and >=1.70

meters.[16] Women with height >=1.70 meters had a 1.27 times higher risk of EC compared to women with height 1.60 to 1.65 meters (95% CI 1.01 -1.60).[16]

1.2.2 Reproductive and hormonal factors

Age at menarche

Higher age at menarche has a protective effect on EOC risk. OC3 showed a borderline association between age at menarche per 1-year increase and the overall risk (OR 0.99, 95% CI 0.97-1.00) (**Table 1-1**).[16] A meta-analysis including 22 case-control studies and five cohort studies showed an inverse association between age at menarche and the risk of ovarian cancer (RR 0.85, 95% CI 0.75-0.97 for the oldest compared to the youngest age group).[44] An update of this meta-analysis that included studies reported in PubMed through April 30, 2018, confirmed the inverse association presented in case-control studies (pooled OR 0.96 per year increase 95% CI 0.93-1.00), but not in cohort studies (pooled OR 0.99 per year increase, 95% CI 0.96-1.01). [45] However, the updated analysis excluded studies with less than 60 cases and did not adjusted for covariates related to ovarian cancer.[45] The researchers of the updated meta-analysis also conducted two Mendelian randomization studies using 1,044 cases and 1,172 controls from a genome-wide association study (GWAS) in China and 29,396 cases and 68,502 controls of European descent extracted by OCAC and Consortium of Investigators of Modifiers of BRCA1/2 studies.[45] Both results supported the inverse association between age at menarche and EOC risk (OR 0.81, 95% CI 0.67 – 0.97 in Chinese women and OR 0.94, 95% CI 0.90-0.98 in European women).[45]

OC3 indicated the age at menarche per 1-year increase was associated with a reduced risk of CCC (RR 0.92, 95% CI 0.85-0.99), but not with other histotypes (**Table 1-1**).[16] Similarly, age at menarche was not associated with the risks of SC, MC, EC, and CCC in a pooled analysis of 10

case-control studies in US white women.[46] The NIH-AARP Diet and Health Study results also did not show any significant association between age at menarche and EOC risks by histotype,[17] although the null associations could be due to small sample sizes (78, 28, and 27 for EC, MC, and CCC, respectively).[17]

Age at menopause

Age at menopause is plausibly associated with increased risks of EOC and by histotype, but the results from studies are controversial. OC3 found a positive association between per 5-year increase in age at menopause and the overall EOC risk (RR 1.37, 95% CI 1.15-1.64) (**Table 1-1**), although the significance disappeared when treating age at menopause as a categorical variable.[16] A study pooling six population-based case-control studies indicated a borderline statistical significant association between age at menopause and EOC risk (hazard ratio (HR) 1.09, 95% CI 0.99-1.20).[47]

OC3 found positive associations between per 5-year increase in age at menopause and risks of SC (RR 1.05, 95% CI 1.01-1.10) and CCC (RR 1.37, 95% CI 1.15-1.64) (**Table 1-1**).[16] Results from the US NHS and NHS II showed a positive association of per 1-year increase in age at menopause and EC risk (RR 1.13, 95% CI 1.04- 1.22).[18] However, no histotype-specific association was found by a study pooling ten case-control studies in US white women or by NIH-AARP Diet and Health Study.[17,46]

Menstrual cycle length

Longer menstrual cycle length could be a protective factor against ovarian cancer risk via suppressing ovulation. While the estimations on the association are not consistent (**Table 1-2**). The results from 14 case-control OCAC studies showed that menstrual cycle length of >35 days was associated with a 30% lower EOC risk (95% CI 0.48-0.84) compared to menstrual cycle length

of <=35 days (**Table 1-1**).[20] The protective effect of menstrual irregularity was also found among women under age 45,[48] in a hospital-based case-control,[49] and a multiethnic population-based case-control study.[50] The results from the Child Health and Development Studies cohort also showed an increased risk for women with menstrual irregularity.[51] However, the association was not found in a population-based case-control study in Massachusetts and New Hampshire[52] and in the New England Case-Control study.[53]

The relationship between menstrual cycle length and EOC may also be histotype-specific. OCAC showed a protective effect of the menstrual cycle length of >35 days on risks of HGSC (OR 0.62, 95% CI 0.48, 0.80), LGSC (OR 0.48, 95% CI 0.25-0.80), and MC (OR 0.38, 95% CI 0.19-0.76),[20] but not in the New England Cases-Control Study.[53] The multiethnic population-based case-control study showed a protective effect of menstrual irregularity on CCC risk (OR 0.3, 95% CI 0.1-0.7).[50]

Table 1-2 Characteristics of studies estimating the association between mentrual cycle length and EOC risk

Study	**Study design**	**Sample Size**	**Definition of exposure**	**Effect estimates (95% confidence intervals)**
Cirillo, 2016[51]	cohort	Cases 116 Total 15,528	self-report or physician report of irregular menstrual cycles, self or physician report of long cycles (>35 days); or physician coded oligomenorrhea, anovulatory cycles or irregular menses	HR stratified by age at follow-up (years) – 65: 1.55 (0.86, 2.80); 70: 2.26 (1.20. 4.26); 75: 3.29 (1.47, 7.37); 80: 4.78 (1.68, 13.61); 85: 6.94 (1.86, 25.92)
Harris, 2017[53]	population-based case-control study	Cases 2041 Controls 2100	menstrual cycle length >35 days	OR 0.83 (0.44, 1.54)
Harris, 2018[20]	14 case-control studies	Cases 16,594 Controls 17,718	menstrual cycle length >35 days	OR 0.70 (1.00, 1.38)

Parazzini,1989[49]	hospital-based case-control study	Cases 634 Controls 1626	frequent menstrual-like episodes of bleeding less than 21 or more than 35 days apart	RR 0.45 (0.31, 0.65)
Tavani, 1993[48]	hospital-based case-control study	Cases 194 Controls 710	irregular menstrual cycles	RR 0.6 (0.3-1.0)
Titus-Ernstoff, 2001[52]	population-based case-control study	Cases 563 Controls 523	menstrual cycle length >30 days vs. <27 days	OR 0.9 (0.6, 1.3)
Tung, 2003[50]	multiethnic population-based case-control study	Cases 558 Controls 607	periods varying from cycle length by 2 or more days	OR 0.7 (0.5, 0.9)

Menstrual pain

OCAC, including 10,592 cases and 13,320 controls, suggested an increased risk of overall ovarian cancer (OR 1.17, 95% CI 1.00-1.38) and CCC (OR 1.48, 95% CI 1.10-1.99) with severe menstrual pain compared to no pain (**Table 1-1**).[21] The Australian Ovarian Cancer (AOC) study and the New England case-control (NECC) study, which were included in the OCAC study, individually estimated the association between menstrual pain and ovarian cancer risk.[54,55] The NECC study also suggested an increased risk of overall ovarian cancer (OR 1.34, 95% CI 1.09-1.65), EC (OR 1.64, 95% CI 1.15-2.34), and CCC (OR 1.91, 95% CI 1.11-3.28) with severe menstrual pain compared to no or mild pain.[54] However, the AOC study found no significant association between menstrual pain and EOC risk overall or by histotype.[55]

Parity and incomplete pregnancy

Parity is a well-known protective factor for EOC risk[16-18,22,46,56,57] and the association varies by histotype. The results from OCAC, OC3 and a study from pooling six population-based case-control studies indicated that there are inverse association between the number of full-term pregnancies and all histologic subtypes, including SC, MC, EC, and CCC (**Table 1-1**). [16,22,46] The Million Women Study also reported that increasing was associated with a per birth 7% lower risk

of LGSC (95% CI 0.90-0.96) and a 16% lower risk of HGSC (95% CI 0.76-0.93).[57] However, there was no association found between parity and MC risk by the NHS and NHS II study (parity vs. none among parous women RR 0.95, 95% CI 0.81-1.13), the NIH-AARP Diet and Health Study (>=3 parities vs. nulliparous RR 0.44, 95% CI 0.18-1.07) or the Million Women Study (per birth increase among parous women RR 0.93, 95% CI 0.84-1.03).[17,18,57] The null association between parity and MC risk was also supported by other induvial case-control studies.[58-60] The discrepancies across histotype suggest MC has a different mechanism of carcinogenesis.

OCAC also indicated that incomplete pregnancy had protective effects on EOC risk, risk of LGSC, EC, and CCC (**Table 1-1**).[22] Similarly, a cohort study observed that four or more incomplete pregnancies was associated with an increased risk of ovarian cancer (HR 1.74, 95% CI 1.20-1.70).[61]

Age of first childbirth

The results on the association between age at first childbirth and risk of ovarian cancer are inconsistent. OC3 and OCAC have not conducted such evaluation. The results from a nested case-control study in Sweden (OR 0.89 per 5-year increase, 95% CI 0.84-0.94), a population-based study in the USA including 1632 cases and 2340 controls (RR 0.87 per 5-year increase, 95% CI 0.79-0.95), a population-based case-control study undertaken as a Nordic collaboration (OR 0.97 per year, 95% CI 0.97-0.98), and a study pooling four case-control studies (OR 1.4 comparing ages < or =19 compared to > or =25, 95% CI 1.1-1.8) found that later age at first childbirth was associated with a reduced risk of ovarian cancer.[62-65] A population-based study in Australia including 620 parous cases and 723 parous controls and the Danish MALOVA Study including 554 cases and 1564 controls found the same trend between age at first childbirth and risk of ovarian cancer; however, the estimates did not reach the statistical significance.[60,66] The Million Women

Study, the NIH-AARP Diet and Health Study, and a case-control study in Mexico City found no association.[17,57,67] In contrast, a cohort study in Taiwan and results from pooling four case-control studies found an increased risk of ovarian cancer with a larger age at first childbirth.[68]

Seven studies evaluated the association of age at first childbirth and EOC risk by histotype.[17,46,52,57,60,62,64] The study pooling ten population-based case-control studies (OR 0.97 per 1-year, 95% CI 0.95-0.98), the Danish MALOVA Study (OR 0.81 per 5-year increase, 95% CI 0.70-.95), and the study undertaken as a Nordic collaboration (OR 0.85, 0.78, 0.54 comparing age 25-29, 30-39, >=40 to <25, respectively) found an inverse association between age at first childbirth and SC risk.[46,60,64] The population-based study in the USA found an inverse associations between age at first childbirth and risk of EC (RR 0.82 per 5-year increase, 95% CI 0.70-0.95) and CCC (RR 0.74 per 5-year increase, 95% CI 0.57-0.96).[62] The same association was found by the study in Massachusetts and New Hampshire combining EC and CCC (OR 0.6 comparing age >=25 at first birth to <25 years, 95% CI 0.4-1.0; P for trend 0.006).[52] There was no association between age at first childbirth and risk of any histotype in the Million Women Study and the NIH-AARP Diet and Health Study.[17,57]

Age of last childbirth

Later age at last childbirth was considered as a potential protective effect on ovarian cancer risk. A meta-analysis published in 2019 pooling 13 studies indicated that the pooled RR was 0.77 comparing the highest level of age at last childbirth to the lowest level (95% CI 0.65- 0.91).[69] Of the 13 studies, only one study conducted in Italy showed that later age at last childbirth was associated with increased ovarian cancer risk.[48] The study only had 52 cases in the group of women with age at last childbirth >=30 and 23 cases in the group of women with age at last childbirth

<25.[48] Another case-control study in Milan, Italy, reported no association between time since last childbirth and ovarian cancer risk among parous women or multiparous women.[70]

Five studies estimated the association by histotype.[50,52,57,60,64] A population-based, case-control study in Massachusetts and New Hampshire showed an non-significant inverse association between age at last childbirth and risk of combing EC and CCC (OR 0.7 comparing age >=30 at first birth to <30 years, 95% CI 0.4-1.1; P for trend 0.0009).[52] A case-control study in Denmark, Finland, Norway, and Sweden also found age at last childbirth was associated with a reduced risk of SC (OR 0.81, 0.78, 0.58 comparing age 25-29, 30-39, >=40 to <25, respectively) and EC (OR 1.01, 0.74, 0.39 comparing age 25-29, 30-39, >=40 to <25, respectively) among parous women.[64] Age at last birth >=30 was associated with 12% lower risk of CCC compared to age at last birthchild <25 (95% CI 0.63- 0.96, p for trend 0.08) in the Million Women Study.[57] However, there was no association between age at last childbirth and EOC risk by histotype in a multiethnic, population-based, case-control study in the USA and the Danish MALOVA Study.[50,60] A multiethnic population-based case-control study evaluated the association between years since last childbirth and EOC risk and by histotype, but did not find any significant association.[50]

Male Offspring

Studies investigating the association between offspring sex and EOC risk presented inconsistent results. No association was found between offspring sex and EOC risk in a multinational pooled analysis of 12 case-control studies from OCAC (**Table 1-1**).[23] The null association was supported by three population-based case-control studies[71-73] and one cohort study,[74] although two of them reported giving birth to male offspring was associated with a non-significant decrease in EOC risk.[71,72] A nested case-control study in Sweden reported that giving birth to a male child was significantly associated with a reduced risk of EOC, and an increasing

number of male offspring was associated with increasing protective effect (adjusted OR, 0.92, 0.87, 0.82, for 1, 2 or 3+ boys, compared to giving birth to all girls; p for trend <0.001).[75]

OCAC reported that increasing numbers of male offspring was associated with an increased risk of MC (OR, 1.31, 1.84, 2.31, for 1, 2, and 3+ boys, compared to giving birth to all girls; P for trend, 0.005). A population-based case-control study in Australia supported the association, reporting that giving birth to only male offspring was associated with a 2.19-fold increased risk of MC (95%CI 1.15-4.17).[73] The cohort study in Norway estimated increased risk of EC, but not other histotypes, among women with singleton births who gave birth to only female offspring compared to women who gave birth to only male offspring.[74]

Breastfeeding

Breastfeeding is considered a protective factor against EOC risk.[56] The results from 13 case-control studies in OCAC indicated that breastfeeding was associated with a significantly reduced risk of ovarian cancer and risk of HGSC, EC and CCC (**Table 1-1**).[24] Another study pooling 13 case-control studies also indicated a protective effect of breastfeeding on SC.[46] However, the results from cohort studies were inconsistent with the results from case-control studies. Although the NHS and NHS II study found that breastfeeding per 1-year increase was associated with a decreased risk of all EOC (RR 0.82, 95% CI 0.74-0.91), and risk of SC (RR 0.84, 95% CI 0.73-0.96) and MC (RR 0.43, 95% CI 0.25-0.74), the OC3 study pooling 21 prospective cohort studies did not find a significant association between duration of breastfeeding per 1-year increase and risk of overall EOC and by histotype (**Table 1-1**).[16] The Million Women Study only indicated that breastfeeding was associated with the overall risk (RR 0.90 per 1-year increase, 95% CI 0.84-0.94), but not associated with risk by histotype.[57]

Oral contraceptive use

Oral contraceptive (OC) use is a known modifiable protective factor for EOC risk, especially in BRCA1/2 carriers.[16,60,62,76-78] However, the results from OC3 (**Table 1-1**) and the Danish MALOVA study both found that OC use appeared to protect against all histotypes except for MC, further suggesting that the etiology of MC differs from that of other histotypes.[16,60]

Lifetime ovulatory years (LOYs)

Lifetime ovulatory years (LOYs) or lifetime ovulatory cycles (LOCs) is a risk factor for overall EOC and specific EOC histotypes. By searching in PubMed through Oct 31, 2020, there were 31 studies examining the association between LOYs/LOCs and EOC risk (**Figure 1-2; Table 1-4**).[18,25,50,60,67,79-104] The studies included 24 case-control studies,[50,60,67,79-86,90-95,97,99-104] 4 pooled case-control studies,[87-89,98] two cohort studies,[18,96] and one pooled prospective cohort study.[25] Of the 24 case-control studies, two were conducted Australia,[92,94] two in China,[84,86] one in Denmark,[60] one in Italy,[81] one in Poland,[103] two in Mexico,[67,90] one in Nigeria,[95] 12 in the United States,[50,79,80,82,83,85,91,93,97,99,100,104] one in Vietnam[101] and one worldwide.[102] The remaining four studies were pooled analyses of case-control studies from the US[87-89] and Italy.[98] Both cohort studies and the pooled prospective study were conducted in the US.[18,25,96] Two case-control studies focused on Black women[87,95,104] and one focused on BRCA1/2 mutation carriers.[102] The line chart was drawn to show the trend of EOC risk along with LOYs increasing using studies that reported effect estimates and 95% CI (**Figure 1-3**). Of the 31 studies examining the LOYs/LOCs -EOC risk relationship, two included LOYs as a continuous variable,[18,96] two did not have estimates of 95% CI[80,89] two were included in other publications,[50,87] one reported anovulatory index,[67] and three did not report effect size[79,82,95]; thus those ten studies were not included in the meta-analysis (**Table 1-4**). The remaining 21 studies reported effect estimates comparing the categories of LOCs/LOYs

based on LOYs/LOCs exposure level. A meta-analysis was conducted to estimate the association between LOYs/LOCs and EOC risk. As shown in **Figure 1-4**, women with the highest level of LOYs had 2.26 times higher odds of EOC risk than women with the lowest level of LOYs (95% CI 1.94- 2.83).

Five studies estimated the association between LOYs/LOCs and risk by EOC histotype;[25,50,60,99,104] however, the NHS+NHS II study was excluded from the meta-analyses because it reported LOYs only as a continuous variable.[18] Of the remaining studies, four reported estimates for SC and EC[50,60,99,104] and three included estimates for MC[50,60,99] (**Figure 1-5**). LOY was statistically significantly associated with risk of SC (pooled OR 2.31, 95% CI 1.60-3.33) and EC (pooled OR 3.05, 95% CI 2.08-4.45). There was no statistically significant association between LOYS and risk of MC (pooled OR 1.52, 95% CI 0.87-2.64). These findings are consistent with the NHS+NHS II results:[18] RR for SC 1.08 (95% CI 1.06-1.10), RR for EC 1.08 (95% CI 1.05-1.11), and RR for MC 1.03 (95% CI 1.00-1.07) per 1-year increase in LOYs.

Table 1-3 Summary of published articles estimating the association between lifetime ovulatory years and risk of epithelial ovarian cancer

Study (Region)	Study design	Population	LOY exposure	Categories of exposure	Outcomes	Number		Confounders	Note
						Cases	Controls		
Casagrande, 1979 (USA)	Case-control	Aged 25-49	Ovulatory age	log (Ovulatory age)	Overall	150	150	No	
Hildreth, 1981 (USA)	Case-control	Aged 45-75	Index of years of ovulation	< 25 y	Overall	5	186	No	excluded from meta-analysis: lacked 95% CIs
				25-29 y		12	205		
				30-34 y		16	329		
				35-39 y		21	253		
				>=40 y		8	63		
La Vecchia, 1983 (Italy)	Case-control	Aged 20-69	Ovulatory years	< 25 y	Overall	26	158	Age in decades	stratified by menopausal status
				25-29 y		26	125		
				30-34 y		48	114		
				>=35 y		53	123		
Risch, 1983 (USA)	Case-control	Aged 20-75	Ovulatory years	per 1-year increase	Overall	284	705		excluded from meta-analysis: lacked point estimate
Wu, 1988 (USA)	Case-control	Aged 18-74	Years of ovulation	< 25 y	Overall	50	191	No	
				25-29 y		43	182		
				30-34 y		81	252		
				35+ y		97	264		
Shu, 1989 (China)	Case-control	Aged 18-70	Ovulatory years	<= 16 y	Overall	42	33	Education, ovarian cyst	
				17-25 y		44	32		
				26-30 y		43	42		
				>=31 y		43	56		
			Times of ovulation	<=229	Overall	31	40	Education, ovarian cyst, number of livebirths and age at menarche	
				230-319		34	45		
				320-389		36	42		
				>=390		57	43		
Whittemore, 1989 (USA)	Case-control	18-74	Years of ovulation	25 y	Overall	31	138	Years of unprotected intercourse	excluded from meta-analysis: included in Whittemore, 1992
				25-30		26	87		
				30-35		47	118		
				35+		57	114		

Chen, 1992 (China)	Case-control	mean age 48.5 among cases and 49.0 among controls	Ovulatory years	<10 y	Overall	10	21	Education (None, Primary, Juniour high school, Senior high school, College)	
				10-19 y		27	74		
				20-29 y		44	97		
				30+ y		31	32		
Whittemore, 1992 (USA)	12 case-control studies	Aged <55	Years of Ovulation	<25 y	Overall	208	2099	Age, and study center	
				25-29 y		131	804		
				30-34 y		198	962		
				35+ y		145	595		
		Aged 55+	Years of Ovulation	<25 y	Overall	24	90		
				25-29 y		24	160		
				30-34 y		121	363		
				35+ y		318	826		
John, 1993 (USA)	7 case-control studies	Black women	Duration of ovulation	<25 y	Overall	38	135	Study, year of birth, and reference age	excluded from meta-analysis: 3 case-control studies with full population already included in analyses
				25-34 y		33	132		
				>=35 y		33	65		
Whittemore, 1993 (USA)	12 case-control studies	Aged <55	Years of Ovulation	<25 y	Overall	NR	NR	Age, year of birth, and study center	excluded from meta-analysis: lacked 95% Cis
				25-29 y		NR	NR		
				30-34 y		NR	NR		
				35+ y		NR	NR		
		Aged 55+	Years of Ovulation	<25 y	Overall	NR	NR		
				25-29 y		NR	NR		
				30-34 y		NR	NR		
				35+ y		NR	NR		
Bernal, 1995 (Mexico)	Case-control	Aged 18-79	Ovulatory Cycles	Quantile 1	Overall	NR	NR	abortions, contraceptive use at fisrt use (<=20 years, 21-30 years), and education	
				Quantile 2		NR	NR		
				Quantile 3		NR	NR		
				Quantile 4		NR	NR		
Schildkraut, 1997 CASH study (USA)	Case-control	Aged 20-54	Lifetime ovulatory cycles (Ovulatory years)	<=234 (<=18 y)	p53-positive cases	4	840	Age, age^2, menopausal status, and nulliparity	
				235-375 (18-29 y)		29	1222		
				376-533 (30-41 y)		67	1159		
				<=234 (<=18 y)		23	840		

			Lifetime ovulatory cycles (Ovulatory years)	235-375 (18-29 y)	p53-negative cases	19	1222		
				376-533 (30-41 y)		45	1159		
Webb, 1998 (Australia)	Case-control	Aged 18-79	Ovulatory years	<23 y	Overall	172	348	Age group (<45, 45-54, 55-64, and >=65 years), menopausal status and parity	stratified by menopausal status and p53 defined tumor
				23-29.9 y		175	210		
				30-34.9 y		155	161		
				>=35 y		175	136		
Salazar-Martinez, 1999 (Mexico)	Case-control	NR	Anovulatory index, month	<=26 mo	Overall	28	159	age, smoking, diabetes mellitus, hypertension, physical activity, menopausal status, and body build index	excluded from meta-analysis: exposure is anovulatory index, not LOC/LOY
				27-59 mo		21	152		
				60-104 mo		21	180		
				>=105 mo		14	177		
Moorman, 2002 The North Carolina Ovarian Cancer Study (USA)	Case-control	Aged 20-74	Lifetime ovulatory cycles (Standard method) (Ovulatory years)	<300 (<23 y)	Overall	58	91	Age	
				300-399 (23- 30.7 y)		73	71		
				>=400 (>=30.7 y)		101	80		
			Lifetime ovulatory cycles (Method 2) (Ovulatory years)	<300 (<23 y)	Overall	75	105		
				300-399 (23- 30.7 y)		75	67		
				>=400 (>=30.7 y)		82	70		
Purdie, 2003 (Australia)[a]	Case-control	Aged 18-79	Ovulatory years	0-9 y	Overall	79	139	Age, age squared, education, area of residence, body mass index, talc use in perineal region, smoking status, tubal sterilization, hysterectomy and a family history of breast or ovarian cancer	within age bands
				10-14 y		86	136		
				15-19 y		108	125		
				20-24 y		158	170		
				25-29 y		266	225		
				30-42 y		94	58		
Tung, 2003 (USA)	Case-control	Aged 18+	Lifetime ovulatory cycles (Ovulatory years)	<=266.4 (<20.5 y)	Overall	unknown	unknown	Age, ethnicity, study site, education and tubal ligation	overall excluded from meta-analysis: more complete data in Tung 2005
				266.5-363.9 (20.5-28 y)					
				364.0-436.7 (28-33.6 y)					
				>=436.8 (>=33.6 y)					

			Lifetime ovulatory cycles (Ovulatory years)	<=266.4 (<20.5 y) 266.5-363.9 (20.5-28 y) 364.0-436.7 (28-33.6 y) >=436.8 (>=33.6 y)	Invasive serous	unknown	unknown		
			Lifetime ovulatory cycles (Ovulatory years)	<=266.4 (<20.5 y) 266.5-363.9 (20.5-28 y) 364.0-436.7 (28-33.6 y) >=436.8 (>=33.6 y)	Invasive endometrioid	unknown	unknown		
			Lifetime ovulatory cycles (Ovulatory years)	<=266.4 (<20.5 y) 266.5-363.9 (20.5-28 y) 364.0-436.7 (28-33.6 y) >=436.8 (>=33.6 y)	Invasive mucinous	unknown	unknown		
			Lifetime ovulatory cycles (Ovulatory years)	<=266.4 (<20.5 y) 266.5-363.9 (20.5-28 y) 364.0-436.7 (28-33.6 y) >=436.8 (>=33.6 y)	invasive clear cell	unknown	unknown		
Odukogbe, 2005 (Nigeria)	Case-control	Gynecolo-gical patients as controls	Total ovulating period	0-9 y 10-19 y 20-29 y 30-39 y	Overall	5 7 3 2	5 17 17 2		excluded from meta-analysis: no point estimates
Rosner, 2005 NHS (USA)[b]	Cohort	Nurses aged 30-55 years	Duration of ovulation, years	per 1-year increase	Overall	472	2,298,068	Duration of menopause (years) and Tubal ligation (yes/no)	excluded from meta-analysis: exposure is continuous measure
Tung, 2005 (USA)	Case-control	Aged 18+	Ovulatory cycles	<22.1 y 22.1-29.1 y 29.2-34.1 y >34.1 y	Overall	118 134 150 156	176 160 141 130	Age, ethnicity, study site, education, tubal ligation, hormone replacement therapy, and ovulation variables	stratified by menopausal status, and age periods
Pelucchi, 2007 (Italy)	2 case-control studies	Aged 17-79	Ovulatory cycles (Ovulatory years)	<357 (<28.8 y) 357-429 (28.8-33 y) 429-481 (33-37 y)	Overall	345 456 456	1169 1086 1059	Study, calendar year at interview, age, center, education, hormone replacement therapy use,	stratified by menopausal status

				>=481 (>=37 y)		479	1069	family history of ovarian and breast cancer in first degree relatives, and, in turn, menopausal status, parity, abortion, oral contraceptive use, and age at menarche	
Terry, 2007 (USA)	Case-control	Aged 18+	Lifetime ovulatory cycles (Ovulatory years)	women ages <=45y: <=196 (<=15 y); women ages 45-60y: <=375 (<=29 y); women ages >60y: <=399 (<=30.7 y)	Overall	145	223	Reference age (continuous), study center (Massachusetts or New Hampshire), cesarean section, tubal ligation, and hysterectomy	by histologic subtypes
				women ages <=45y: 197-298 (15-23 y); women ages 45-60y: 375-436 (29-33.5 y); women ages >60y: 400-457 (30.7-35.1 y)		182	224		
				women ages <=45y: >298 (>23 y); women ages 45-60y: >436 (>33.5 y); women ages >60y: >457 (>35.1 y)		274	227		
			Lifetime ovulatory cycles (Ovulatory years)	women ages <=45y: <=196 (<=15 y); women ages 45-60y: <=375 (<=29 y); women ages >60y: <=399 (<=30.7 y)	Invasive serous	60	223		
				women ages <=45y: 197-298 (15-23 y); women ages 45-60y: 375-436 (29-33.5 y); women ages >60y: 400-457 (30.7-35.1 y)		65	224		
				women ages <=45y: >298 (>23 y); women ages 45-60y: >436 (>33.5 y); women ages >60y: >457 (>35.1 y)		121	227		

	women ages <=45y: <=196 (<=15 y); women ages 45-60y: <=375 (<=29 y); women ages >60y: <=399 (<=30.7 y)		18	223
Lifetime ovulatory cycles (Ovulatory years)	women ages <=45y: 197-298 (15-23 y); women ages 45-60y: 375-436 (29-33.5 y); women ages >60y: 400-457 (30.7-35.1 y)	Endometrioid	22	224
	women ages <=45y: >298 (>23 y); women ages 45-60y: >436 (>33.5 y); women ages >60y: >457 (>35.1 y)		58	227
	women ages <=45y: <=196 (<=15 y); women ages 45-60y: <=375 (<=29 y); women ages >60y: <=399 (<=30.7 y)		12	223
Lifetime ovulatory cycles (Ovulatory years)	women ages <=45y: 197-298 (15-23 y); women ages 45-60y: 375-436 (29-33.5 y); women ages >60y: 400-457 (30.7-35.1 y)	Mucinous	24	224
	women ages <=45y: >298 (>23 y); women ages 45-60y: >436 (>33.5 y); women ages >60y: >457 (>35.1 y)		19	227
	women ages <=45y: <=196 (<=15 y); women ages 45-60y: <=375 (<=29 y); women ages >60y: <=399 (<=30.7 y)		16	223
Lifetime ovulatory cycles (Ovulatory years)	women ages <=45y: 197-298 (15-23 y);	Clear cell	28	224

				women ages 45-60y: 375-436 (29-33.5 y); women ages >60y: 400-457 (30.7-35.1 y) women ages <=45y: >298 (>23 y); women ages 45-60y: >436 (>33.5 y); women ages >60y: >457 (>35.1 y)		36	227		
Sogaard, 2007 The MALOVA study (Denmark)	Case-control	Aged 35-79	Ovulatory years	<=24 y	Overall	60	367	Age (in 5-year categories)	by histologic subtypes
				25-29 y		71	221		
				30-35 y		112	304		
				>=36 y		100	217		
			Ovulatory years	<=24 y	Serous	35	367		
				25-29 y		47	221		
				30-35 y		73	304		
				>=36 y		66	217		
			Ovulatory years	<=24 y	Endometrioid	9	367		
				25-29 y		7	221		
				30-35 y		12	304		
				>=36 y		12	217		
			Ovulatory years	<=24 y	Mucinous	8	367		
				25-29 y		5	221		
				30-35 y		10	304		
				>=36 y		6	217		
Schildkraut, 2008 The North Carolina Ovarian Cancer Study (USA)	Case-control	Aged 20-74	Lifetime ovulatory cycles (Ovulatory years)	<265 (20.4 y)	Cyclin E+ cases	41	193	Age at diagnosis/interview (cubic spline), race (Black/non-Black), BMI (kg/m2; continuous), tubal ligation (yes/no), family history of breast/ovarian cancer in first-degree relative (yes/no), and infertility (yes/no)	stratified by menopausal status
				265-390 (20.4-30 y)		68	200		
				>390 (>30 y)		104	219		
			Lifetime ovulatory cycles (Ovulatory years)	<265 (20.4 y)	Cyclin E- cases	98	193		
				265-390 (20.4-30 y)		118	200		
				>390 (>30 y)		89	219		
Gates, 2010 NHS and NHS II study (USA)[b]	Cohort	Nurses aged 30-55 years in NHS and nurses aged 25-42 years in NHS II	Ovulatory years	per 1-year increase	Overall	924	220,942	Cohort (NHS or NHSII), parous (yes/no), menopausal status (postmenopause vs. premenopause/perimenopause), missing data on	excluded from meta-analysis: exposure is continuous measure
			Ovulatory years	per 1-year increase	Serous	83	220,942		
			Ovulatory years	per 1-year increase	Endometrioid	80	220,942		

			Ovulatory years	per 1-year increase	Mucinous	79	220,942	breastfeeding duration (yes/no) because of noncompletion of questionnaire, duration of menopause (1-year increase), tubal ligation (yes/no), hysterectomy (yes/no) and estrogen sued (5-year increase)
Le, 2012 (Vietnam)	Case-control	Age under 60	Years of ovulation	<20 y	Overall	31	118	Age, education level (primary school, basic school, secondary school or higher), parity (para 1–5), body mass index (BMI; b20.00, 20.00–22.45, 22.50–24.99, ≥25.00 kg/m2), menopausal status, age at menarche (≤13, 14–15, ≥16 years) and OC use
				20-29 y		157	517	
				>=30 y		72	120	
Kotsopoulos, 2015 (worldwide 20 countries)	Case-control	BRCA1 and BRCA2 mutation carriers aged 20-70	Ovulatory cycles	<=293.5 (<=22.6 y)	Overall	461	253	Ethnicity (other white, Jewish, French-Canadian, other) and tubal ligation (yes/no)
				>293.5-<=348.0 (22.6-30.7 y)		684	256	
				>348.0-<=398.8 (26.8 y-30.7 y)		852	255	
				>398.8 (30.7 y)		2317	253	
Yang, 2016 The Polish Cancer Study (Poland)	Case-control	Post-menopausal women	Ovulatory cycles algorithm C (Ovulatory years)	279.5-438 (21.5-33.7 y)	Overall	86	301	Age (in 5-year age categories), study site (Lodz or Warsaw), age at menopause (<45, 45–49, 50–54, or ≥55 years), age at menarche (<13, 13, 14, 15, or ≥16 years), oral contraceptive use (never, ever), and number of live births (0, 1, 2, or ≥3)
				439-467 (33.7-36 y)		76	333	
				468-504 (36-38.8 y)		51	314	
				505-619.1 (38.8-47.6 y)		75	343	
			Ovulatory cycles algorithm D (Ovulatory years)	176.0-389.5 (13.5-30 y)	Overall	86	319	
				389.6-425.8 (30-32.8 y)		67	315	
				425.9-453.35 (32.8-34.9 y)		53	315	
				453.36-565.7 (34.9-43.5 y)		76	320	
			Ovulatory cycles algorithm G	196.3-402 (15.1-30.9 y)	Overall	72	308	
				403-444.5 (30.9-34.2 y)		78	322	
				444.6-479.9 (34.2-36.9 y)		59	318	

			(Ovulatory years)	480.0-602.3 (36.9-46.3 y)		71	315		
			Ovulatory cycles algorithm M (Ovulatory years)	218.8-412 (16.8-31.7 y)	Overall	84	301		
				413-452.5 (31.7-34.8 y)		66	301		
				452.6-480 (34.8-36.9 y)		49	282		
				481-611 (36.9-47 y)		72	325		
			Ovulatory cycles algorithm R (Ovulatory years)	183.5-377.525 (14.1-29.0 y)	Overall	80	330		
				377.526-413.525 (29.0-31.8 y)		75	304		
				413.526-443.52 (31.8-34.1 y)		52	311		
				444.53-564 (34.1-43.4 y)		75	323		
Peres, 2017 (USA)	Case-control	African American aged 20-79	Ovulatory cycles (Ovulatory years)	<=304 (<=23.4 y)	Overall	115	235	Age, study site, family history of breast or ovarian cancer in a first degree relative, tubal ligation, premenopausal hysterectomy, BMI, physical activity, smoking status, body powder exposure, any NSAID use, endometriosis, and pelvic inflammatory disease	by histologic subtypes; stratified by age group
				305-410 (23.4-31.5 y)		188	247		
				>=411 (>=31.5 y)		231	240		
			Ovulatory cycles (Ovulatory years)	<=304 (<=23.4 y)	Serous	68	235		
				305-410 (23.4-31.5 y)		134	247		
				>=411 (>=31.5 y)		162	240		
			Ovulatory cycles (Ovulatory years)	<=304 (<=23.4 y)	Endometrioid	14	235		
				305-410 (23.4-31.5 y)		10	247		
				>=411 (>=31.5 y)		36	240		
Trabert, 2020 OC3 (USA)[b]	Pooled prospective studies	Aged 18+	Lifetime ovulatory cycles years	<24.5 y	Overall	214	657,188	Baseline age (continuous), BMI (<20, 20–24.9, 25–29.9, 30–34.9, 35 kg/m2), smoking status (never, former, current), and duration of menopausal hormone therapy use (never, 5, >5–10, >10 years)	by histologic subtypes
				24.5-30.8 y		405	1,001,723		
				30.8-36.6 y		767	1,634,435		
				36.6-40.0 y		917	1,750,003		
				40.0-42.8 y		488	909,033		
				>=42.8 y		459	744,342		
			Lifetime ovulatory cycles years	per 5-y increase	Overall	NR	NR	Baseline age (continuous), BMI (<20, 20–24.9, 25–29.9, 30–34.9, 35	

	Lifetime ovulatory cycles years	per 5-y increase	Serous	NR	NR	kg/m2), smoking status (never, former, current), and duration of menopausal hormone therapy use (never, 5, >5–10, >10 years), duration of oral contraceptive use and pregnancy history
	Lifetime ovulatory cycles years	per 5-y increase	Endometrioid	NR	NR	
	Lifetime ovulatory cycles years	per 5-y increase	Mucinous	NR	NR	
	Lifetime ovulatory cycles years	per 5-y increase	Clear cell	NR	NR	

NR, not report

[a] number of cases and controls are estimated from the percentages in each category multiplied by total number

[b] person-years instead of number of controls were reported

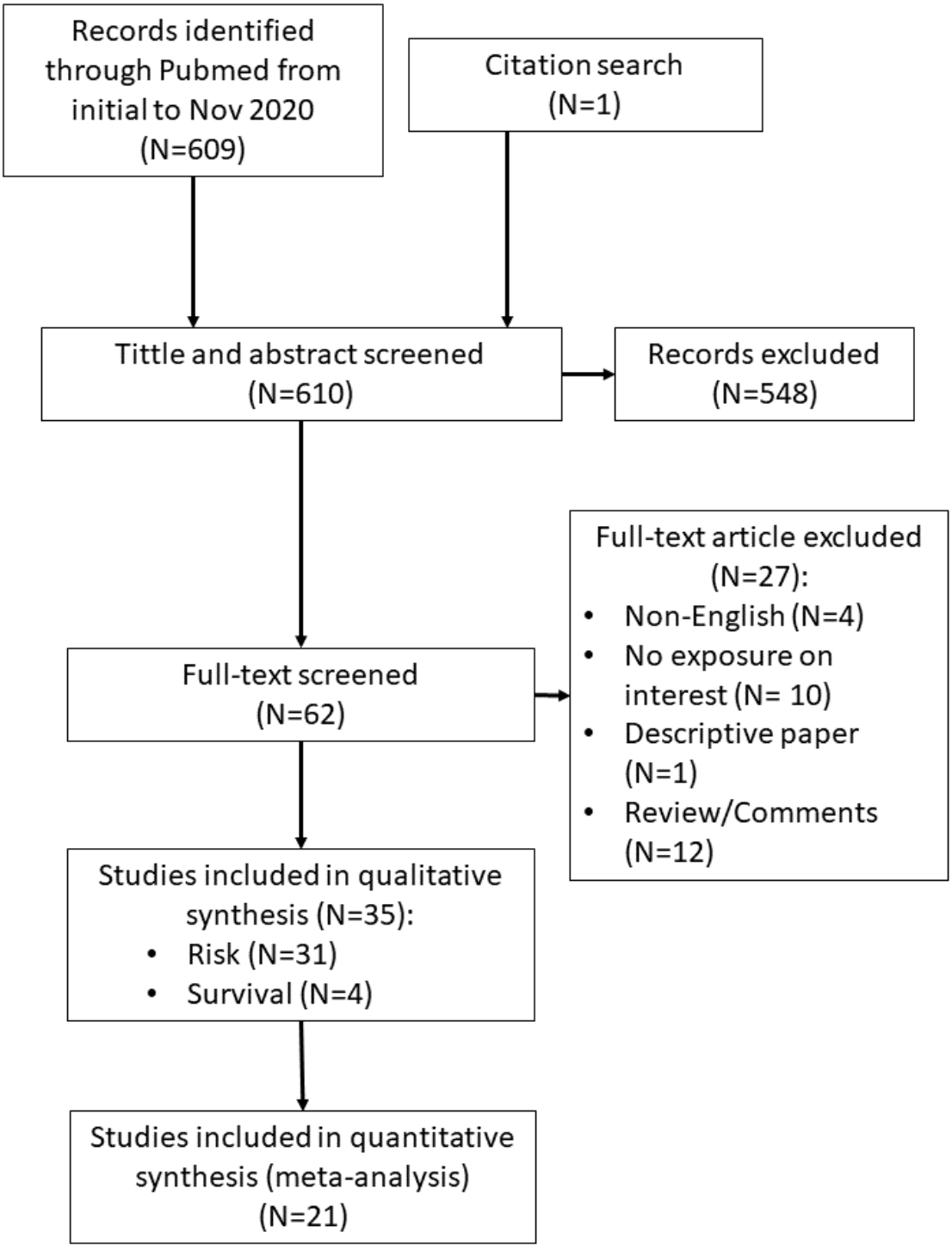


Figure 1-2 Flow diagram of literature and citation search

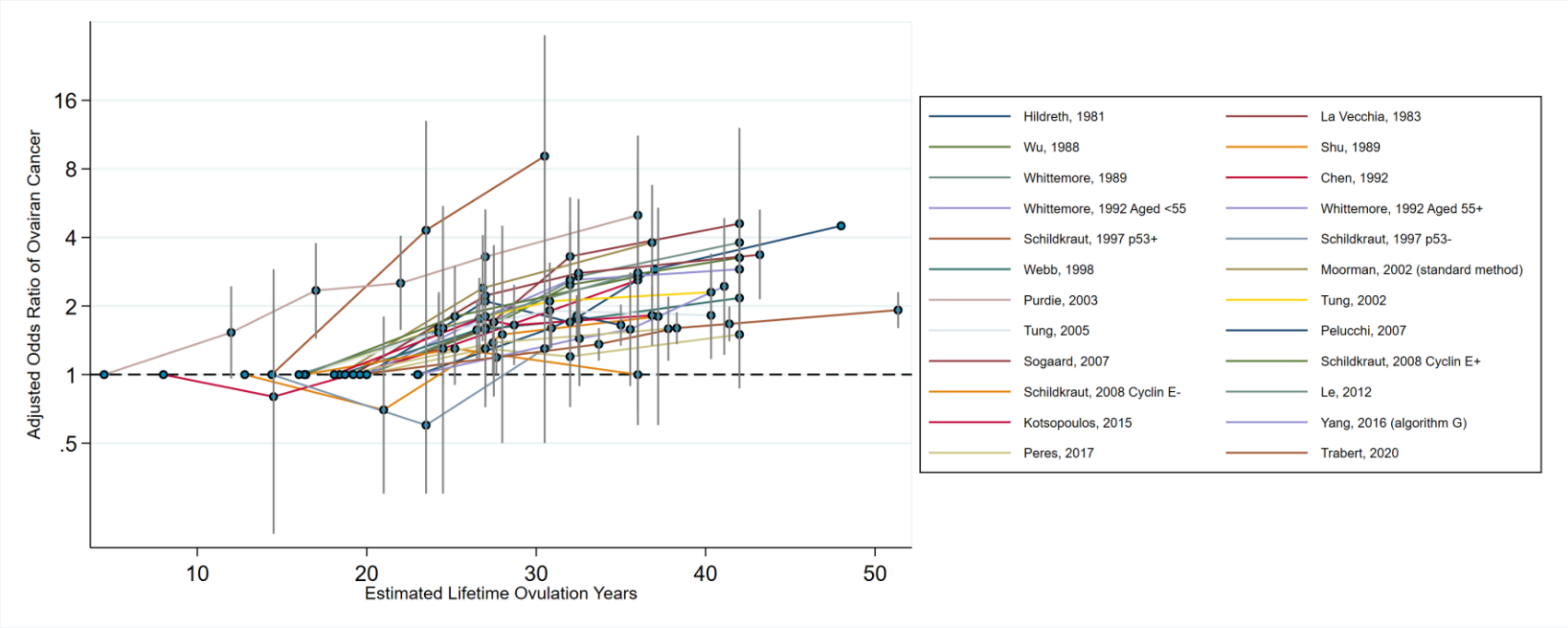


Figure 1-3 Line chart of the trend of ovarian cancer risk by lifetime ovulatory years

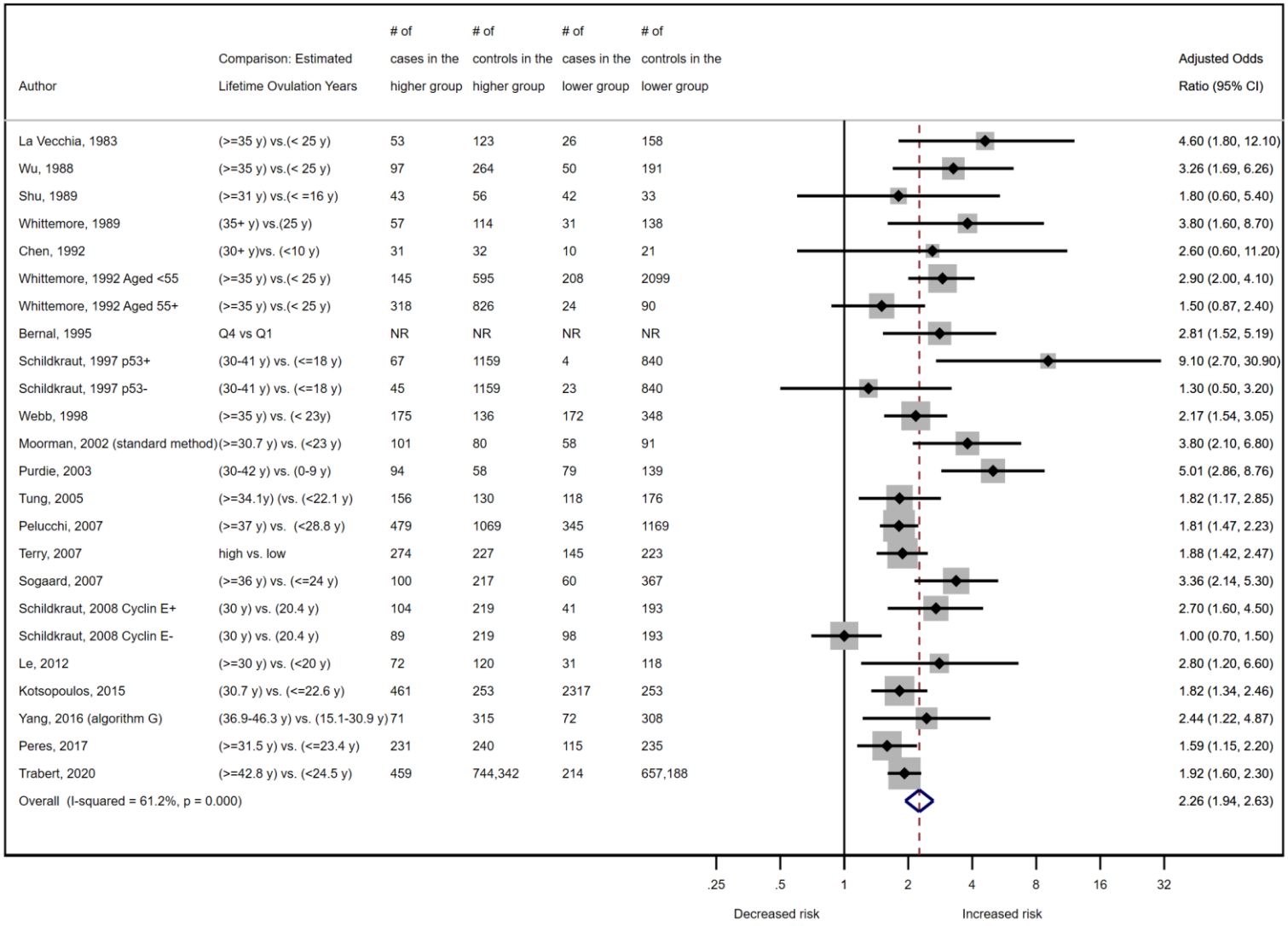


Figure 1-4 Forest plot estimating the association between lifetime ovulatory years and the overall risk of ovarian cancer

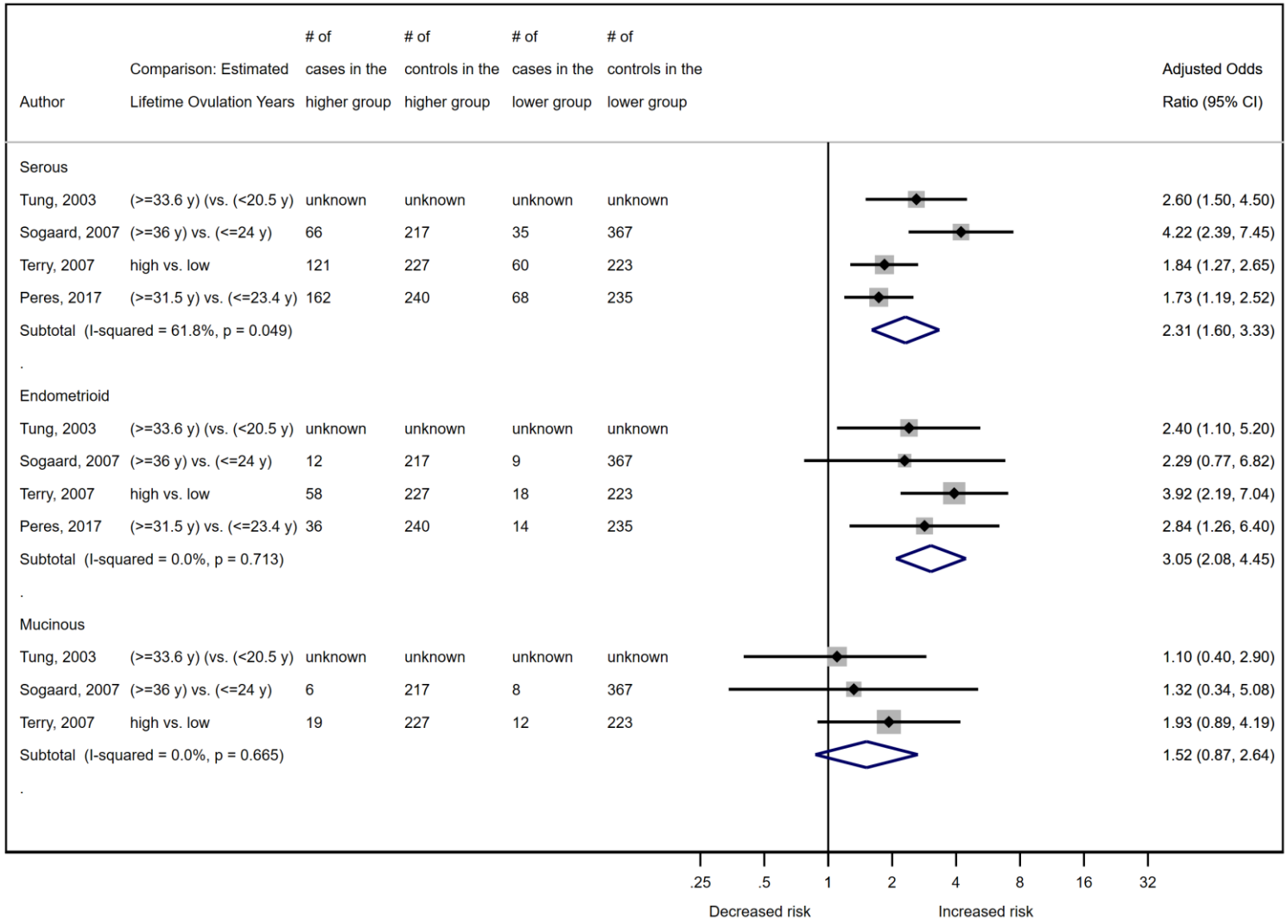


Figure 1-5 Forest plot estimating the association between lifetime ovulatory years and risk of ovarian cancer by histotype

Hormone replacement therapy (HRT)

Hormone replacement therapy (HRT), regardless of the type, is a risk factor for EOC.[16-18,26,60,105,106] The association varies by histotype. OC3 found that HRT use per 5-year increase was associated with an increased risk of SC (RR 1.21, 95% CI 1.17-1.25) and EC (RR 1.25, 95% CI 1.15-1.36), but associated with a decreased risk of CCC (RR 0.69, 95% 0.52-0.92) and no associated with a risk of MC (**Table 1-1**).[16] The NHS and NHS II study and the NIH-AARP Diet and Health Study indicated the same association between HRT and risk of SC and EC.[17,18] Two meta-analyses indicated the association between HRT use with SC but not with other histotypes.[105,106] The Danish MALOVA Study also indicated the discrepancies in the association of MC risk versus the association of non-mucinous ovarian cancer risk.[60] The association might depend on the type of HRT. OCAC found that estrogen-only therapy was associated with higher risks of ovarian cancer overall, SC and EC among women with a simple hysterectomy,[26] while, postmenopausal estrogen-progestin combined therapy use was associated reduced risk of ovarian cancer overall and MC among postmenopausal women (**Table 1-1**).[27]

Polycystic ovary syndrome (PCOS)

Polycystic ovary syndrome (PCOS), which is associated with elevated androgen levels, might be a potential risk factor for EOC risk. A meta-analysis pooling the results from three studies indicated a non-significant positive association between PCOS and EOC risk (OR 1.41, 95% CI 0.93-2.15),[107] Notably, one of the three studies, which included only women younger than 54 years, reported a significant positive association between PCOS and EOC risk (OR 2.5 with 95% CI 1.1-5.9).[108] However, OCAC pooling 14 case-control sites and the NECC study, one of the OCAC sites, found no association between PCOS and risk of EOC overall and by histotype.[20,53] Similarly,

the Australian Ovarian Cancer Study did not find any association between PCOS and risk of EOC and SC.[109]

Tubal ligation

Tubal ligation was associated with a decreased risk of EOC risk in OCAC (OR 0.81, 95% CI 0.74-0.89), OC3 (RR 0.82, 95% CI 0.73-0.93), the NHS and NHS II study (RR 0.68, 95% CI 0.56-0.84), the Million Women Study (RR 0.80 95% CI 0.76-0.85), and a meta-analysis including 11 studies (RR 0.70 95% CI 0.64-0.75).[16,18,28,110,111] However, the results on the histotype-specific association were inconsistent (**Table 1-4**). OCAC found the protective effects of tubal ligation on the risk of HGSC, EC, CCC and MC, but not on the risk of LGSC.[28] OC3 did not find a significant association between tubal ligation and risk of SC and MC, but found a significant association between tubal ligation and risk of EC and CCC.[16] The meta-analysis did not found a significant association between tubal ligation and risk of MC.[111] The Million Women Study indicated that tubal ligation was associated with a decreased risk of SC, HGSC, EC, and CCC.[110] The NHS and NHS II study did not find any significant histotype-specific association, which could be due to the limited sample size.[18]

Table 1-4 Assocition between tubal ligation and risk of EOC by histotype

Study	Serous	High-grade serous	Low-grade serous	Endometrioid	Clear cell	Mucinous
OCAC[28]	-	**0.80 (0.73, 0.89)**	0.89 (0.65, 1.22)	**0.48 (0.40, 0.59)**	**0.52 (0.40, 0.67)**	**0.68 (0.52, 0.89)**
OC3[16]	0.91 (0.79, 1.06)	-	-	**0.60 (0.41, 0.88)**	**0.35 (0.18, 0.69)**	1.01 (0.60, 1.71)
Meta-analysis[111]	**0.75 (0.65, 0.88)**	-	-	**0.45 (0.33, 0.61)**	**0.75 (0.55, 0.94)**	0.88 (0.70, 1.09)
The Million Women[110]	**0.84 (0.77, 0.92)**	**0.77 (0.67, 0.89)**	-	**0.54 (0.43, 0.69)**	**0.55 (0.39, 0.77)**	0.99 (0.84, 1.18)
NHS and NHS II[18]	0.83 (0.63, 1.09)	-	-	0.59 (0.34, 1.02)	0.50 (0.25, 1.01)	-

Hysterectomy

OC3 did not find a significant association between hysterectomy and EOC risk, but found a reduced risk of CCC associated with hysterectomy (RR 0.57 95% CI 0.36-0.88).[16] A meta-analysis pooling 24 studies indicated that hysterectomy was associated with a reduced risk of EOC risk, which remained even when stratified by type of hysterectomy or study design.[111] The association retains stratified by study design or type of hysterectomy.[111] The Danish MALOVA study, a case-control study participating in OCAC, did not find any association between hysterectomy and EOC risk or risk of any histotype,[60] while, the NHS and NHS II study, a cohort study participating in OC3 indicated hysterectomy was associated with a decreased risk of EOC risk (RR 0.69, 95% CI 0.85-0.91) and risk of MC (RR 0.45, 95% CI 0.20-0.98).[18]

1.2.3 Gynecologic factors

Genital powder use (Talc use)

Genital powder use has been considered as a potential risk factor for EOC risk via inflammation. OCAC confirmed a positive association between genital powder use and EOC risk (**Table 1-1**),[29] which was reported by several case-control studies[55,112-114] and the NHS study.[115] OCAC also found that genital powder use was associated with an increased risk of SC (OR 1.24, 95% CI 1.13-1.35), EC (OR 1.20, 95% CI 1.03-1.40), and CCC (OR 1.26, 95% CI 1.04-1.52), but not MC.[29] One case-control study reported a significant association between genital powder use and risk of SC (OR 1.21, 95% CI 1.03-1.44),[55] but the NHS study and the combined NHS and NHS II study did not find any histotype-specific association, except for invasive SC. [18,115]

Pelvic inflammatory disease (PID)

Pelvic inflammatory disease (PID), which induces chronic inflammation, might be a risk factor for EOC. However, the association varies by study design. OCAC pooling 13 case-control studies did not find a significant association between PID and risk of EOC overall or by histotype (**Table 1-1**).[30] In contrast, a meta-analysis including six cohort studies and seven case-control studies found that PID was associated with an increased risk of ovarian cancer (pooled RR 1..24, 95% CI 1.06-1.44).[116] However, the association was not significant when limiting to the case-control studies.[116] An updated meta-analysis in 2020 including sixteen studies found PID was associated with an increased risk of ovarian cancer (HR 1.18, 95% CI 1.13-1.22), and the association were not altered stratified by study design or by serous versus non-serous ovarian cancer.[117] A more recent retrospective cohort study from Taiwan also supported that PID was associated with an increased risk of ovarian cancer (HR 1.49, 95% CI 1.21-1.84).[118]

Endometriosis

Endometriosis is a well-known risk factor for EOC with effect estimates ranging from 1.35 to 1.96, especially for EC (OR 2.04 in OCAC and RR 2.32 in OC3) and CCC (OR 3.05 in OCAC and RR 2.87 in OC3) (**Table 1-1**).[16,31,119] OCAC also found endometriosis was associated with an increased risk of LGSC (OR 2.11, 95% CI 1.39-3.20).[31]

1.2.4 Genetic factors

Family history of ovarian cancer or/and breast cancer

OC3 found that a family history of ovarian or/and breast cancer was associated with an increased risk of EOC (**Table 1-1**).[16] The same association was also found by other individual cohort studies and case-control studies.[120-126] When considering histotypes, OC3 found that family

history of ovarian cancer was only associated with an increased risk of SC (RR 1.61, 95% CI 1.32-1.97), and family history of breast cancer was associated with increased risk of SC (RR 1.13, 95% CI 1.02-1.26) and EC (RR 1.47, 95% CI 1.15-1.87).[16] The Cancer and Steroid Hormone Study conducted in 1988 among women aged 20-54 years only found that family history of breast cancer was associated with an increased risk of EC (OR 2.3, 95% CI 1.1-4.7), but not with SC.[126] A case-control study among women with the mean age of 54.8 years found that family history of ovarian or/and breast cancer was associated with increased risk of SC (OR 2.22， 95% CI 1.37-3.58) and EC (OR 2.31, 95% CI 1.09-4.90).[123]

1.2.5 Lifestyle factors

Physical activity

Pooling nine case-control studies, OCAC found that physical inactivity was associated with a higher risk of EOC (OR 1.32, 95% CI 1.12-1.56).[32] However, a prospective cohort study among U.S. women did not found a significant association between physical activity and risk of ovarian cancer.[127] A meta-analysis found a significant inverse association between physical activity and risk of ovarian cancer (pooled OR 0.79, 95% CI 0.70-0.85) among seven case-control studies but a non-significant association(pooled RR 0.81, 95% CI 0.57-1.17) among seven cohort studies.[128]

Regarding the histotype-specific associations, OCAC found that physical inactivity was significantly associated with risk of HGSC (OR 1.30, 95% CI 1.08-1.53), LGSC (OR 1.33, 95% CI 1.01-1.76), CCC (OR 1.40, 95% CI 1.11-1.74) and MC (OR 1.50, 95% CI 1.17-2.10), but not associated with EC (**Table 1-1**).[32] While, two case-control studies suggested an inverse association for all histotypes except MC.[129,130]

Alcohol intake

Pooling 12 case-control studies, OCAC reported no association between alcohol intake and overall risk of EOC regardless of alcohol types (**Table 1-1**).[33] The null association was also found in three meta-analysis studies.[131-133] The meta-analysis of only prospective observational studies suggested a positive association between alcohol intake and risk of ovarian cancer in the non-U.S. population (OR 0.96, 95% CI 0.92-1.00).[132] An inverse association with alcohol and risk of ovarian cancer was found in a Australian population (OR 0.49 comparing >=2 standard drinks per day to non-drinkers, 95% CI 0.30-0.81).[134] While OCAC found an inverse association between alcohol intake and risk of EC (OR 0.49, 95% CI 0.27-0.91),[33] which was consistent with the results from a meta-analysis (RR 0.82, 95% CI 0.70-0.96).[131]

Smoking

Both OCAC and OC3 did not find an association between smoking and overall risk of ovarian cancer, but a significant positive association of MC (**Table 1-1**).[16,34] A meta-analysis pooling individual participant data from 28,114 women with and 94,942 without ovarian cancer found the same association between smoking and MC risk (RR 1.79 comparing current smokers to never smokers, 95% CI 1.47-2.17).[135] OCAC and the meta-analysis found a reduced risk of CCC in current smokers (Comparing current smokers to never smokers OR 0.74 95% CI 0.56-0.98; RR 0.80, 95% CI 0.63-1.01, respectively),[34,135] and the meta-analysis also found a reduced risk of EC (RR 0.81 comparing current smokers to never smokers, 95% CI 0.63-0.94).[135] The sheterogeneity across histotypes was well-summarized by a review, which suggested detecting the histotype-specific associations in a larger number of participants with rare histotypes.[136]

Caffeine intake

Neither OCAC nor OC3 conducted a study to evaluate the association between caffeine intake and EOC risk. Several meta-analyses report a null association between coffee intake and EOC risk.[137-139] One of the meta-analyses found an inverse association between tea intake and overall EOC risk (RR 0.85 comparing the highest to the lowest tea consumption group, 95% CI 0.71-1.01).[139] The association was strengthened by restricting to cohort studies (RR 0.71, 95% CI 0.55-0.93).[139] The Netherlands Cohort Study found an inverse association between tea intake and risk of SC, and a positive association between tea intake and risk of EC and MC (data not shown in the original article).[139] Among all individual studies, one cohort study in a non-white population indicated a reduced risk of ovarian cancer with higher coffee intake (HR 0.33, 95% ci 0.17-0.65).[140]

Diet

The association between diet and ovarian cancer risk is challenging to assess. One systematic review in 2014 that identified 24 publications summarized the association of with dietary fat, vegetable and fruit intake, micronutrient, and plant-based bioactive intake, and other dietary components, such as sugar, with risk of ovarian cancer.[141] The systematic review suggested that total, animal and dairy fat, nitrate, and vitamin C were associated with an increased risk of ovarian cancer and vegetables were associated with a decreased risk of ovarian cancer.[141] The data on histotype-specific association were limited due to sample sizes of individual studies.[141]

A meta-analysis estimating the association between calcium intake and risk of ovarian cancer suggested that dietary calcium, but not dairy calcium intake and supplemental calcium intake, was associated with a reduced risk of EOC (RR 0.78, 95% CI 0.69-0.88) .[142] A Mendelian randomization study from OCAC indicated that lower 25-hydroxyvitamin D concentrations were associated with a higher risk of ovarian cancer in Europeans (OR 1.27 per 20 nmol/L decrease in

25(OH)D concentration, 95% CI 1.06-1.51) by combining the individual SNP associations using inverse variance weighting.[143] In contrast, a case-control study in African-American women did not find an association between vitamin D intake and ovarian cancer risk.[144] While an inverse association between supplemental selenium and risk of ovarian cancer was observed in African-American women (OR 0.67, 95% CI 0.46-0.97).[145]

1.3 Prognostic factors of epithelial ovarian cancer and by histotypes

Several factors have been associated with improved outcome in EOC, as discussed below. However, there are limitations to the evidence. First, most studies examined the relationships between prognostic factors for EOC in general but not by histotypes. Second, prognostic factors for EOC are usually identified using Cox proportional hazard regression analysis (CoxPHR). The proportional hazards assumption is fundamental to the CoxPHR. Many studies did not report whether the proportional hazards assumption was assessed. Moreover, even when studies did report that the assumption was violated, many failed to address the concern. A violation of this assumption lowers statistical power with an increased sample size.[146]

Despite these limitations, an understanding of potential prognostic factors can help guide clinical decision making and point the way to potential new therapeutic approaches.

1.3.1 Clinical factors

Stage

Stage is a well-known independent prognostic factor for EOC.[147-150] Patients with advanced stage presented worse survival.

Grade

Grade has not been considered as an important prognostic factor for EOC.[151] Data from the Taiwan Cancer Registry from 2009 to 2013 showed that the overall survival of patients with early-stage EOC and patients with advanced-stage EOC did not differ by grade.[148]

Histotype

As a potential prognostic factor, histotype was observed to significantly affect EOC survival, especially among patients with advanced stage.[12,148] Patients with LGSC had a significantly better outcome than patients with HGSC.[152-154] Patients with MC and CCC presented a worse outcome compared to LGSC or combined SC, especially restricting to patients with advanced stage .[12,148,150,155,156]

Residual disease after cytoreductive surgery

The success of cytoreductive surgery was associated with better outcomes.[151] The Gynecologic Oncology Group defined the maximum diameter of residual less than or equal or 1cm as optimal residual disease, and more than 1cm but less than 2cm as suboptimal residual disease.[151] The benefit of optimal residual disease was observed in several studies.[149,155,157] A meta-analysis indicated <=2 cm residual disease also benefited the patients with stage III and IV ovarian cancer (Comparing patients left with tumor masses > 2 cm to patients with nil and < = 2 cm residual disease after surgery at 5 years, OR 5.51, 95% CI 4.340-6.90; OR 4.35, 95% CI 2.87-6.61 for patients at stage III and stage IV, respectively).[158]

Age at diagnosis

The data from the Surveillance, Epidemiology, and End Results Program from 1988 to 2001 indicated that younger women with EOC have better survival compared to older women with EOC,[159] which may be due to an earlier stage at diagnosis.[147,160-162] The associations were consistent among women with CCC and women with non-CCC.[159] However, age might not be an independent prognostic factor after considering stage and residual disease.[161]

Type of treatment

The standard of care chemotherapeutic treatment for advanced ovarian cancer employs platinum/taxane agents.[163] There are two typical regimens. One is neoadjuvant chemotherapy, which involves three cycles of chemotherapy treatment before debulking surgery and an additional 3-5 cycles of chemotherapy after debulking surgery.[164] The other is adjuvant chemotherapy, which involves 6-8 cycles of chemotherapy after surgery.[164] In early stage disease, patients who received adjuvant chemotherapy presented better survival compared to patients who received no chemotherapy (HR for five-year overall survival 0.71, 95% CI 0.53-0.93).[165] However, adjuvant chemotherapy did not benefit CCC patients with stage IA and IB compared to observation alone.[166] Compared to adjuvant therapy, neoadjuvant therapy presents no significant survival advantage.[164,167] Nonetheless, the Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline recommended that women with advanced stage EOC with a low likelihood of achieving cytoreduction to <1 cm of residual disease should receive neoadjuvant chemotherapy.[168]

Chemotherapy response

Compared to the type of chemotherapy, the response to chemotherapy may be a potential prognostic factor. Chemotherapy responses can be defined into a three-tiered score system as no or minimal response, partial response, and complete or near-complete response.[169] A positive association between complete or near-complete response and EOC overall survival was observed compared to no or minimal response or partial response in a systematic review and meta-analysis pooling individual data of HGSC patients with advanced stage from 16 sites(pooled HR for overall survival 0.65, 95% CI 0.50-0.85).[170] The same association was observed in HGSC patients without BRCA mutation.[171]

Platinum sensitivity is another marker of chemotherapy response and is defined as the time between the last dose of platinum-based chemotherapy and the evidence of cancer progression after more than 6 months.[172] Results from 91 HGSC patients with advanced stage in the Republic of Macedonia and from 203 HGSC patients with more than ten-year survival from a multi-center research consortium showed that platinum sensitivity was associated with better outcomes.[157,173]

BRCA1/BRCA2 mutation

BRCA1/BRCA2 mutation carriers had improved survival compared with noncarriers.[171,174,175] Several systematic review and meta-analysis studies confirmed the association and suggested BRCA mutation as a favorable prognostic factor for ovarian cancer.[176-178]

TP53 mutation

The findings of the association between TP53 mutation and outcomes are inconsistent. The results from 190 patients with stage III and IV and 316 samples from The Cancer Genome Atlas (TCGA) ovarian GHSC study found that the TP 53 mutation was associated poorer survival.[179,180] In contrast, the results from 81 patients suggested TP53 mutation was associated with a short-term survival benefit.[181] The OncoMap data of Korean EOC samples showed a null association between TP53 mutation and outcomes.[182] The controversial results could be explained by two more recent studies, which classified different TP53 mutations.[183,184] The studies suggested that only some specific mutations were associated with outcomes.[184,185]

1.3.2 Biomarkers

Cancer Antigen 125 (CA125)

Serum Cancer Antigen 125 (CA125) is considered the gold standard of biomarkers for diagnosis and prognosis for ovarian cancer.[185,186] There have been multiple studies estimating the association between CA-125 levels and ovarian cancer survival and suggesting CA-125 as an independent prognostic factor for patients with advanced ovarian cancer,[186-197] although CA-125 level assessed at different time-point presented different associations with ovarian cancer survival (**Table 1-5**). The timepoint for CA-125 assessment with maximum prognostic significant remains unknown.

Table 1-5 Suumary of the associtin between CA125 levels at different time point and ovarian cancer survival in some publications

Time point	Study	Association with better survival
Before the initiation of treatment	Gronlund, 2005[189] Markman, 2006[190]	Null
In early cycles of chemotherapy	Ron, 1994 [191] Markman, 2006[190]	Reduction was associated with better survival
Post-chemotherapy	Kim, 2008[192] Juretzka, 2007[193]	Inverse
Pre-operation	Buller, 1996[194] Geisler, 1996[195]	Null or inverse
Post-operation	Sevelda, 1989[187] Akeson, 2009[188]	Inverse
Half-life	Gadducci, 2004[197] Riedinger, 2006[196]	Inverse
Nadir	Riedinger, 2006[196] Salminen, 2020[186]	Inverse

Human Epididymis Protein 4 (HE4)

The role of Human Epididymis Protein 4 (HE4) as a prognostic factor for ovarian cancer has been widely studied.[198-202] Two studies suggested that the reduction of HE4 level during treatment could be an independent prognostic factor for ovarian cancer,[198,199] which is consistent with the results from a meta-analysis suggesting that the preoperative HE4 levels could predict ovarian cancer survival (pooled HR for overall survival 1.91, 95% CI 1.40-2.61).[202] The combination of HE4 and CA125 could improve the accuracy of prognosis in ovarian cancer patients.[200,203]

Biomarkers from in the Ovarian Tumor Tissue Analysis (OTTA) consortium

The association between nine immunohistochemistry (IHC) biomarkers available in the Ovarian Tumor Tissue Analysis (OTTA) consortium coordinating center are summarized below. The nine biomarkers included three hormone receptors as tumor-specific features, which may be associated with prognosis.[204-206] In addition to hormone receptors, other tumor markers reported by OTTA, such as myeloid differentiation primary response gene 88 (MyD88), toll-like receptor 4 (TLR4), folate receptor 1 (FOLR1), CD8+ tumor-infiltrating lymphocytes (CD8+ TILs), p16, and phosphatase and tensin homolog (PTEN), were associated with survival in a histotype-specific way (**Table 1-6**).[207-211]

Table 1-6 Histotype-specific associations between biomarkers and ovarian cancer survival reported by OTTA

Panel A.		**High grade serous cancer**		
	Level	**N (%)**	**HR (95% CI)**	**Confounders**
MyD88 (Block et al., 2018[207])	Weak	712 (26)	ref	Adjusted for study, age (continuous) and stage (I/II, III/IV. Unknown)
	Strong	2064 (74)	**1.13 (1.01-1.26)**	
TLR4 (Block et al., 2018[207])	Weak	734 (29)	ref	Adjusted for study, age (continuous) and stage (I/II, III/IV. Unknown)
	Strong	1788 (71)	1.06 (0.94, 1.18)	
FOLR1	Negative (Abstract/weak)	358 (23.8)	ref	Stratified by study and adjusted for age at diagnosis,

(Köbel et al., 2014[209])	Positive (1-50%, membranous >50%, cytoplasmic 50-95%, and cytoplasmic >95%)	1149 (76.2)	0.99 (0.84, 1.18)	residual disease (not macroscopic, macroscopic, or missing) and FIGO stage (I/II, III/IV or missing)
	Negative (none)	546 (17.1)	ref	
CD8+ TILs (Ovarian Tumor Tissue Analysis et al., 2017[208])	Low (1-2 IEL/40 x HPF)	546 (17.1)	**0.86 (0.75, 0.99)**	Adjusted for study, age (continuous), and stage (I/II, III/IV, unknown)
	Moderate (3-19 IEL/40 x HPF)	1394 (43.6)	**0.77 (0.69, 0.87)**	
	High (20+ IEL/40 x HPF)	710 (22.2)	**0.57 (0.49, 0.65)**	
p16 (Rambau et al., 2018[210])	Heterogeneous	1550 (37.9)	ref	Adjusted for study, age, time interval, stage and residual tumor
	Absent	244 (6.0)	1.06 (0.90, 1.25)	
	Block	2292 (56.1)	1.03 (0.95, 1.11)	
Progesterone receptor (Sieh et al., 2013[204])	Negative	1144 (68.9)	ref	Stratified by site, and adjusted for age, age-squared, and stage (localized, regional, advanced) at diagnosis
	Weak	393 (23.7)	1.02 (0.89, 1.18)	
	Strong	124 (7.5)	**0.71 (0.55, 0.91)**	
Estrogen receptor alpha (Sieh et al., 2013[204])	Negative	326 (19.3)	ref	Stratified by site, and adjusted for age, age-squared, and stage (localized, regional, advanced) at diagnosis
	Weak	347 (20.5)	1.08 (0.89, 1.31)	
	Strong	1018 (60.2)	1.05 (0.89, 1.24)	
PTEN (Martins, 2020[211])	Negative	500 (19)	**0.78 (0.65, 0.94)**	Stratified by site, and adjusted for age, stage, grade and presence of residual disease post-surgery
	Weak	1455 (50)	0.93 (0.81, 1.06)	
	Positive	733 (25)	ref	
	Heterogeneous	177 (6)	0.95 (0.75, 1.21)	

Panel B.	**Low grade serous cancer**			
	Level	**N (%)**	**HR (95% CI)**	**Confounders**
MyD88 (Block et al., 2018[207])	Weak	49 (27)	ref	Adjusted for study, age (continuous) and stage (I/II, III/IV. Unknown)
	Strong	133 (73)	**0.49 (0.29, 0.84)**	
TLR4 (Block et al., 2018[207])	Weak	42 (29)	ref	Adjusted for study, age (continuous) and stage (I/II, III/IV. Unknown)
	Strong	108 (71)	**0.44 (0.21, 0.89)**	
FOLR1 (Köbel et al., 2014[209])	Negative (Abstract/weak)	46 (50.5)	ref	Stratified by study and adjusted for age at diagnosis, residual disease (not macroscopic, macroscopic or missing) and FIGO stage (I/II, III/IV or missing)
	Positive (1-50%, membranous >50%, cytoplasmic 50-95%, and cytoplasmic >95%)	45 (49.5)	1.31 (0.56, 3.07)	
CD8+ TILs	Negative (none)	43 (26.5)	ref	

(Ovarian Tumor Tissue Analysis et al., 2017[208])	Low (1-2 IEL/40 x HPF)	44 (27.2)	0.94 (.50, 1.74)	
	Moderate (3-19 IEL/40 x HPF)	63 (38.9)	0.98 (0.52, 1.83)	Adjusted for study, age (continuous), and stage (I/II, III/IV, unknown)
	High (20+ IEL/40 x HPF)	12 (7.4)	0.92 (0.33, 2.59)	
p16 (Rambau et al., 2018[210])	Heterogeneous	166 (81.4)	ref	Adjusted for study, age, time interval, stage, and residual tumor
	Absent	25 (12.3)	**2.95 (1.61, 5.38)**	
	Block	13 (6.4)	1.54 (0.72, 3.29)	
Progesterone receptor (Sieh et al., 2013[204])	Negative	43 (42.6)	ref	Stratified by site, and adjusted for age, age-squared, and stage (localized, regional, advanced) at diagnosis
	Weak	25 (24.8)	0.53 (0.23, 1.24)	
	Strong	33 (32.7)	**0.39 (0.18, 0.86)**	
Estrogen receptor alpha (Sieh et al., 2013[204])	Negative	13 (12.5)	ref	Stratified by site, and adjusted for age, age-squared, and stage (localized, regional, advanced) at diagnosis
	Weak	17(16.4)	1.18 (0.30, 4.37)	
	Strong	74 (71.2)	0.84 (0.24, 2.92)	
PTEN (Martins, 2020[211])	Negative	131 (12)	1.45 (0.75, 1.79)	Stratified by site, and adjusted for age, stage, grade, and presence of residual disease post-surgery
	Weak	505 (48)	0.86 (0.53, 1.41)	
	Positive	354 (33)	ref	
	Heterogeneous	70 (7)	0.82 (0.32, 2.12)	

Panel C.			**Endometrioid**	
	Level	**N (%)**	**HR (95% CI)**	**Confounders**
MyD88 (Block et al., 2018[207])	Weak	213 (32)	ref	Adjusted for study, age (continuous) and stage (I/II, III/IV. Unknown)
	Strong	447 (68)	0.96 (0.69, 1.34)	
TLR4 (Block et al., 2018[207])	Weak	169 (28)	ref	Adjusted for study, age (continuous) and stage (I/II, III/IV. Unknown)
	Strong	443 (72)	1.00 (0.67, 1.49)	
FOLR1 (Köbel et al., 2014[209])	Negative (Abstract/weak)	398 (70.6)	ref	Stratified by study and adjusted for age at diagnosis, residual disease (not macroscopic, macroscopic, or missing) and FIGO stage (I/II, III/IV or missing)
	Positive (1-50%, membranous >50%, cytoplasmic 50-95%, and cytoplasmic >95%)	166 (29.4)	0.93 (0.57, 1.51)	
CD8+ TILs (Ovarian Tumor Tissue Analysis et al., 2017[208])	Negative (none)	206 (28.3)	ref	Adjusted for study, age (continuous), and stage (I/II, III/IV, unknown)
	Low (1-2 IEL/40 x HPF)	130 (31.6)	0.80 (0.54, 1.18)	
	Moderate (3-19 IEL/40 x HPF)	283 (38.8)	**0.50 (0.34, 0.74)**	

	High (20+ IEL/40 x HPF)	110 (15.1)	0.76 (0.47, 1.23)	
p16 (Rambau et al., 2018[210])	Heterogeneous	650 (77.4)	ref	Adjusted for study, age, time interval, stage, and residual tumor
	Absent	117 (13.9)	0.98 (0.66, 1.45)	
	Block	73 (8.7)	**1.88 (1.30, 2.75)**	
Progesterone receptor (Sieh et al., 2013[204])	Negative	150 (32.6)	ref	Stratified by site, and adjusted for age, age-squared, and stage (localized, regional, advanced) at diagnosis
	Weak	106 (23.0)	**0.61 (0.37, 0.99)**	
	Strong	204 (44.4)	**0.38 (0.22, 0.65)**	
Estrogen receptor alpha (Sieh et al., 2013[204])	Negative	222 (23.4)	ref	Stratified by site, and adjusted for age, age-squared, and stage (localized, regional, advanced) at diagnosis
	Weak	78 (16.4)	**0.47 (0.22, 0.75)**	
	Strong	286 (60.2)	**0.41 (0.26, 0.63)**	
PTEN (Martins, 2020[211])	Negative	2174 (38)	1.58 (0.84, 2.97)	Stratified by site, and adjusted for age, stage, grade, and presence of residual disease post-surgery
	Weak	2240 (39)	1.18 (0.64, 2.17)	
	Positive	1131 (20)	ref	
	Heterogeneous	201 (3)	**3.24 (1.13, 9.26)**	

Panel D.		**Clear Cell**		
	Level	**N (%)**	**HR (95% CI)**	**Confounders**
MyD88 (Block et al., 2018[207])	Weak	250 (41)	ref	Adjusted for study, age (continuous) and stage (I/II, III/IV. Unknown)
	Strong	358 (59)	1.01 (0.77, 1.32)	
TLR4 (Block et al., 2018[207])	Weak	335 (60)	ref	Adjusted for study, age (continuous) and stage (I/II, III/IV. Unknown)
	Strong	226 (40)	1.04 (0.79, 1.38)	
FOLR1 (Köbel et al., 2014[209])	Negative (Abstract/weak)	305 (68.3)	ref	Stratified by study and adjusted for age at diagnosis, residual disease (not macroscopic, macroscopic, or missing) and FIGO stage (I/II, III/IV or missing)
	Positive (1-50%, membranous >50%, cytoplasmic 50-95%, and cytoplasmic >95%)	141 (31.7)	1.15 (0.80, 1.64)	
CD8+ TILs (Ovarian Tumor Tissue Analysis et al., 2017[208])	Negative (none)	309 (47.7)	ref	Adjusted for study, age (continuous), and stage (I/II, III/IV, unknown)
	Low (1-2 IEL/40 x HPF)	141 (17.6)	116 (0.84, 1.60)	
	Moderate (3-19 IEL/40 x HPF)	118 (18.2)	0.88 (0.62, 1.24)	
	High (20+ IEL/40 x HPF)	80 (12.3)	0.92 (0.61, 1.39)	
p16 (Rambau et al., 2018[210])	Heterogeneous	463 (66.8)	ref	Adjusted for study, age, time interval, stage, and residual tumor
	Absent	138 (19.9)	0.67 (0.47, 0.96)	
	Block	192 (13.3)	**2.02 (1.47, 2.77)**	

Progesterone receptor (Sieh et al., 2013[204])	Negative	334 (92.0)	ref	Stratified by site, and adjusted for age, age-squared, and stage (localized, regional, advanced) at diagnosis
	Weak	18 (5.0)	0.81 (0.36, 1.83)	
	Strong	11 (3.0)	1.13 (0.42, 3.02)	
Estrogen receptor alpha (Sieh et al., 2013[204])	Negative	307 (80.6)	ref	Stratified by site, and adjusted for age, age-squared, and stage (localized, regional, advanced) at diagnosis
	Weak	22 (5.8)	1.94 (0.97, 3.88)	
	Strong	52 (13.7)	1.11 (0.64, 1.92)	
PTEN (Martins, 2020[211])	Negative	1462 (32)	0.93 (0.57, 1.52)	Stratified by site, and adjusted for age, stage, grade, and presence of residual disease post-surgery
	Weak	2248 (50)	0.87 (0.54, 1.38)	
	Positive	720 (16)	ref	
	Heterogeneous	70 (2)	1.47 (0.50, 4.34)	

Panel E.	**Level**	**N (%)**	**Mucinous HR (95% CI)**	**Confounders**
MyD88 (Block et al., 2018[207])	Weak	96 (28)	ref	Adjusted for study, age (continuous) and stage (I/II, III/IV. Unknown)
	Strong	249 (7)	1.12 (0.70, 1.79)	
TLR4 (Block et al., 2018[207])	Weak	79 (26)	ref	Adjusted for study, age (continuous) and stage (I/II, III/IV. Unknown)
	Strong	224 (74)	1.54 (0.91, 2.60)	
FOLR1 (Köbel et al., 2014[209])	Negative (Abstract/weak)	171 (88.6)	ref	Stratified by study and adjusted for age at diagnosis, residual disease (not macroscopic, macroscopic, or missing) and FIGO stage (I/II, III/IV or missing)
	Positive (1-50%, membranous >50%, cytoplasmic 50-95%, and cytoplasmic >95%)	22 (11.4)	0.74 (0.26, 2.12)	
CD8+ TILs (Ovarian Tumor Tissue Analysis et al., 2017[208])	Negative (none)	168 (49.0)	ref	Adjusted for study, age (continuous), and stage (I/II, III/IV, unknown)
	Low (1-2 IEL/40 x HPF)	277 (22.4)	0.91 (0.55, 1.51)	
	Moderate (3-19 IEL/40 x HPF)	85 (24.8)	**0.56 (0.34, 0.93)**	
	High (20+ IEL/40 x HPF)	13 (3.8)	0.79 (0.23, 2.68)	
p16 (Rambau et al., 2018[210])	Heterogeneous	163 (43.9)	ref	Adjusted for study, age, time interval, stage, and residual tumor
	Absent	187 (50.4)	1.05 (0.72, 1.55)	
	Block	21 (5.7)	1.28 (0.61, 2.64)	
Progesterone receptor (Sieh et al., 2013[204])	Negative	163 (83.06)	ref	Stratified by site, and adjusted for age, age-squared, and stage (localized, regional, advanced) at diagnosis
	Weak	15 (7.7)	0.69 (0.20, 2.34)	
	Strong	17 (8.7)	1.31 (0.50, 3.45)	
Estrogen receptor alpha	Negative	156 (79.2)	ref	Stratified by site, and adjusted for age, age-squared, and stage
	Weak	10 (5.1)	1.33 (0.34, 5.17)	

(Sieh et al., 2013[204])	Strong	31 (15.7)	0.52 (0.23, 1.21)	(localized, regional, advanced) at diagnosis
PTEN (Martins, 2020[211])	Negative	452 (20)	0.47 (0.20, 1.15)	Stratified by site, and adjusted for age, stage, grade, and presence of residual disease post-surgery
	Weak	881 (39)	1.28 (0.68, 2.39)	
	Positive	808 (36)	ref	
	Heterogeneous	130 (6)	1.60 (0.52, 1.15)	

CD8+ TILs, CD8+ tumor-infiltrating lymphocytes; FOLR1, folate receptor 1; HR, hazard ratio; MyD88, myeloid differentiation primary response gene 88; PTEN, phosphatase and tensin homolog; TLR4, toll-like receptor 4.

Androgen receptor (AR)

Androgen receptor (AR) signaling plays a crucial role in the progression of ovarian cancer.[212,213] OTTA has not published the estimation of the effect of AR on EOC survival. One study in 121 patients showed that AR+ expression was more likely to appear in EC tumors (19%) and then in SC tumors (10%), did not find a statistical significance inverse association between AR expression and overall survival.[214] The Malmö Diet and Cancer Study (MDCS) and Malmö Preventive Project (MPP) cohorts with 90 SC suggested that AR expression could be an independent favorable prognostic factor for SC.[206] The Swedish cohort study with similar percentages of AR+ expression in SC (45%) and EC (42%) found that patients with AR+PR+ tumors presented a better survival and suggested a prognostic role for PR and AR together in ovarian cancer.[205]

Estrogen receptor alpha (ER alpha)

The expression of estrogen receptors (ER alpha and ER beta) was presented in almost all ovarian cancer tumors.[215,216] A meta-analysis found that ER (HR 0.80, 95% CI 0.66-0.95), primarily ER alpha (HR 0.78, 0.62-0.98), was associated with better EOC outcomes.[217] The OTTA study observed that ER alpha was more likely to be expressed in HGSC, LGSC, and EC tumors, but not MC and CC tumors.[204] An improved survival associated with ER alpha expression was observed in patients with EC (**Table 1-6 Panel C**), but not in patients with other histotypes.[204]

Progesterone receptor (PR)

Progesterone receptor (PR) might mediate the protective effects of progesterone on EOC risk.[218] The OTTA study found that PR was more likely to be expressed in LGSC and EC tumors (32.7% and 44.4%, respectively) and rarely expressed in CCC tumors (3.5%).[204] PR+ expression improved survival in patients with HGSC, LGSC, and EC (**Table 1-6 Panel A, B and, C**). [204]

Myeloid differentiation primary response gene 88 (MyD88)

Myeloid differentiation primary response gene 88 (MyD88) was first identified in 1990, involved in signaling within the innate and adaptive immune response.[219,220] The percentages of strong MyD88 expression observed in the OTTA study range from 59% in CCC tumors to 74% in HGSC tumors.[207] Patients with strong MyD88 expression in tumors tended to be with more advanced stage in HGSC patients.[207] Strong MyD88 expression was observed to improve survival in LGSC patients (**Table 1-6 Panel B)** but a worse survival in HGSC patients (**Table 1-6 Panel A)**.[207]

Toll-like receptor 4 (TLR4)

Toll-like receptor 4 (TLR4) plays a fundamental role in the activation of innate immunity.[221] TLR4 was expressed in about 70% of HGSC, LGSC, EC, and MC tumors but only 40% of CCC tumors.[207] There was no difference in clinical features between patients with weak expression and strong expression in HGSC patients.[207] Strong TLR4 expression was observed to associate with improved survival in LGSC patients only.[207]

Folate receptor 1 (FOLR1)

Folate receptor 1 (FOLR1) helps regulate the transport of the B-vitamin folate into cells, which participates in the production and repair of DNA.[222,223] The OTTA study observed absent or weak TOLR expression in MC (88.6%), EC (70.6%), and CCC (68.3%) tumors.[209] Although a

null association between FOLR1 expression and overall survival by histotype was observed, FOLR1 positive expression was associated with improved survival in the first two years in HGSC patients.[209]

CD8+ tumor-infiltrating lymphocytes (CD8+ TILs)

CD8+ tumor-infiltrating lymphocytes (CD8+ TILs) play the main role in killing cancer cells.[224,225] CD8+ TILs were presented from 51% of MC tumors to 83% of HGSC tumors.[208] A dose-response association between CD8+ TILs and survival was observed in HGSC patients (**Table 1-6 Panel A**).[208] Moderate CD8+ TILs were also associated with improved survival in EC and MC patients compared to negative CD8+ TILs (**Table 1-6 Panel A, C and E**).[208]

p16

p16 is a tumor suppressor, which regulates the progression of the cell cycle from the G1 phase to the S phase.[226] HGSC tumors were more likely to be with block p16 expression, while MC tumors were more likely to be with absent p16 expression.[210] The OTTA study showed that compared to heterogeneous p16 expression, absent p16 expression was associated with worse outcomes in LGSC patients (**Table 1-6 Panel B**), while block p16 expression was associated with worse outcomes in EC patients and CCC patients (**Table 1-6 Panel C** and **Panel D**).[210]

Phosphatase and tensin homolog (PTEN)

Phosphatase and tensin homolog (PTEN) is a protein helping to regulate cell division coded by the tumor suppressor gene PTEN.[227,228] The OTTA study observed that MC tumors and LGSC tumors tended to be cytoplasmic PTEN positive and EC tumors with no nuclear PTEN expressed.[211] Cytoplasmic PTEN loss was associated with improved survival in HGSC patients and heterogeneous cytoplasmic PTEN expression was associated with worse survival in EC patients compared to cytoplasmic PTEN positive expression.[211] The OTTA study also indicated

that PTEN loss was associated with hormone receptor expression and CD8+ TILs in HGSC and CCC tumors.[211]

1.3.3 Epidemiologic factors

The associations of potential epidemiologic factors with survival are summarized in the following session. The difference between the epidemiologic factors associated with ovarian cancer risk and survival is compared in **Table 1-7**.

Table 1-7 The difference of epidemiologic facotrs asscoaited with ovarian cancer risk and survival

Factors	Risk	Worse survival
Demographic		
Body mass index	+	+
Reproductive and hormonal		
Age at menarche	0	?
Age at menopause	+	?
Lifetime ovulatory years	+	?
Parity	--	-
Breastfeeding	--	0
Oral contraceptive use	--	?
Hormone replacement therapy	+	?
Gynecologic		
Tubal ligation	-	0
Hysterectomy	0	0
Endometriosis	++	--
Lifestyle		
Physical inactivity	+	?
Smoking	0	+

Strongly Positive (++), positive (+), null (0), inverse (-), strongly inverse(--) unknown (?)

Body mass index

An inverse association between BMI and survival in ovarian cancer patients was observed by the OCAC study that included 21 studies (pooled HR 1.03 per 5 kg/m^2 increase, 95% CI 1.00-1.07), [229] and a systematic review and met-analysis pooling 14 studies (pooled HR 1.17, 95% CI 1.03-1.32 comparing obese to non-obese women).[230] A systematic review and meta-analysis also

found the same association between obesity in early adulthood and ovarian cancer survival (HR 1.60, 95% CI 1.10-2.34 comparing women with overweight to obesity women with normal weight or underweight).[231] Regarding the histotype-specific association, a significant association for HGSC was observed (pooled HR 1.04 per 5 kg/m^2 increase , 95% CI 1.00-1.09) and no association was observed for MC and CCC.[229] The inverse associations for EC (pooled HR 1.08per 5 kg/m^2 increase, 95% CI 0.95-1.23) and LGSC (pooled HR 1.12 per 5 kg/m^2 increase, 95% CI 0.96-1.31) did not reach significance.[229]

Age at menarche, age at menopause and lifetime ovulatory years

The association between age at menarche and EOC survival is not consistent. The Cancer and Steroid Hormone study in 1980 to 1982 suggested that older age at menarche was associated with better survival in ovarian cancer patients (HR at 5 year, 10 year and 15-year survival 0.63, 0.53, 0.46 comparing age at menarche >=14 to <12, respectively).[232] However, the New England Case-Control study found that older age at menarche was associated with worse survival (HR for overall survival 1.24 and 1.24 comparing >13 years, 13 years to <13 years, respectively).[233] Results from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort from 1992 – 2010 suggested that early age at menarche was not associated with overall survival of invasive EOC, but with poorer survival of CCC (HR for overall survival 0.52 and 0.40 comparing >=15 and 14 years to <13 years, respectively).[234] The same association was also observed for HGSC.[233] The New England Case-Control study also observed that older age at menopause was associated with poorer survival for overall ovarian cancer (HR 1.23, 95% CI 1.03-1.46) and the combination of EC and CCC (HR 2.45, 95% CI 1.33-4.50).[233] The same association was observed by the EPIC cohort for EC and CCC separately.[234]

The association between LOCs/LOYs and EOC survival was controversial.[232,235-237] Two studies indicated that larger LOCs/LOYs was associated with worse EOC survival.[232,235] Results from the NHS and NHS II showed that LOYs was associated with a higher hazard of death among patients with positive ADRB2 (HR 1.60, 95% CI 1.15-2.21) but not statistically significantly associated with hazard of death among negative ADFRB2 (HR 1.11, 95% CI 0.96-1.27).[236] In contrast, the results from 1421 ovarian cancer patients in Ontario, Canada showed that larger LOC was associated with improved survival (compared LOC >436.42 to <=322.28 HR 0.63, 95% CI 0.43-0.94).[237]

Parity

Some studies found a non-significant association between parity and improved survival,[233,238-240] while two more recent studies found that parity was associated with improved survival (**Table 1-7**).[237,241] The results pooling fours studies found that parity was associated with better outcomes in less aggressive cases.[242] One EPIC cohort study from 1992 to 2010 found that ever full-term pregnancy was associated with improved survival in patients with SC (HR0.73, 95% CI 0.58-0.92), MC (HR 0.53, 95% CI 0.30-0.95), and CCC (HR 0.34, 95% CI 0.18-0.64), but not with EC (HR 0.65, 95% CI 0.40-1.06).[234] However, the number of children was associated with improved survival in patients with CCC (HR 0.37, 0.32, 0.33 for 1, 2, 3+ children vs. no, respectively; p for trend 0.01).[234]

Table 1-8 Summary of effects of parity on ovarian cancer survival in studies reporterd after 2010

Study (Country)	Number of cases	Exposure of interest	Conclusion	Confounders
Zhang, 2012[239] (China)	195	Number of full-term pregnancy (0, 1, 2+)	Null association	age at diagnosis (in years, continuous), body mass index (BMI) (continuous), menopausal status (no, yes), International Federation of Gynecology and Obstetrics (FIGO) stage (I, II, III, and IV), histopathological grade (well, moderately, poorly differentiated, not available), ascites (no, yes), chemotherapy status (no, yes)

Poole, 2013[242] (NHS, AARP and NECC in U.S. and AOCS in Australia)	2934	Ever vs. never; Per 1 child increase	An improved survival in case that did not die of ovarian cancer within 3 years	age, parity, duration of breastfeeding, duration of oral contraceptive use, tubal ligation, family history of ovarian cancer, and menopausal status. AARP models adjusted for age, parity, duration of oral contraceptive use, and menopausal status
Bešević, 2015[240] (EPIC in Europe from 1992 - 2000)	1025	Yes vs. no; Number of full-term pregnancy (1, 2, 3+)	Null association	age at diagnosis (continuous), year of diagnosis (continuous), BMI (<23 kg m−2, ⩾23–<25 (reference), ⩾25 –<30, ⩾30), tumor stage (local (reference), regional, metastatic, and unknown), smoking status (never (reference), former, current and unknown) and stratified by study center
Fortner, 2015[234] (EPIC in Europe from 1992 - 2010)	664	Yes vs. no; Number of full-term pregnancy (1, 2, 3+)	An improved survival in type I comparing yes vs. no; An improved survival in type I and type II comparing number of full-term pregnancies	age at recruitment and study center and adjusted for ever full-term pregnancy, ever OC use, menopausal status at recruitment, age at menopause, and ever HRT use.
Shafrir, 2016[233] (NECC in U.S.)	1649	Parous vs. nulliparous; Number of children (nulliparous, 1-2, 3-4, 5+)	Null association	age at diagnosis, year of diagnosis, study center (NH, MA), menopause status (pre, post, uncertain), smoking status (never, current, former), parity (ever, never), OC use (ever, never), BMI (kg m−2), disease stage (I/II, III/IV), grade (1, 2, 3, missing), histology (serous, endometrioid, mucinous, clear cell, other), debulking status (not optimal, optimal, unknown), and chemotherapy (no chemotherapy, platinum+taxol, other chemotherapy, unknown chemotherapy type)
Kim, 2017[237] (Canada)	1421	Parous vs. nulliparous; parity as continuous among parous women	An improved survival compared parous vs. nulliparous; null association with parity as a continuous variable	age at diagnosis (continuous), histology (serous, mucinous, endometrioid, clear cell, other), stage (I, II, III, IV), and residual disease (no residual disease, any residual disease)
Khalafi-Nezhad, 2020[241] (Iran)	385	Parity (0, 1, 2-5, 5+)	An improved survival	Stratified by age, adjusted for marriage status (single, married), stage (early stage, advanced stage), histology (serous, mucinous, endometrioid, other types)

AARP, the NIH-AARP Diet and Health Study; AOCS, the Australian Ovarian Cancer Study; EPIC, the European Prospective Investigation into Cancer and Nutrition cohort; NECC, the New England Case-Control study; NHS, the Nurses' Health Study; SD, standard deviation.

Breastfeeding

A null association between breastfeeding and survival was observed in several studies.[233,237,239,240] However, the study pooling the NHS, AARP and NECC in U.S. and AOCS in Australia found that breastfeeding was associated with better outcomes among parous women in

both rapidly fatal cases and less aggressive cases.[242] There was no association observed between breastfeeding and survival by histotype.[234]

Oral contraceptive use

Most studies suggested a null association between OC use and ovarian cancer survival.[233,234,237,239,240,243] The study pooling the NHS, AARP and NECC in U.S. and AOCS in Australia observed that OC use was associated with improved survival in rapidly fatal cases (HR 0.69 per 5-year increase, 95% CI 0.58-0.82).[242] While, the results from two EPIC studies regarding to the association between duration of OC use and survival were opposite.[234,240] One EPIC study from 1992 to 2000 suggested that a longer duration of OC use was associated with poorer survival (HR 0.98, 1.26, 1.74 comparing >1-<=5 years, >5-<=10 years, >10 years to <=1 years; p for trend 0.01) and no associated with survival for SC.[240] The other EPCIC study from 1992 to 2010 suggested that longer duration of OC use had a protective effect on the risk of death for all invasive EOC (HR 0.96, 0.88, and 0.57 comparing 2-4 years, 5-9 years, and >=10 years to <=1 year; p for trend <0.01), SC (HR 0.96, 0.88, and 0.57 comparing 2-4 years, 5-9 years, and >=10 years to <=1 year; p for trend <0.01), EC (HR 0.96, 0.88, and 0.57 comparing 2-4 years, 5-9 years, and >=10 years to <=1 year; p for trend <0.01) and CCC (HR 0.96, 0.88, and 0.57 comparing 2-4 years, 5-9 years, and >=10 years to <=1 year; p for trend <0.01).[234]

Hormone replacement therapy

A null association between HRT use and survival was observed by several studies.[233,234,237,239,244] While, one EPIC study from 1992 to 2000 found that a longer duration of HRT use was associated with improved survival for EOC (HR 0.70 comparing users with >=5 years to no-users, 95% 0.50-0.99), and SC (HR 0.55 comparing users with >=5 years to no-users, 95% CI 0.35-0.87).[240] Regarding the histotype-specific associations, the EPIC study from 1992 to

2010 found that HRT use was associated with poorer survival of SC (HR 1.27, 95% CI 1.01-1.60) and EC (HR 1.797, 95% CI 1.07-3.01).[234]

Tubal ligation and hysterectomy

Overall, tubal ligation or hysterectomy was not associated with ovarian cancer survival.[233,234,237,242] Only one study conducted in southeast China observed that tubal ligation was associated with worse outcomes (HR 1.62, 95% CI 1.01-2.59).[239]

Endometriosis

One meta-analysis showed that endometriosis was significantly associated with improved survival in patients with ovarian cancer (HR 0.74, 95% CI 0.63-0.87)[245] and another meta-analysis suggested a null association.[246] A recent study including 32,419 patients from the Netherlands Cancer Registry also observed that patients with endometriosis had a significantly better prognosis (HR 0.89, 95% CI 0.83-0.95).[247] Patients with endometriosis were more likely to had more favorable tumor characteristics, such as early stage and less aggressive histotype.[246-248]

Physical activity

A literature review summarized the association between physical activity and ovarian cancer survival.[249] Three studies have estimated the association, but all used different measurements on self-reported physical activity.[250-252] Therefore, although the three studies suggested that physical activity appeared to benefit ovarian cancer survival, the literature review reserve the opinion to draw a meaningful conclusion.[249]

Smoking

Most studies suggested that smoking was associated with poorer survival in ovarian cancer patients.[237,253-256] While, a study pooling the NHS, AARP and NECC in U.S. and AOCS in Australia and a study in Sweden did not observe an association between smoking and ovarian

cancer survival.[242,250] The OCAC study, which observed a significant adverse association for SC (HR 1.11 comparing current smokers to never smokers, 95% CI 1.00-1.23) and MC (HR 1.91 comparing current smokers to never smokers, 95% CI 1.01-3.65), suggested a heterogeneity on the histotype-specific associations.[253] The data from the Alberta Cancer Registry in patients with neoadjuvant chemotherapy only observed the adverse association between smoking and survival for MC (HR 8.56 comparing current smokers to non-smokers, 95% CI 1.50-48.7), but no other histotype.[257]

1.4 Hypothesis of epithelial ovarian cancer development

1.4.1 Origins of epithelial ovarian cancer

Accumulating evidence suggested that the origins of EOC varies by histotype (**Table 1-8**). High-grade serous and low-grade serous tumors mainly originate from the fallopian tube and then the abnormal cells spread to the ovaries.[258-260] Endometrioid and clear cell tumors are suggested to originate from the endometrium.[11,260] Unlike serous, endometrioid and clear cell tumors, the origin of mucinous tumors is not clear. Mucinous tumors might arise from the ovaries or fallopian tube-peritoneal junction, teratomas or Brenner rumors, or other sources.[11,260] To some extent, the histotype-specific origins of EOC could explain the heterogeneity of risk factors by histotype. This underscores the need to study by histotype the biologic mechanisms underlying EOC, which would enable developing more targeted histotype-specific prevention and treatment strategies.

Table 1-9 The potential origin of five main histotypes of epithelial ovarain cacner

	Histotype	**Origins**
Type II	High-grade serous	The fallopian tube
Type I	Low-grade serous	The fallopian tube
	Endometrial	The endometrium
	Clear cell	The endometrium
	Mucinous	The ovaries or fallopian tube-peritoneal junction; or, teratomas or Brenner tumors

1.4.2 "Incessant ovulation" hypothesis

The "incessant ovulation" hypothesis in EOC, which was first proposed by Fathalla, 1971 and has been widely accepted, proposes that ovulation is associated with disruption and subsequent repair of the ovarian epithelium and further leads to genetic damage in an ovarian epithelial cell.[261] Therefore, the longer ovulation is suppressed, the lower the risk of EOC. The hypothesis was supported by an animal model of laying hens, which was considered the most appropriate animal model for studying human ovarian cancer compared to primates or rodents.[262-264] The 2-year-old hens were at the same reproductive as middle-aged women that developed spontaneous ovarian cancer at high incidence rates.[265,266] The hypothesis is supported by epidemiologic studies in humans, such as the protective effect of parity and OC use on EOC.[267,268] However, based on the hypothesis, the risk of EOC should only rely on the lifetime ovulation numbers regardless of the cause of anovulation. The hypothesis might be too simplistic since anovulation alone cannot explain the magnitude of the protective effect and considering other risk factors with no such apparent association with ovulation.[269]

1.4.3 Hormonal hypothesis

As mentioned before, ovulation alone cannot explain the magnitude of the protective effects from these exposures. Hormones, such as gonadotrophin, androgen, estrogen, and progesterone, may also play a role in ovarian carcinogenesis. The four main hormonal hypotheses for ovarian carcinogenesis were summarized in the following session.

1.4.3.1 Gonadotropin hypothesis

The gonadotropin hypothesis is the first hormonal hypothesis for ovarian carcinogenesis proposed by Cramer and Welch in 1983.[270] It postulates that excessive gonadotropin exposure increases stimulation by estrogen or estrogen precursors, which further causes proliferation and malignant transformation of ovarian surface epithelium (OSE) cells.[269,270] The hypothesis is supported by the protective effect of parity and OC use, which reduces gonadotropin secretion.[271] However, the hypothesis cannot explain the lack of increase in risk due to early age at menopause, although gonadotropin levels increase typically after menopause.[272] One study observed the association between low serum gonadotropin levels and an increased risk of ovarian cancer, which was conflicted with the hypothesis.[273]

1.4.3.2 Androgen hypothesis

The androgen hypothesis proposes that excess androgen stimulation of ovarian cancer leads to an increased risk of EOC.[269] The increased cell proliferation of normal OSE cells after androgen administration was observed by *in vitro* studies[274,275] and by an animal model of guinea pigs.[276,277] The hypothesis is supported by some epidemiologic evidence, such as the protective factor of OC use (which recued androgen level[278]), and the risk factors of obesity (associated with androgen dysregulation[279]). Moreover, the findings from the studies that directly estimated the association between androgen level and risk of ovarian cancer support the hypothesis.[273,280]

1.4.3.3 Estrogen hypothesis

Estrogen is associated with an increased risk of EOC but may not play such an essential etiologic role as androgen in the overall ovarian carcinogenesis.[269] An animal study observed that estrogenic hormones induced bilateral serous ovarian cysts in guinea pigs.[277] Epidemiologic

evidence supporting the estrogen hypothesis includes the protective factor of OC use (which is associated with a decreased level of estrogen[281,282]), and the risk factor of HRT use (which increased both plasma and serum estradiol level[283,284]).

Epidemiologic evidence shows that the role of estrogen in the development of ovarian cancer varies by histotype. Estrogen could play an etiologic role in the development of endometrioid and clear cell tumors.[285] Endometriosis, associated with a high level of estrogen, is consistently associated with an increased risk of EC and CCC.[286] While, smoking, which is not directly associated with estrogen level but alters the mentalism of estradiol, so-called as an antiestrogenic effect,[287] has an opposite impact on CCC and MC.

1.4.3.4 Progesterone hypothesis

Progesterone might protect against the development of ovarian cancer proposed by Risch, 1998.[269] One of the epidemiologic evidence supporting this hypothesis is the beneficial effect of twin pregnancies,[288] which was associated with higher progesterone levels compared to singleton pregnancies.[289,290] Moreover, epidemiologic evidence from studies observed that the estrogen-progestin HRT users had a reduced risk of ovarian cancer than estrogen-only HRT users.[291,292]

Progesterone might play a histotype-specific role in the development of ovarian cancer. As mentioned before, endometriosis is a risk factor for CCC and EC, which could impact progesterone levels. Endometriosis leading to progesterone resistance, which refers to “disrupts coordinated progesterone responses throughout the reproductive tract,” lessen the protective effects of progesterone.[293]

1.4.4 Inflammation hypothesis

The inflammation hypothesis proposes that inflammation underlying ovulatory events may induce mutagenic effects via cell damage and repair, oxidative stress, and elevated cytokines and prostaglandins, and further contribute to the development of ovarian cancer.[294] The role of inflammation was studied to complete the explanations for the ovarian carcinogenesis that cannot be stratified by the "incessant ovulation" hypothesis or the hormonal hypothesis.[294-296] Accumulating epidemiological studies have linked the exposure related to inflammatory factors to ovarian cancer risk, including smoking, talc use, pelvic inflammatory disease and endometriosis.[16,29-31,297,298] Moreover, the epidemiologic studies estimating the association of the inflammatory markers, such as tumor necrosis factor-alpha (TNF-α), C-reactive protein (CRP), and interleukin 6 (IL6), and ovarian cancer directly, provide more intuitive evidence supporting this hypothesis and future the knowledge of the role of inflammation in ovarian carcinogenesis.[299-302]

2.0 Specific Aims

2.1 Summary and research gaps

Ovarian cancer is the most lethal gynecologic cancer. The exact mechanism of ovarian cancer development remains unknown. The protective effects of parity and OC use support the "incessant ovulation" hypothesis.[261,267] However, anovulation alone cannot explain the magnitude of the protective effect. Hormonally-linked risk factors appear to play a role in EOC risk. OC use is not only associated with suppressed ovulation but also associated with altered hormonal milieus.[281,282,303] History of endometriosis, which is associated with excess estrogen and reduced progesterone, is associated with endometrioid ovarian cancer risk.[286] The "hormone" hypothesis proposes that ovarian epithelium's excess androgen stimulation leads to an increased risk of EOC, whereas progesterone simulation has a protective effect on EOC.[269] Estrogen is associated with an increased risk of EOC but may not play such as essential an etiologic role as androgen.[269] Moreover, the "inflammation" hypothesis was proposed in light of immunological and genetic studies.[296] Smoking, which is associated with increased inflammatory markers,[298] is associated with an increased risk of mucinous ovarian cancer but not associated with other histotypes.[34]

Increasing evidence indicated that risk factors of EOC vary by histotypes. Risk factors have multifaceted effects on ovulation, hormonal milieu, and inflammation. The discrepancies of risk factors associated with multiple hypotheses and EOC histotypes complicates identifying possible mechanisms underlying EOC etiology. LOYs calculated from the components related to ovulation, hormones, and inflammation might provide insight into the etiology of ovarian cancer. However, published studies do not have enough power to explore the association of LOYs by histotypes.

Exploring the association of LOYs by histotypes could improve our knowledge of potential mechanisms. Furthermore, the role of hormone receptors in ovarian cancer risk and survival is unclear. Understanding the relationship between hormonally-linked risk factors and EOC defined by tumor hormone receptors could further increase insight into EOC development and outcome. Finally, there is no study to predict clinical outcome and survival based on tumor biology. To date, there have been no studies evaluating prediction models of EOC survival. Developing such models could provide further insight into tumor behavior and identify potential targets for improving survival. The knowledge regarding these research gaps can inform future interventions of EOC.

2.2 Specific research questions

This dissertation consists of three manuscripts with the following specific aims:

Specific Aim I: To evaluate the association between lifetime ovulatory years and risk of epithelial ovarian cancer.

Hypothesis: The number of lifetime ovulatory years is positively associated with the risk of epithelial ovarian cancer.

Specific Aim IIa: To evaluate the association between hormonally-linked EOC risk factors and EOC tumors defined by hormone receptor status of androgen receptor (AR), estrogen receptor (ER), and progesterone receptor (PR).

Hypothesis i: Hormonally-linked risk factors are associated with the risk of EOC tumors defined by AR, ER, and PR.

Specific Aim IIb: To estimate survival of EOC patients with tumors defined by hormone receptor status of AR, ER, and PR.

Hypothesis ii: EOC Survival differs by hormone receptor status of AR, ER, and PR.

Specific Aim IIc: To evaluate the association of hormonally-linked risk factors with survival of EOC patients by tumors defined by hormone receptor status of AR, ER, and PR.

Hypothesis iii: Hormonally-linked risk factors are associated with survival of EOC patients by tumors defined by AR, ER, and PR.

Specific Aim III: To build a predictive model for long-term survivors of epithelial ovarian cancer using machine learning techniques.

3.0 Paper I: Lifetime ovulation years and risk of epithelial ovarian cancer: a multinational pooled analysis of 25 case-control studies from the Ovarian Cancer Association Consortium

3.1 Abstract

Introduction: The "incessant ovulation" hypothesis for epithelial ovarian cancer (EOC) is widely accepted and supported by the protective effect of parity and oral contraceptive use for EOC. However, anovulation alone cannot explain the magnitude of the protective effect. The current study explored the association between lifetime ovulatory years (LOYs) and its component parts with EOC risk.

Method: LOYs were calculated using 15 algorithms by subtracting years of anovulation from menstrual span. Anovulatory years was algorithm-specific and included diverse calculations for pregnancy, oral contraceptive, and breastfeeding duration. The pairwise correlations of LOYs algorithms and the correlations of the individual components and the corresponding algorithms were compared using Pearson's correlations. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using multivariable logistics regression to estimate the association between LOYs and EOC risk among 26,204 cases and 21,267 controls from 25 case-control studies. ORs and 95% CIs were also calculated to estimate the association between the individual components and EOC risk. Chi-square and P-value were obtained from the likelihood-ratio test for the removal of each component from the full model. The same analyses were conducted for EOC histotype-specific associations.

Results: The highest quartiles of LOYs were significantly associated with increased EOC risk compared to the corresponding lowest quartiles (ORs ranged from 1.24 with 95% CI 1.16-1.34 to 2.39 with 95% CI 2.23-2.56). The individual components comprising LOYs, except age at menarche, were significantly associated with EOC risk. The relative estimated coefficients for the components were larger than the theoretical estimates indicting that the "incessant ovulation" hypothesis alone does not explain the protective effects of the components on EOC risk. LOYs per year increase was significantly associated with risks of invasive high-grade serous, endometrioid, and clear cell histotypes (ORs 1.048, 1.067, and 1.108, respectively), but not mucinous or low-grade serous cancers. The relative estimated coefficients of the individual components varied by histotypes.

Conclusion: LOYs are positively associated with overall EOC risk and risk of invasive high-grade serous, endometrioid, and clear cell histotypes. The mechanism of carcinogenesis for the individual components in LOYs and the histotype-specificity should be further investigated.

3.2 Introduction

Ovarian cancer is the most lethal gynecologic cancer. About 13,770 women will die from ovarian cancer in 2021 in the U.S..[304] Epithelial ovarian cancer (EOC) accounts for nearly 90% of ovarian cancer.[1] About 80% of EOC are diagnosed at Stage III or IV, and the 5-year survival for these women is less than 40%.[1] Lifetime ovulatory years (LOYs) calculated from the components related to ovulation, hormone levels and inflammation might be an etiologic factor for ovarian cancer.[25,97,305] Estimating the association between LOYs and risk of EOC in general and by histotypes can improve our knowledge of the mechanism.

A higher number of LOYs is associated with the risk of EOC.[18,25,50,60,82,83,99,103,104] One of the leading hypotheses behind the association is the "incessant ovulation" hypothesis, which proposes that ovulation is associated with disruption and subsequent repair of ovarian epithelium and further leads to genetic damage to ovarian epithelial cells.[261,268] However, it is now widely accepted that the different histotypes of EOC derive from tissue other than the ovarian surface epithelium, with the most common histotype, high-grade serous cancers, believed to arise mostly from the fallopian tube.[260,306] Possible mechanisms underlying the effect of LOY may be the altered hormone levels associated with ovulation[82,269] or the increased pro-inflammatory milieu.[296,307] Risch et al. proposed the "hormone" hypothesis when exploring the magnitude of the protective effect of the individual components in LOYs on EOC risk, such as oral contraceptive (OC) use, lactation, and parity.[82] However, while a handful of studies have suggested LOYs might be associated with only specific EOC subtypes (5-9), no study has explored the magnitude of the effect of the individual components in LOYs by histotype. The data are further complicated by lack of consistency across studies in defining LOYs.

In the current study, LOYs were calculated from 15 algorithms using data from the Ovarian Cancer Association Consortium (OCAC). The main aim of this study was to assess the effects of LOYs and its individual components on risk of EOC in general and by histotypes.

3.3 Method

Study population

OCAC was founded in 2005 to foster collaborative efforts in discovering and validating associations between genetic polymorphisms and ovarian cancer risk.[308] The current study included 25 case-control studies conducted in Australia, Canada, China, Germany, Japan, Netherlands, Poland, the United Kingdom, and the United States.[55,113,125,309-332] Studies were excluded if more than fifty percent of the values for age at menarche and the number of pregnancies were missing. Characteristics of the included studies are presented in **Table 3-1**. Cases were mostly identified from the hospital, local or national cancer registry, and national surveillance. Controls were identified from patients from the same hospital without ovary cancer, population-based recruitment, or the same cohort study. All participants provided informed consent. Study protocols were approved by the respective Institutional Review Board for each site.

Study variables

LOYs were calculated using 15 algorithms identified from previous studies (**Supplemental Table 3-1**). The basic formula to calculate LOYs:

$$LOY = menstrual\ span - \ years\ of\ anovulation$$

where "menstrual span" was calculated from age at last menstrual period (LMP) before diagnosis (cases) or interview (controls) minus age at menarche. The 15 algorithms were divided into 4 broad classes based on how "years of anovulation" was defined (**Figure 3-1**). The first class (Algorithms A-D) only used data on pregnancies to calculate years of anovulation. The second class (Algorithms E-H) included a term for OC used. The third class (Algorithm I-L) expanded the second class algorithms by adding a term for duration of breastfeeding. Finally, the fourth class (Algorithms M-O) adjusted LOYs from algorithms J-L for average cycle length. Information on

the components of LOYs calculation, including age at LMP before diagnosis or interview, age at menarche, number of pregnancy (regardless of outcomes), number of full-term births, duration of being pregnant, duration of breastfeeding, and duration of OC use, was obtained from the OCAC core dataset.

Age at LMP before diagnosis (cases) or interview (controls) were assigned using age at hysterectomy, age at first hormone replacement therapy (HRT) use, and the published average age at menopause by country [333-337] based on the following criteria (**Figure 3-2**):

- *For participants without hysterectomy or HRT use, use the minimum of age at diagnosis (cases) or interview (controls) and the average age at menopause by country.*
- *For participants with hysterectomy or HRT use only, use the age at hysterectomy or first HRT use if it is larger than the average age at menopause by country; otherwise, use the minimum of age at diagnosis (cases) or interview (controls) and the average age at menopause by country.*
- *For participants with hysterectomy and HRT use, use minimum of age at hysterectomy and age at first HRT use if it is larger than the average age at menopause by country; otherwise, use the minimum of age at diagnosis (cases) or interview (controls) and the average age at menopause by country.*

Data on age at LMP before diagnosis (cases) or interview (controls) were obtained from seven sites: CON, DOV, HOP, NEC, POL, SON, and TOR. Sensitivity analyses were conducted comparing data on age at LMP before diagnosis (cases) or interview (controls) from these sites to the assigned age at LMP using the above algorithm. To deal with potential errors, data on age at LMP less than 40-year-old and less than the age at hysterectomy or age at first HRT use were reassigned as the larger number of age at diagnosis (cases) or (interview) and the average age at

menopause by country. Missing values were assigned using the same criteria. The comparisons of observed and assigned values in age at LMP are shown in **Supplemental Table 3-2**.

OCAC sites with more than 50% of missing values[338,339] in any component of LOYs algorithms by case-control status, except age at LMP before diagnosis (cases) or interview (controls), were excluded from the LOYs calculation for those algorithms. The percentage of missing values in the components of LOY by study sites and case/control status are shown in **Supplemental Table 3-3**. Other relevant variables from the OCAC core dataset included age at diagnosis (cases) or interview (controls), race (white, black, Asian, other, or unknown), body mass index (BMI) 1-year or 5-year prior (<18.5, 18.5-24.9, 25-29.9, >=30 kg/m^2, or unknown), family history of ovarian or breast cancer (yes, no, or unknown), smoking status (never, current, former, or unknown), history of endometriosis (yes, no, or unknown), and tubal ligation (yes, no, or unknown).

Statistical analysis

$\chi 2$ test was used to compare categorical variables and student's t-test was used to compare continuous variables by case-control status. The pairwise correlations of LOYs calculated from the different algorithms and the correlations of the individual components and the corresponding algorithms were computed using Pearson's correlations using participants with complete data. Quartile categories for each LOY were determined based on the distribution among the controls with complete data. Multivariable logistic regression was used to estimate odds ratios (ORs) and their 95% confidence intervals (95% CIs) for the association between LOYs and EOC risk. The main multivariate model was adjusted for study site, age at diagnosis (cases) or interview (controls) (continuous), BMI 1-year or 5-year prior (<18.5, 18.5-24.9, 25-29.9, >=30 kg/m^2, or unknown), smoking status (never, former, current, unknown) and family history (yes, no, unknown). The

associations between LOYs calculated from the first class of algorithms (Algorithms A-D) and EOC risk were additionally estimated by the model further adjusted by the duration of OC use (continuous). The associations between LOYs calculated from the second class of algorithms (Algorithms E-H) and EOC risk were additionally estimated using the maximum of 6 months and duration of breastfeeding per episode multiplied by number of live births to calculated LOYs. Sensitivity analyses were performed with multivariable logistic regression with multiple imputation by chained equation (MICE) to assess the effect of missing values on the association between LOYs and EOC risk.[340] Nested imputations were done for the number of pregnancies, the number of full-term births, duration of breastfeeding, and duration of OC use using the binary variables of being pregnant, breastfeeding, and OC use. Imputations were done 5 times with auxiliary variables defined as the Pearson's correlation larger than 0.4.[341] The imputation model included the same variables as the main models.

The associations of each component in LOYs and EOC risk were estimated using logistic regression adjusted for study site, age at diagnosis (cases) or interview (controls) (continuous), BMI 1-year or 5-year prior (<18.5, 18.5-24.9, 25-29.9, >=30 kg/m^2, or unknown), smoking status (never, former, current, unknown), family history (yes, no, unknown) and other components in LOYs. Based on the "incessant ovulation" hypothesis, the theoretical estimates of coefficients for age at menarche per year, OC use per year, number of non-full-term pregnancies, number of full-term births, and breastfeeding per year should be -1, -1, -0.25, -0.75 and -1 time greater than relative the coefficient of the age at LMP per year, respectively. The relative estimates of coefficients, defined as the estimated coefficients divided by the estimated coefficient of age at LMP, were reported and compared with the theoretical estimates of the coefficients. Chi-square statistics and p-values were obtained from the likelihood-ratio test for the removal of each

component from the full model. The associations of LOYs and the components in LOYs with EOC risk by the histotypes were also estimated by multivariable logistic regression adjusted for the same covariates. All statistical tests were two-sided with a significance level of 5%. Statistical analyses were performed in Stata/SE version 16.1 (StataCorp, College Station, TX).

3.4 Results

Description of participants

There were 26,204 cases and 21,267 controls from 25 case-control studies in the current study (**Table 3-2**). Compared to controls, women with EOC were more likely to be former or current smokers, have a family history of breast or ovarian cancer, and report a history of endometriosis. Cases also had a shorter duration of OC use and breastfeeding, as well as fewer pregnancies. Among 26,204 cases, there were 10,423 invasive high-grade serous ovarian cancer (HGSOC), 513 invasive low-grade serous ovarian cancer (LGSOC), 2,536 endometrioid ovarian cancer, 1,134 mucinous ovarian cancer, and 1,310 clear cell ovarian cancer.

Calculation of lifetime ovulatory years

The distribution of LOYs calculated from the 15 algorithms by case-control status was presented in **Figure 3-3** and **Supplemental Table 3-4**. The medians of LOYs ranged from 31.36 years in Algorithm O to 35.75 years in Algorithm B and D. The pairwise correlations of LOYs ranged from 0.69-0.71 between the algorithms in the first class (Algorithm A-D) and the fourth class (Algorithm M-O) to ≥0.98 for pairwise correlations for LOYs within the same class (**Supplemental Table 3-5**). Correlations for LOYs within the most complicated class of algorithms, Algorithm M-O, were close to 1. Correlations between the individual components and the corresponding LOYs are presented in **Supplemental Table 3-6**. As the algorithm complexity increased, the correlations between age at LMP and the LOYs decreased. Duration of OC use was moderately negatively correlated with LOYs (rho ranged from -0.60 to-0.68) but the correlations between the other components and the LOYs were low.

Estimation of EOC risk related to LOY and individual components

The ORs of LOYs per year increase for EOC risk ranged from 1.019 (95% CI 0.014-0.024) in Algorithm B to 1.045 (95% CI 1.042-1.048) in Algorithm E and Algorithm G (**Table 3-3**). The highest quartiles of LOYs from all algorithms were significantly associated with increased EOC risk compared to the corresponding lowest quartiles (ORs ranged from 1.24 with 95% CI 1.16-1.34 in Algorithm B to 2.39 with 95% CI 2.23-2.56 in Algorithm E). In general, ORs of LOYs from the first class of algorithms (Algorithm A-D) were slightly larger when additionally adjusting for duration of OC use as a continuous variable (data not shown). The associations of LOYs calculated from the third class of algorithms (Algorithm I-L) were not changed when months of breastfeeding was truncated at 6 for any women reporting more than 6 months per birth (data not shown). Sensitivity analyses with multiple imputation of missing values with MICE did not alter the associations of LOYs and EOC risk. The estimated ORs of LOYs calculated from the third and fourth classes of algorithms (Algorithm I – O) with MICE were slightly increased compared to ORs from the main analyses (**Table 3-3**).

Each of the individual components in Algorithm K, except for age at menarche, were significantly associated with EOC risk (**Table 3-4**). The relative estimated coefficient of OC use per year is 2.95 times larger than the theoretical estimate (**Table 3-4**). The relative estimated coefficients for non-full-term and full-term pregnancies were more than 7-fold of the theoretical estimates. The estimated coefficient of breastfeeding per year was -5.49, instead of the theoretical estimate, -1.

Estimation of EOC risk by histotypes related to LOY and individual components

LOY (per year) was significantly associated with the risk of invasive HGSOC (OR 1.048, 95% CI 1.041-1.056), endometrioid ovarian cancer (OR 1.067, 95% CI 1.056-1.079), and clear cell ovarian cancer (OR 1.108, 95% CI 1.091-1.125) (**Table 3-5**). The estimated coefficients of

OC use, number of non-full-term pregnancies, and full-term pregnancies for HGSOC were close to the theoretical estimates. The estimated coefficient of breastfeeding was 2.42 times higher than the theoretical estimate. The estimated coefficients of the individual components, except for age at menarche, were larger than the theoretical estimates for endometrioid cancer and clear cell cancer. LOYs were not significantly associated with the risk of LGSOC. However, there were significant protective effects of the individual components in LOYs on LGSOC, including duration of OC use, number of non-full-term pregnancies, and duration of breastfeeding. There was no significant association between LOYs and the risk of mucinous cancer. Age at menarche (per year) was associated with the increased risk of mucinous cancer (OR 1.079, 95% CI 1.030, 1.130). OC use, the number of non-full-term pregnancies, and the number of full-term pregnancies were significantly associated with decreased risk of mucinous cancer.

3.5 Discussion

The results pooling from 25 case-control studies indicated a positive association between LOY and the overall risk of EOC. We also found a positive association between LOY and risks of HGSOC, endometrioid, and clear cell histotypes but not with mucinous histotype or LGSOC. The LOYs calculated from different algorithms were highly correlated, and the LOY-EOC associations were not altered when using different LOY algorithms or by limiting to studies with data on age of menopause. The components of LOY, except age at menarche, were significantly associated with the overall risk of EOC. The associations between the components of LOY and the risk of ovarian cancer varied by histotype.

Our results showed a positive association between LOYs using different algorithms and the overall risk of EOC, which is consistent with the results from prior studies.[18,25,50,60,80-83,85,88,90-94,96-101,103,104] LOYs calculated from 15 algorithms were highly correlated. The Polish Cancer study also demonstrated high correlations of LOYs from different algorithms in prior studies.[103] The results from the US Nurses' Health Study (1976-2006) (NHS) and Nurses' Health Study II (1989-2005) (NHS II) studies by Gates et al. indicated that the overall risk of EOC per 1-year increase in LOY increased by 1.07 (95% CI 1.05 -1.08),[18] which is close to our estimated (1.02 from Algorithm C to 1.05 from Algorithm E and G). Most studies evaluated the associations by quantiles. Comparing Quantile 4 to Quantile 1, our estimates ranged from 1.25 with Algorithm B to 2.39 with Algorithm E and were closer to the results from the recent studies, which ranged from 1.28 to 2.44.[25,103,104] It is reassuring that our results were like what has been previously published. However, because of the different LOYs algorithms used in each study, a direct comparison of the estimated magnitude is not possible. A standardized definition of LOYs would facilitate cross-study comparisons and allow for more robust prospective data analysis moving forward.

Our results showed a positive association between LOYs and risk of HGSOC, but a null association between LOYs and risk of LGSOC. There was no previous study estimating the association between LOYs and risk of HGSOC and LGSOC separately. The MALOVA study, NHS and NHS II study, OC3 study and three case-control studies in the U.S. indicated a positive association between LOYs and risk of serous ovarian cancer.[18,25,50,60,99,104] The null association between LOYs and the risk of LGSOC could be due to the limited sample size of LGSOC and insufficient power to identify an association. Our results also indicated that LOYs was positively associated with the risk of endometrioid and clear cell histotypes, which were consistent with the findings from the MALOVA study, NHS and NHS II study, OC3 study and the three case-control studies in the U.S..[18,25,50,60,99,104] The results from our study, the MALOVA study, OC3 study and two case-control studies in the U.S. indicated a null association between LOY and risk of mucinous ovarian cancer,[25,50,60,99] while the NHS and NHS II study had a borderline significant association between LOY and risk of mucinous ovarian cancer (RR 1.03, 95% CI 1-1.07 per 1-year increase).[18]

Results regarding to the associations between components in LOY and overall risk of EOC appeared generally consistent with previous studies.[18,50,82,93,98,103] Beyond considering statistical significance, our study also compared the magnitudes of each component's effect on EOC risk. A longer duration of OC use, higher number of pregnancies, and longer duration of breastfeeding are associated with a decreased risk of EOC.[18,50,82,93,98,103] Older age at menopause, as the central component in LOY, was associated with increased risk of EOC.[18,93,98] While only the Polish Cancer study indicated that older age at menarche was associated with a decreased risk of EOC.[103] Four studies used different scales for LOY components when estimating the association between components in LOY and the overall risk of EOC,[18,50,93,103] which made the comparisons of the magnitude of each component's effect on EOC risk across studies difficult. For example, the NHS

and NHS II study estimated the effects of parity per 1 child, breastfeeding per 1-year increase, duration of OC use per 5-year increase.[18] The Polish Cancer study evaluated the effects of the number of live births, age at menopause as categorical variables, and OC use as binominal variables.[103] Only one case-control study in the U.S. in 1983 and one study pooling 2 case-control studies in Italy conducted logistic regression treating the components in LOYs as continuous variables and reported comparable estimated coefficients or ORs for each component.[82,98]

Based on the "incessant ovulation" hypothesis proposed by Fathalla in 1971,[261] women with the same LOYs value should have the same risk profiles. However our study confirms the result observed in the case-control study in the U.S. in 1983 and the study pooling 2 case-control studies in Italy, which indicated that pregnancies and OC use produced stronger protective effects on EOC.[82,98] Our study also confirmed the results observed in the case-control study in the U.S. in 1983 that breastfeeding produced stronger protective effects on EOC than expected based on cumulative years.[82] Thus, other mechanisms must underlie the LOY-EOC association, such as hormonal hypotheses[269,270] and inflammation,[294] and possibly proposition that an inflammatory reaction is induced by ovulation. The NHS and NHS II study estimating the association between LOY and its components with circulating inflammatory biomarkers, including C-reactive protein, interleukin 6, and soluble tumor necrosis factor alpha receptor 2 suggested that repeated local acute inflammation induced by ovulation and menstruation may outweigh the long-term reduction of systemic inflammation. This provides a potential explanation for age at menopause being a relatively weak predictor of ovarian cancer despite being a key driver of LOYs.[342]

Our results indicated heterogeneity in the associations between the components in LOY and risks by histotypes. The estimated coefficients of the reproductive components in LOY for HGSOC were close to the theoretical estimates of coefficients, except for breastfeeding (**Table 3-**

5). The NHS and NHS II study presented a 16% risk reduction in serous ovarian cancer per 1-year increase in breastfeeding (95% CI 0.73-0.96), while a 22% risk reduction per 5-year increase in OC use.[18] The OCAC study also indicated breastfeeding was associated with a lower risk of HGSOC.[24] Studies suggested that HGSOC primarily arises from the fallopian tube,[260,306,343] where release of follicular fluid by ovulation results in inflammation and DNA damage.[344] The transformation activity of follicular fluid further caused HGSOC development.[345] Some animal studies showed that breastfeeding suppressed ovarian follicular growth.[346,347]

The estimated coefficient of the number of pregnancies was much larger than the theoretical coefficients for endometrioid and clear cell histotypes (-7.51 and -6.09, respectively, vs. -0.75). The hormone exposure might explain the extra protective effects for endometrioid and clear cell ovarian cancer. Studies suggested the heterogeneity of androgen and estrogen exposure across histotypes and indicated more association of hormone exposure with the risk of endometrioid[348] and non-serous ovarian cancer.[349,350] Age at menarche had little effect on the risks of HGSOC, endometrioid ovarian cancer, and clear cell histotypes. Due to the small sample size of LGSOC, the association between the components and risk of LGSOC could be drawn by chance. Mucinous histotype had different pathological features and genomic profile than other histotypes.[351,352] We did not find an association between the age at last menstrual period, years of breastfeeding and the risk of mucinous histotype. However, there was a positive association between age at menarche and risk of mucinous histotype. The protective effects of reproductive factors, including pregnancies, OC use, and breastfeeding, differed between mucinous and non-mucinous histotype.[16,59,60,353] Our results supported that mucinous histotype develop via different causal mechanisms than other histotypes.

The major strength of our study was pooling 25 case-control studies from OCAC, allowing us to estimate the association between LOY and risk of EOC by histotypes and generalize our results to diverse populations. However, limitations still exist. One limitation was recall bias due to the study design. Some studies, such as HOPE, used the calendar to recall important events to help reduce recall bias. Regardless of the limitation of study design itself, our estimates were consistent with previous studies, including NHS and NHS II study, and the prospective design of pooled studies, OC3 study. Another limitation of our study is heterogeneity by study site. We adjusted for the study site in our multivariable logistic regression. However, it might not eliminate the heterogeneity caused by health care, study design and data collection. Moreover, we made some assumptions about the components in LOY. For age at menopause, we created an algorithm based on average age at menopause by country, age at first HRT use, or age at hysterectomy if the age at menopause was not available. However, to, account for this assumption, we compared the observed age at menopause and imputed age at menopause from 7 sites (**Supplemental Table 2**) and conducted sensitivity analyses by using LOY calculated from the observed age at menopause, which did not alter the associations. We also performed sensitivity analyses using 6 months for women with more than 6 months of breastfeeding to prevent overestimating the duration of anovulation due to breastfeeding. The results were not changed. Although the calculation of LOY was not precise, it should not alter the overall association between LOY and risk of EOC and by histotypes.

In conclusion, an increasing LOY is associated with increased overall risk of EOC, risk of HGSOC, endometrioid ovarian cancer, and clear cell ovarian cancer. The association between LOY and risk of EOC was not altered when core components including age at menarche, age and menopause, and duration of OC use, pregnancy, and breastfeeding were used to calculate with

different methods. Our study also indicated potential heterogeneity of each component in LOY affecting the risk of EOC across histotypes. However, the assumptions made to calculate LOY slightly affected the magnitude of the associations. Further studies using better assessment of each LOY component should examine the biological mechanisms by component and histotypes.

3.6 Figures and tables

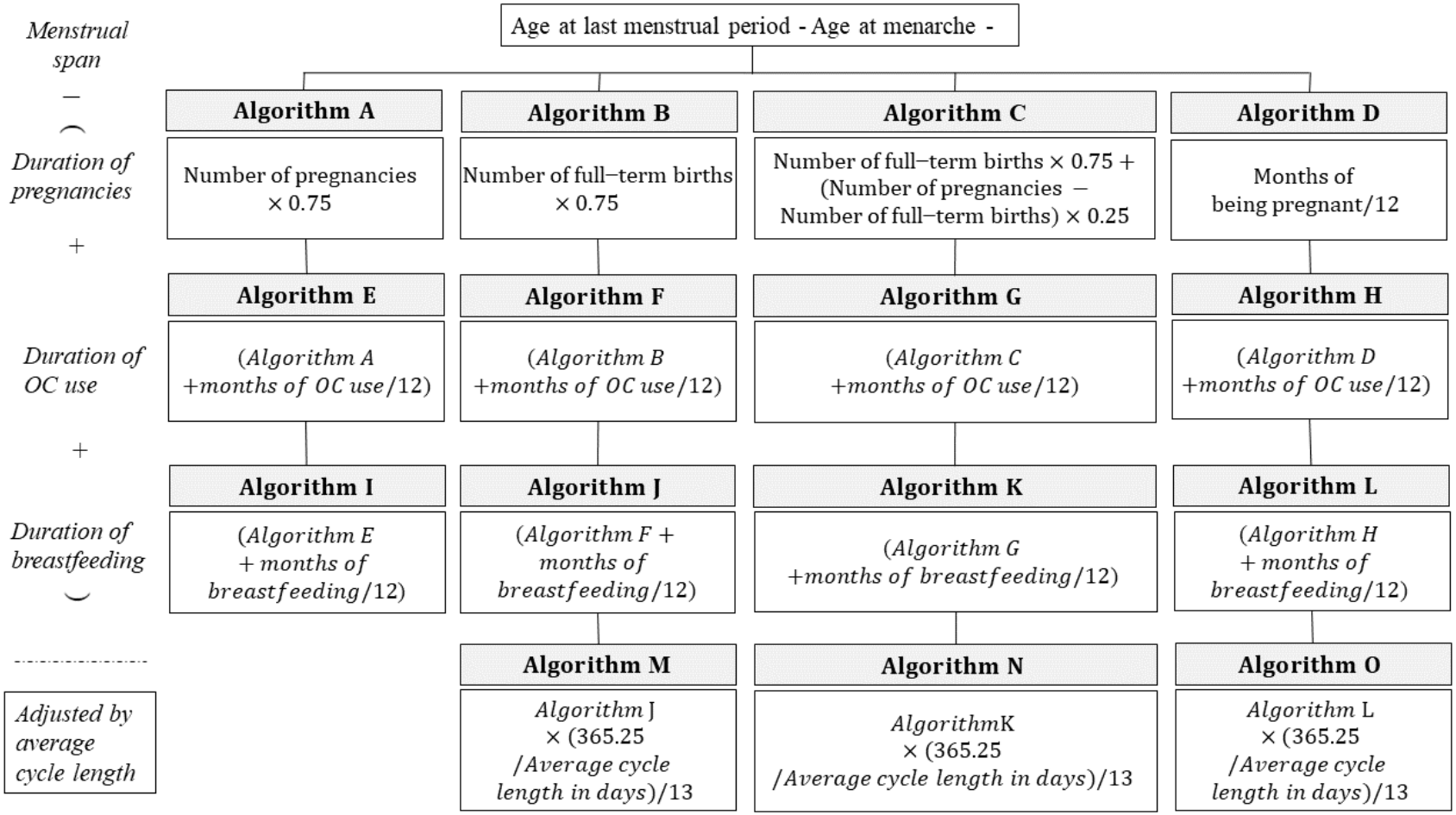


Figure 3-1 Flow chart for algorithms to calculate lifetime ovulatory year

OC, oral contraceptive.

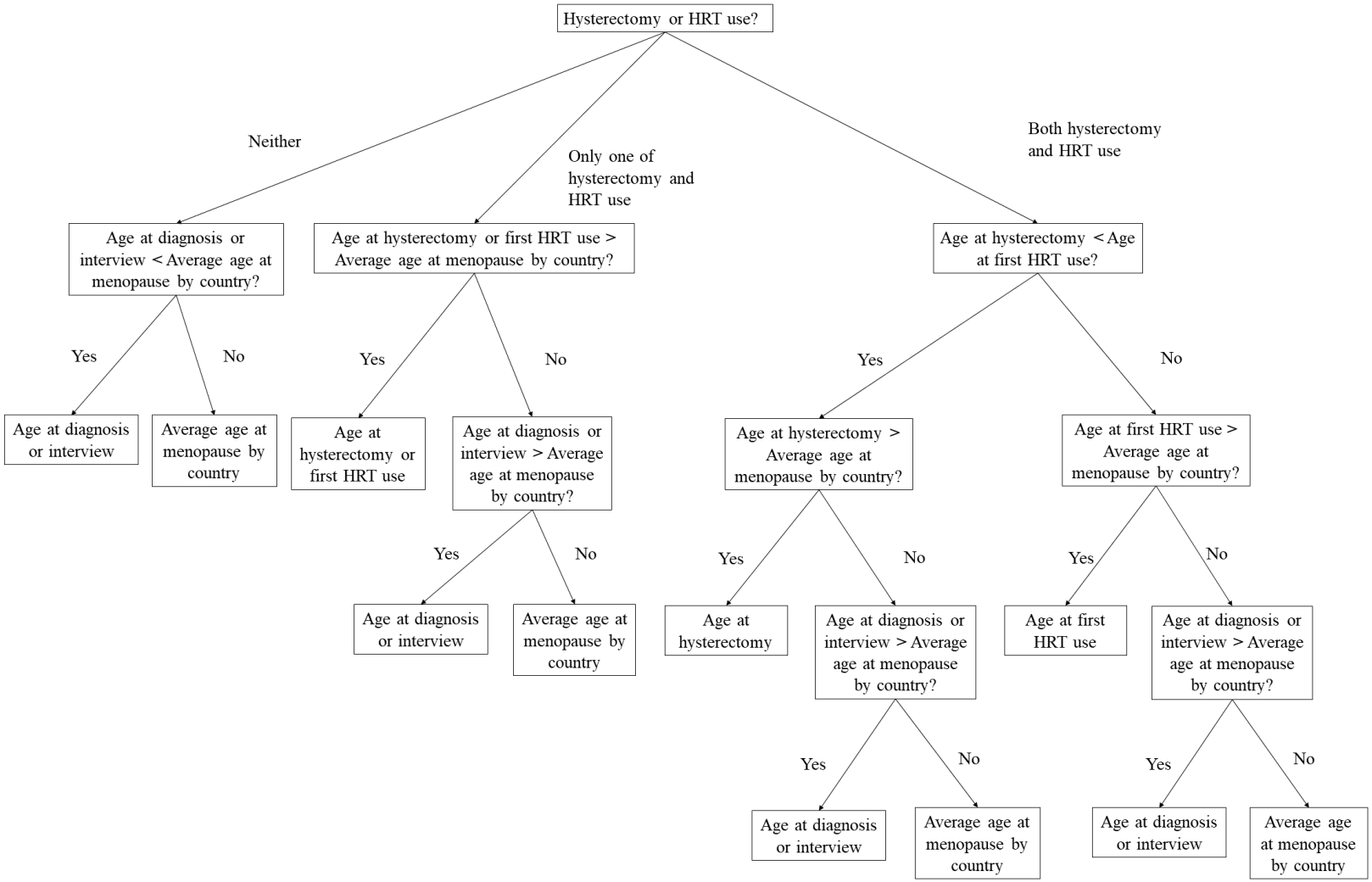


Figure 3-2 Flow chart for imputation of age at menopause

HRT, hormone replacement therapy.

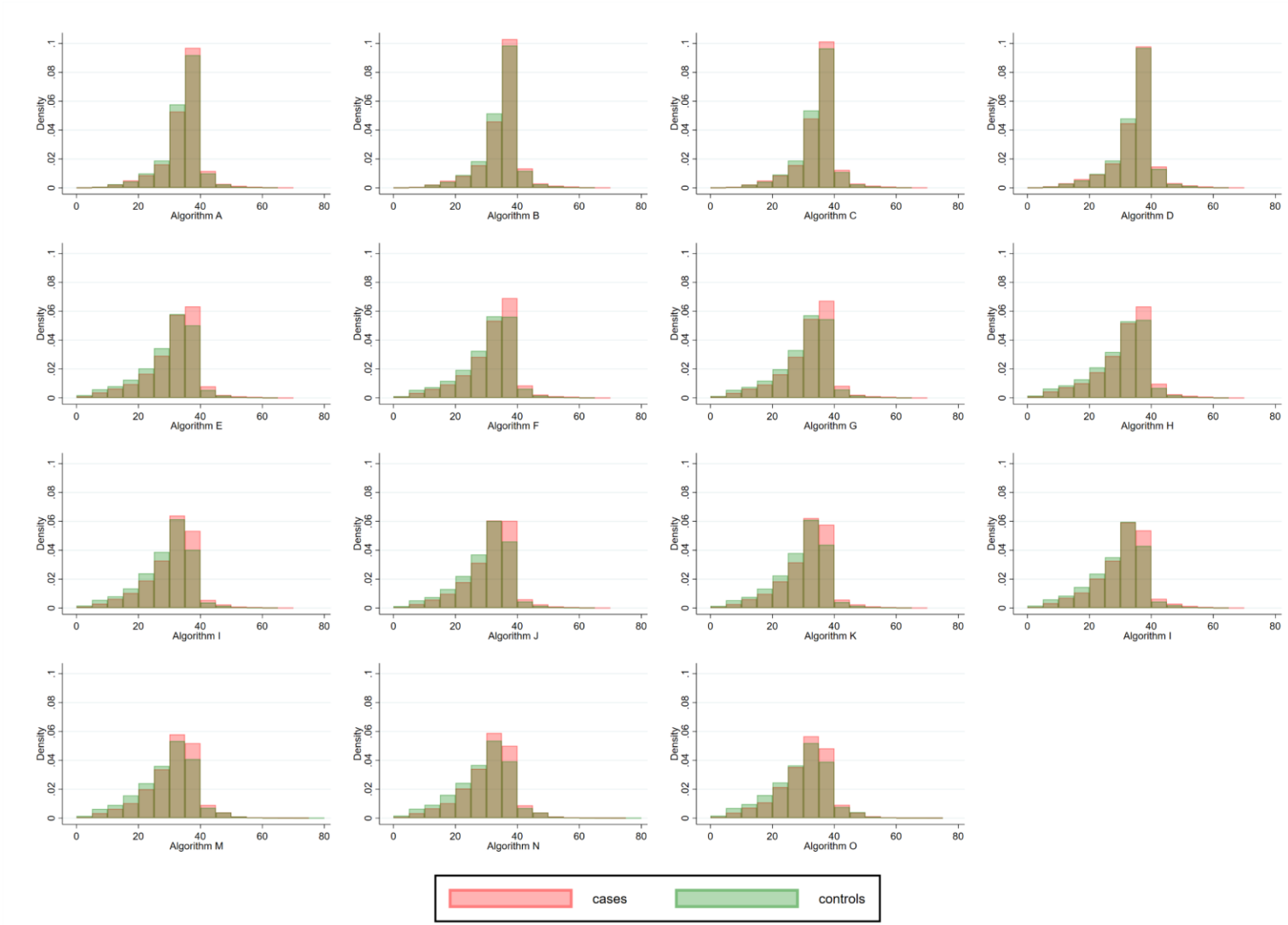


Figure 3-3 Distribution of lifetime ovulatory years calculated from different algorithms

Table 3-1 Characteristics of the case-control Studies from the Ovarian Cancer Association Consortium, conducted in Asia, Australia, Europe, and North America from 1989 to present

Study	Region	Study Name	Study Period	Cases Type	Method of Data Collection	Age (years), mean (SD)	Cases, n (%)	Controls, n (%)
AUS[55]	Australia	Australian Ovarian Cancer Study/Australian Cancer Study	2002-2006	Population-based	Self-completed questionnaire	56.88 (12.28)	1506 (43.15)	1984 (56.85)
BAV[309]	Germany	Bavarian Ovarian Cancer Cases and Controls	2002-2006	Hospital/Clinic-based	Interview	57.31 (13.77)	629 (47.91)	684 (52.09)
CON[310]	USA	Connecticut Ovarian Cancer Study	1998-2003	Population-based	Interview	55.27 (11.04)	551 (52.58)	497 (47.42)
DOV[311]	USA	Diseases of the Ovary and their Evaluation	2002-2009	Population-based	Interview	55.78 (9.26)	1849 (54.21)	1562 (45.79)
GER[312]	Germany	German Ovarian Cancer Study	1993-1996	Population-based	Self-completed questionnaire	55.07 (12.24)	533 (67.38)	258 (32.62)
HAW[313]	USA	Hawaii Ovarian Cancer Case-Control Study	1993-2008	Population-based	Interview	54.98 (14.28)	1103 (55.21)	895 (44.79)
HOP[314]	USA	Hormones and Ovarian cancer PrEdiction	2003-2009	Population-based	Interview	58.66 (12.52)	1802 (68.31)	836 (31.69)
JPN[315]	Japan	Hospital-based Research Program at Aichi Cancer Center	2001-2005	Hospital/Clinic-based	Interview	52.36 (11.17)	233 (60.52)	152 (39.48)
MAY[316]	USA	Mayo Clinic Ovarian Cancer Case-Control Study	1999-2018	Hospital/Clinic-based	Interview	60.51 (13.58)	2299 (55.46)	1846 (44.54)
MCC[317]	Australia	Melbourne Collaborative Cohort Study	1990-2008	Defined Cohort	Self-completed questionnaire	64.07 (9.62)	471 (73.14)	173 (26.86)
NCO[318]	USA	North Carolina Ovarian Cancer Study	1999-2008	Population-based	Interview	55.28 (11.53)	1085 (47.59)	1195 (42.41)
NEC[319]	USA	New England Case Control Study	1992-2003	Population-based	Interview	53.54 (12.35)	2100 (50.30)	2075 (49.70)
NJO[320]	USA	New Jersey Ovarian Cancer Study	2002-2008	Population-based	Interview	61.48 (11.60)	458 (65.90)	237 (34.10)
NTH[321,322]	Netherlands	Nijmegen Ovarian Cancer Study	1997-2008	Population-based	Self-completed questionnaire	55.90 (10.79)	600 (69.36)	265 (30.64)

OVA	Canada	Ovarian Cancer in Alberta and British Columbia	2002-present	Population-based	Self-completed questionnaire	56.81 (10.62)	2698 (62.24)	1637 (37.76)
POL[323]	Poland	Polish Ovarian Cancer Case Control Study	2000-2003	Population-based	Interview	55.70 (10.62)	1128 (79.32)	294 (20.68)
SON[324]	Canada	Southern Ontario Ovarian Cancer Study	1989-1993	Population-based	Interview	56.86 (11.97)	564 (55.62)	450 (44.38)
STA[325]	USA	Family Registry for Ovarian Cancer AND Genetic Epidemiology of Ovarian Cancer	1997-2001	Population-based	Interview	47.77 (10.07)	567 (46.02)	665 (53.98)
SWH[326]	China	Shanghai Women's Health Study	1996-present	Defined Cohort	Interview	53.36 (9.70)	986 (86.64)	152 (13.36)
TBO[327]	USA	Tampa Bay Ovarian Cancer Study	2000-present	Population-based	Interview	60.53 (10.85)	205 (41.84)	285 (58.16)
TOR[328]	Canada	Familial Ovarian Tumour Study (FOTS) AND Health Watch (HW)	1995-1999 and 2000-2003	Population-based	Interview	56.62 (12.77)	322 (21.63)	1167 (78.37)
UCI[125]	USA	University California Irvine Ovarian Study	1993-2005	Population-based	Interview	54.29 (13.17)	614 (49.12)	636 (50.88)
UKO[329]	UK	United Kingdom Ovarian cancer Population Study	2006-2010	Hospital/Clinic-based	Interview	63.06 (8.93)	1182 (58.49)	839 (41.51)
USC[113,330,331]	USA	Los Angeles County Case-Control Studies of Ovarian Cancer	1992-2009	Population-based	Interview	55.07 (12.41)	2595 (52.16)	2380 (47.84)
VTL[332]	USA	VITamins And Lifestyle Cohort Study	2000-2010	Defined Cohort	Self-completed questionnaire	68.19 (7.62)	124 (54.63)	103 (45.37)
Total						56.55 (12.20)	26204 (54.63)	21267 (44.80)

Table 3-2 Characteristics of ovarian cancer cases and controls

Variables	Control, n (%) N= 26204	Case, n (%) N=21267	p value
Age, years, mean (SD)	56.51 (12.06)	56.59 (12.36)	0.4612
Race			<0.001
White	22586 (86.19)	18685 (87.86)	
Black	566 (2.16)	460 (2.16)	
Asian	2019 (7.70)	1227 (5.77)	
Other	775 (2.96)	692 (3.25)	
Unknown	258 (0.98)	203 (0.95)	
Body Mass Index (BMI) at 18, kg/m^2			<0.001
<18.5	2637 (10.06)	2008 (9.44)	
18.5-24.9	10697 (40.82)	8809 (41.42)	
25-29.9	992 (3.79)	1002 (4.71)	
≥30	310 (1.18)	353 (1.66)	
Unknown	11568 (44.15)	9095 (42.77)	
Body Mass Index 1 or 5 years prior, kg/m^2			<0.001
<18.5	286 (1.09)	274 (1.29)	
18.5-24.9	7472 (28.51)	5672 (26.67)	
25-29.9	4541 (17.33)	3570 (16.79)	
≥30	3074 (11.73)	3021 (14.21)	
Unknown	10831 (41.33)	8730 (41.05)	
Smoking Status			<0.001
Never Smoker	13311 (50.80)	10106 (47.52)	
Former Smoker	2900 (11.07)	2682 (12.61)	
Current Smoker	7449 (28.43)	5930 (27.88)	
Unknown	2544 (9.71)	2549 (11.99)	
Family History of Breast or Ovarian Cancer in first-relative			<0.001
No	16038 (61.20)	11574 (54.42)	
Yes	1569 (5.99)	1808 (8.50)	
Unknown	8597 (32.81)	7885 (37.08)	
Tubal ligation			<0.001
No	16351 (62.40)	15035 (70.70)	
Yes	5138 (19.61)	3345 (15.73)	
Unknown	4715 (17.99)	2887 (13.58)	
Menopausal status			<0.001
Pre/peri-menopausal	8206 (31.32)	5775 (27.15)	
Post-menopausal	16749 (63.92)	14422 (67.81)	
Unknown	1249 (4.77)	1070 (5.03)	
Endometriosis			<0.001
No	18294 (69.81)	15128 (71.13)	
Yes	1291 (4.93)	1615 (7.59)	

Unknown	6619 (25.26)	4524 (21.27)	
Hysterectomy			<0.001
No	20969 (80.02)	14562 (68.47)	
Yes	4004 (15.28)	5008 (23.55)	
Unknown	1231 (4.70)	1697 (7.98)	
Hormone replacement therapy			<0.001
No	15547 (59.33)	13097 (61.58)	
Yes	7472 (28.51)	5921 (27.84)	
Unknown	3185 (12.15)	2249 (10.58)	
Components of lifetime ovulatory years			
Age at last menstrual period before diagnosis or interview	26204	21267	
mean (SD)	48.77 (6.03)	48.84 (6.42)	0.2204
Age at Menarche	25255	20101	
mean (SD)	12.91 (1.68)	12.79 (1.60)	<0.0001
Duration of Oral Contraceptive Use, months	24948	19762	
mean (SD)	52.12 (71.30)	37.42 (59.29)	<0.0001
Number of Pregnancies, regardless of outcome	25429	20429	
mean (SD)	2.75 (1.83)	2.40 (1.92)	<0.0001
Total number of months of being pregnant, regardless of outcome(s)	14438	12195	
mean (SD)	21.42 (22.32)	16.39 (17.64)	<0.0001
Total number of full-term births	22835	18304	
mean (SD)	2.13 (1.48)	1.85 (1.57)	<0.0001
Total months of breastfeeding	18578	13619	
mean (SD)	9.52 (14.35)	6.86 (13.10)	<0.0001
Menstrual cycle length, days	11574	11444	
mean (SD)	28.89 (5.49)	28.74 (6.37)	0.0633
Behavior - Histotypes			
LMP		3602 (16.94)	
Invasive		17465 (82.12)	
Serous		10423 (59.68)	
High-grade		7492 (71.88)	
Low-grade		513 (4.92)	
Unknown		2418 (23.20)	
Endometrioid		2536(14.52)	
Mucinous		1134 (6.49)	
Clear cell		1310 (7.50)	
Mixed		566 (3.24)	
Others		1496 (8.57)	
Unknown		200 (0.94)	

Table 3-3 Odds ratio for ovarian cancer by lifetime ovulatory years using complete data and full data with imputation

	Main analyses[2]			Sensitivity analyses[2]
	control, n(%)	case, n(%)	Odds Ratio[1] (95% Confidence Interval)	Odds Ratio[1] (95% Confidence Interval)
The first class of algorithms				
Algorithm A				
per 1 unit			1.021 (1.016, 1.025)	1.020 (1.015, 1.024)
Q1 (<=31.75)	6140 (24.48)	4420 (22.06)	ref	ref
Q2 (31.75-35.15)	6400 (25.52)	4821 (24.06)	1.08 (1.01, 1.16)	1.08 (1.02, 1.16)
Q3 (35.15-37.25)	6033 (24.05)	4838 (24.14)	1.13 (1.05, 1.21)	1.13 (1.06, 1.21)
Q4 (>37.25)	6508 (25.95)	5961 (29.75)	1.31 (1.22, 1.40)	1.28 (1.20, 1.37)
Algorithm B				
per 1 unit			1.019 (1.014, 1.024)	1.019 (1.014, 1.023)
Q1 (<=32.25)	5511 (24.47)	4042 (22.44)	ref	ref
Q2 (32.25-35.50)	5036 (22.36)	3748 (20.81)	1.07 (1.00, 1.15)	1.02 (0.95, 1.09)
Q3 (35.50-37.50)	5645 (25.07)	4481 (24.88)	1.08 (1.01, 1.16)	1.05 (0.98, 1.13)
Q4 (>37.50)	6327 (28.10)	5742 (31.88)	1.24 (1.16, 1.34)	1.25 (1.16, 1.34)
Algorithm C				
per 1 unit			1.020 (1.016, 1.025)	1.020 (1.015, 1.025)
Q1 (<=32.00)	5463 (24.27)	3926 (21.81)	ref	ref
Q2 (32.00-35.50)	5550 (24.66)	4153 (23.07)	1.11 (1.03, 1.19)	1.02 (0.95, 1.09)
Q3 (35.50-37.50)	5628 (25.00)	4520 (25.11)	1.13 (1.05, 1.22)	1.08 (1.00, 1.16)
Q4 (>37.50)	5868 (26.07)	5404 (30.02)	1.32 (1.22, 1.42)	1.27 (1.18, 1.37)
Algorithm D				
per 1 unit			1.020 (1.014, 1.025)	1.015 (1.001, 1.020)
Q1 (<=32.00)	3330 (24.49)	2393 (22.66)	ref	ref
Q2 (32.00-35.60)	3529 (25.96)	2574 (24.37)	1.12 (1.02, 1.22)	1.03 (0.95, 1.12)
Q3 (35.60-37.50)	3041 (22.37)	2302 (21.80)	1.19 (1.08, 1.31)	1.08 (0.99, 1.19)
Q4 (>37.50)	3696 (27.18)	3292 (31.17)	1.36 (1.24, 1.50)	1.25 (1.14, 1.37)
The second class of algorithms				
Algorithm E				
per 1 unit			1.045 (1.042, 1.048)	1.044 (1.041, 1.047)
Q1 (<=25.00)	6012 (24.56)	3648 (18.88)	ref	ref
Q2 (25.00-32.67)	7570 (30.92)	5344 (27.66)	1.51 (1.42, 1.60)	1.48 (1.39, 1.57)
Q3 (32.67-35.50)	4591 (18.75)	3854 (19.95)	1.92 (1.78, 2.06)	1.90 (1.77, 2.03)

Q4 (>35.50)	6307 (25.76)	6477 (33.52)	2.39 (2.23, 2.56)	2.33 (2.17, 2.49)
Algorithm F				
per 1 unit			1.044 (1.041, 1.048)	1.045 (1.041, 1.048)
Q1 (<=25.75)	5453 (24.86)	3489 (19.74)	ref	ref
Q2 (25.75-32.25)	5439 (24.80)	3872 (21.91)	1.42 (1.33, 1.52)	1.44 (1.35, 1.54)
Q3 (32.25-35.92)	5557 (25.34)	4594 (25.99)	1.80 (1.68, 1.93)	1.79 (1.67, 1.92)
Q4 (>35.95)	5482 (25.00)	5721 (32.37)	2.31 (2.15, 2.49)	2.33 (2.16, 2.50)
Algorithm G				
per 1 unit			1.045 (1.042, 1.048)	1.045 (1.042, 1.049)
Q1 (<=25.50)	5380 (24.54)	3434 (19.44)	ref	ref
Q2 (25.50-32.00)	5429 (24.77)	3797 (21.49)	1.41 (1.32, 1.51)	1.44 (1.35, 1.53)
Q3 (32.00-35.75)	5468 (24.94)	4544 (25.72)	1.83 (1.71, 1.97)	1.81 (1.68, 1.94)
Q4 (>35.75)	5644 (25.75)	5891 (33.35)	2.34 (2.17, 2.52)	2.37 (2.20, 2.54)
Algorithm H				
per 1 unit			1.044 (1.040, 1.049)	1.042 (1.038, 1.047)
Q1 (<=25.00)	3237 (24.67)	2050 (19.78)	ref	ref
Q2 (25.00-32.09)	3337 (25.45)	2517 (24.29)	1.48 (1.37, 1.61)	1.45 (1.34, 1.57)
Q3 (32.09-35.92)	3288 (25.08)	2623 (25.31)	1.83 (1.67, 2.00)	1.78 (1.64, 1.95)
Q4 (>35.92)	3249 (24.78)	3172 (30.61)	2.37 (2.15, 2.61)	2.28 (2.08, 2.50)
The third class of algorithms				
Algorithm I				
per 1 unit			1.041 (1.037, 1.046)	1.048 (1.044, 1.051)
Q1 (<=24.33)	3588 (24.88)	2079 (18.58)	ref	ref
Q2 (24.33-30.75)	3563 (24.70)	2405 (21.49)	1.42 (1.31, 1.54)	1.48 (1.38, 1.60)
Q3 (30.75-34.75)	3615 (25.06)	2972 (26.56)	1.77 (1.62, 1.93)	1.86 (1.72, 2.02)
Q4 (>34.75)	3658 (25.36)	3733 (33.36)	2.13 (1.94, 2.34)	2.50 (2.30, 2.71)
Algorithm J				
per 1 unit			1.041 (1.037, 1.046)	1.047 (1.043, 1.050)
Q1 (<=25.00)	3582 (24.83)	2097 (18.72)	ref	ref
Q2 (25.00-31.42)	3686 (25.55)	2492 (22.25)	1.40 (1.29, 1.52)	1.44 (1.34, 1.55)
Q3 (31.42-35.25)	3534 (24.50)	2933 (26.19)	1.76 (1.61, 1.92)	1.89 (1.75, 2.05)
Q4 (>35.25)	3624 (25.12)	3677 (32.83)	2.10 (1.91, 2.30)	2.35 (2.17, 2.55)
Algorithm K				
per 1 unit			1.041 (1.037, 1.046)	1.047 (1.043, 1.051)
Q1 (<=24.75)	3572 (24.76)	2070 (18.50)	ref	ref
Q2 (24.75-31.20)	3633 (25.19)	2480 (22.16)	1.44 (1.32, 1.56)	1.47 (1.37, 1.58)

Q3 (31.20-35.00)	3536 (24.51)	2862 (25.58)	1.75 (1.60, 1.91)	1.88 (1.74, 2.04)
Q4 (>35.00)	3683 (25.53)	3777 (33.76)	2.16 (1.97, 2.36)	2.41 (2.22, 2.62)
Algorithm L				
per 1 unit			1.042 (1.037, 1.048)	1.049 (1.044, 1.053)
Q1 (<=24.25)	2113 (24.94)	1232 (18.96)	ref	ref
Q2 (24.25-31.42)	2156 (25.45)	1654 (25.45)	1.52 (1.37, 1.68)	1.57 (1.43, 1.72)
Q3 (31.45-35.25)	2075 (24.49)	1621 (24.95)	1.78 (1.59, 2.00)	2.00 (1.81, 2.21)
Q4 (>35.25)	2129 (25.13)	1991 (30.64)	2.21 (1.96, 2.49)	2.54 (2.29, 2.82)
The fourth class of algorithms				
Algorithm M				
per 1 unit			1.032 (1.027, 1.036)	1.038 (1.034, 1.041)
Q1 (<=23.77)	2283 (24.99)	1472 (17.26)	ref	ref
Q2 (23.77-30.87)	2283 (24.99)	2035 (23.86)	1.52 (1.38, 1.67)	1.58 (1.45, 1.72)
Q3 (30.87-35.37)	2274 (24.90)	2369 (27.78)	1.87 (1.68, 2.07)	2.00 (1.83, 2.18)
Q4 (>35.37)	2294 (25.11)	2653 (31.11)	2.07 (1.86, 2.30)	2.43 (2.21, 2.66)
Algorithm N				
per 1 unit			1.032 (1.028, 1.037)	1.038 (1.034, 1.042)
Q1 (<=23.58)	2268 (24.83)	1463 (17.16)	ref	ref
Q2 (23.58-30.69)	2300 (25.18)	2050 (24.04)	1.52 (1.38, 1.67)	1.58 (1.45, 1.72)
Q3 (30.69-35.20)	2276 (24.92)	2367 (27.76)	1.85 (1.67, 2.06)	1.99 (1.82, 2.18)
Q4 (>35.20)	2289 (25.06)	2648 (31.05)	2.07 (1.86, 2.31)	2.45 (2.23, 2.68)
Algorithm O				
per 1 unit			1.030 (1.025, 1.035)	1.037 (1.032, 1.042)
Q1 (<=23.49)	1553 (25.00)	924 (17.95)	ref	ref
Q2 (23.49-30.69)	1534 (25.02)	1305 (25.35)	1.54 (1.37, 1.73)	1.58 (1.43, 1.74)
Q3 (30.69-35.29)	1536 (25.05)	2418 (27.55)	1.79 (1.58, 2.03)	1.99 (1.80, 2.21)
Q4 (>35.29)	1529 (24.93)	1500 (29.14)	1.95 (1.71, 2.22)	2.33 (2.09, 2.61)

[1] Adjusted for study site, age, body mass index 1 or 5 years prior (underweight, normal, overweight, obese, unknown), smoking status (never, former, current, unknown) and family history (yes, no, unknown).

[2] Main analyses included participants without missing values in any component for LOY calculation; sensitivity analyses included all participants with imputation

.

Table 3-4 Odds ratio for ovarian cancer by individual components of lifetime ovulatory years in algorithm K using complete data

	Odds Ratio[1]	95% Confidence Interval	Theoretical estimate of coefficient	Estimated coefficient	chi-square for removal from model	P-value for removal from model
Age at last menstrual period before diagnosis or interview						
per 1 unit	1.018	1.012, 1.025	1	1 (defined)	29.82	<0.0001
Age at Menarche						
per 1 unit	1.010	0.995, 1.025	-1	-0.54	1.59	0.2075
Duration of Oral Contraceptive Use, years						
per 1 unit	0.948	0.943, 0.953	-1	-2.95	438.86	<0.0001
Number of non-full-term pregnancies						
per 1 unit	0.965	0.943, 0.988	-0.25	-1.97	9.13	0.0025
Total number of full-term births						
per 1 unit	0.892	0.875, 0.910	-0.75	-6.34	129.92	<0.0001
Total years of breastfeeding						
per 1 unit	0.906	0.884, 0.928	-1	-5.49	65.14	<0.0001

[1] adjusted for study site, age, body mass index 1 or 5 years prior (underweight, normal, overweight, obese, unknown), smoking status (never, former, current, unknown), family history (yes, no, unknown), and other components of lifetime ovulatory cycles in the model.

Table 3-5 Odds ratio for ovarian cancer histotypes by individual components of lifetime ovulatory years in algorithm K using complete data

	Theoretical estimate of coefficient	Low malignant potential N=3252 OR[1] (95% CI)	β̂	Invasive high-grade serous N=5836 OR[1] (95% CI)	β̂	Invasive low-grade serous N=425 OR[1] (95% CI)	β̂	Invasive endometrioid N=2243 OR[1] (95% CI)	β̂	Invasive mucinous N=982 OR[1] (95% CI)	β̂	Invasive clear cell N=1132 OR[1] (95% CI)	β̂
Lifetime ovulatory years[2]													
per 1 unit		0.984 (0.974, 0.993)		1.048 (1.041, 1.056)		1.008 (0.986, 1.031)		1.067 (1.056, 1.079)		0.997 (0.982, 1.012)		1.108 (1.091, 1.125)	
Age at last menstrual period before diagnosis or interview													
per 1 unit	1	0.973 (0.961, 0.986)	1 (defined)	1.054 (1.044, 1.065)	1 (defined)	1.009 (0.979, 1.040)	1 (defined)	1.039 (1.024, 1.055)	1 (defined)	0.999 (0.978, 1.021)	1 (defined)	1.078 (1.056, 1.101)	1 (defined)
Age at Menarche													
per 1 unit	-1	1.032 (1.002, 1.062)	-1.168	1.004 (0.982, 1.026)	0.008	0.980 (0.912, 1.053)	-2.662	1.066 (0.972, 1.042)	0.166	1.079 (1.030, 1.130)	-79.026	0.959 (0.911, 1.008)	-0.560
Duration of Oral Contraceptive Use, years													
per 1 unit	-1	0.971 (0.962, 0.980)	10.836	0.948 (0.940, 0.955)	-0.920	0.958 (0.935, 0.981)	-4.726	0.927 (0.914, 0.939)	-1.974	0.971 (0.955, 0.987)	30.962	0.911 (0.892, 0.930)	-1.237
Number of non-full-term pregnancies													
per 1 unit	-0.25	0.991 (0.951, 1.034)	0.319	0.980 (0.948, 1.013)	-0.389	0.867 (0.766, 0.980)	-15.607	0.938 (0.888, 0.991)	-1.660	0.915 (0.844, 0.992)	92.056	0.836 (0.764, 0.914)	-2.381
Total number of full-term births													
per 1 unit	-0.75	0.852 (0.817, 0.889)	5.950	0.953 (0.927, 0.980)	-0.823	0.947 (0.860, 1.044)	-5.933	0.749 (0.712, 0.788)	-7.505	0.930 (0.870, 0.994)	75.566	0.632 (0.583, 0.686)	-6.087
Total years of breastfeeding													
per 1 unit	-1	0.965 (0.919, 1.012)	1.337	0.880 (0.847, 0.913)	-2.419	0.842 (0.731, 0.969)	-18.809	0.915 (0.858, 0.976)	-2.301	0.998 (0.925, 1.076)	2.478	0.900 (0.811, 0.999)	-1.393

CI, confidence interval; OR odds ratio; β̂, estimated coefficient.

[1] adjusted for study site, age, body mass index 1 or 5 years prior (underweight, normal, overweight, obese, unknown), smoking status (never, former, current, unknown), family history (yes, no, unknown), and other components of lifetime ovulatory cycles in the model.

[2] adjusted for study site, age, body mass index 1 or 5 years prior (underweight, normal, overweight, obese, unknown), smoking status (never, former, current, unknown) and family history (yes, no, unknown).

4.0 Paper II: Hormonally-linked risk factors for ovarian cancer tumors defined by hormone receptors: an analysis from the Ovarian Cancer Association Consortium and the Ovarian Tumor Tissue Analysis consortium

4.1 Abstract

Introduction: Many factors associated with epithelial ovarian cancer (EOC) risk are related to sex hormones. The association between these factors and the biology of tumors defined by sex hormone status is unknown. In this study, we identified hormonally-linked factors related to EOC risk and survival according to the presence of androgen receptor (AR), estrogen receptor (ER), and/or progesterone receptor (PR) in tumors.

Method: We linked epidemiologic and immunohistochemistry (IHC) data from 13 case-control studies in the Ovarian Cancer Association Consortium (OCAC) and the Ovarian Tumor Tissue Analysis (OTTA) consortium to estimate relative risk ratios (RRRs) and 95% confidence intervals (CIs) for the associations between hormonally linked risk factors with EOC risk by tumor types defined by the individual and joint presence of hormonal receptors using polytomous logistic regression. We used clinical, epidemiologic, and IHC data from 14 case-control studies and 5 case-only studies in OCAC and OTTA to perform survival analyses. Kaplan-Meier curves were used to visualize survival among all cases and histotype-specific cases by the individual and joint presence of hormonal receptors. Cox proportional hazards model with left truncation was used to estimate hazard ratios (HRs) and 95% CIs for the association between hormonally-linked risk factors and survival by tumor types defined by the individual and joint presence of hormonal receptors and by histotypes.

Results: Menopause status was associated with a higher risk of PR- tumors relative to controls (RRR 1.52, 95% CI 1.26-1.83) but not associated with PR+ tumors relative to controls (P for heterogeneity 0.0008). The associations were not altered by the presence or absence of AR or ER. Women with ER-PR+ high-grade serous tumors showed the best survival compared to women with the other three tumors defined by ER and PR. Women with ER+ or PR+ endometrioid tumors had a longer survival time compared to women with ER- or PR- endometrioid tumors. The association was not altered by the presence of AR. Women with ER- clear cell tumors had a longer survival time than women with ER+ clear cell tumors. There was no interaction effect between hormonally-linked risk factors and the presence of hormone receptors on EOC survival in general nor for survival by histotype.

Conclusion: EOC tumor types defined by hormone receptor status have varying risk and prognostic profiles in general and based on tumor histology. The potential biologic mechanisms underlying the association of hormonally-linked risk factors and EOC risk and outcomes need to be studied by histotypes and by tumor hormone receptor status.

4.2 Introduction

Ovarian cancer is the most lethal gynecologic cancer[2] and epithelial ovary cancer (EOC) accounts for nearly 90% of malignant ovarian cancer.[1] The consistent association of oral contraceptive (OC) use and pregnancy with reduced risk of EOC strongly indicates a role of hormones in EOC risk.[82] The "hormone" hypothesis[82] postulates that excess androgen and estrogen stimulation of the ovarian epithelium leads to an increased EOC risk, while progesterone simulation has a protective effect on EOC.[269] This hypothesis was supported by the protective effect of OC use, associated with reduced androgen and estrogen levels,[281,282,303] and parity, associated with excess progesterone.[354] It was also supported by the risk effect of endometriosis, which leads to progesterone resistance,[293] and hormonal treatment (HRT) use, which is associated with increased estrogen.[283,355] However, the underlying biological mechanisms whereby these factors influence EOC etiology remain unknown. One possibility is through impacting hormone receptors, which may also influence survival.

Hormonal receptors, including androgen receptor (AR), estrogen receptor (ER), and progesterone receptor (PR), have been associated with the EOC survival in a histotype-specific way.[204] Data pooling 12 studies participating in the Ovarian Tumor Tissue Analysis (OTTA) consortium estimated the histotype-specific associations between ER or/and PR and survival.[204] A Swedish study indicated that women with AR+ and PR+ in serous and endometrioid tumors had the best survival.[205] AR expression alone was observed to be a favorable prognostic factor for the serous subtypes.[206] However, to date, no study has estimated the survival by the joint presence of AR and ER, and all three receptors, or evaluates the association of hormonally-linked risk factors with the survival of EOC tumors defined by hormone receptor status of AR, ER, and PR.

In the current study, we pooled data from studies participating in the Ovarian Cancer Association Consortium (OCAC) and OTTA to evaluate the association between hormonally-linked factors with the risk and survival of EOC tumor types defined by hormone receptor status of AR, ER, and PR. Because EOC is now believed to be a group of etiologically distinct diseases,[16,59] we used the large, pooled sample size to further investigate the impact of hormone receptor status on risk and survival according to EOC histotype. Insight into the relationship between hormonally-linked risk factors and tumor biology could help us better understand the exposure-EOC relationships. Thus, the aim of this work was to investigate the association between hormonally-linked factors with the risk and survival of EOC tumor types defined by hormone receptor status as well as the impact of hormone receptor status on risk and survival according to EOC histotypes.

4.3 Method

Study participants

The OCAC was established in 2005 to promote collaborative research on discovering and validating associations between epidemiologic and genetic factors and ovarian cancer risk.[308] The OTTA was formed in 2010 to validate prognostic markers for ovarian cancer by histotypes.[356] We included 20,888 controls and 4,762 cases from 13 case-control studies with epidemiologic factors in OCAC and hormone receptor status via immunohistochemistry (IHC) in OTTA to estimate the association between hormonally-linked risk factors and EOC risk.[55,60,309,312-314,316,325,357,358] The characteristics of the 13 case-control studies are presented in **Table 4-1**. We included 5,737 invasive cases from 14 case-control studies (cases from POC not linked to OCAC) and 5 case-only studies with hormone receptor status in OTTA to estimate survival by tumor types defined by hormone receptor status.[55,60,309,312-314,316,325,357-359] We estimated the association between hormonally-linked risk factors and survival of EOC tumor types defined by hormone receptor status by combining OCAC and OTTA datasets. The characteristics of the case-control and case-only studies included in the survival analyses are presented in **Table 4-2**. The participating institutions obtained approval from relevant ethics committees and all participants provided informed consent.

Hormonal receptor status via immunohistochemistry

Data on AR, ER, and PR staining was obtained from the OTTA. Briefly, tumors were obtained at initial debulking surgery and arrayed on tissue microarrays (TMAs) for immunohistochemistry (IHC) analysis. IHC analyses were performed by Genetic Pathology Evaluation Centre (Vancouver, BC, Canada) for estrogen receptor (ER) and progesterone receptor (PR) and by Ventana Medical Systems Inc. (Tucson, AZ, USA) for androgen receptor (AR) in

Vancouver using the Ventana Discovery Ultra machine [204,211]. Two observers independently scored the staining intensity for each IHC biomarker. In the original OTTA dataset, a 5-tiered system (no tumoral tissue, necrosis or hemorrhage, no staining in tumoral cells or just cytoplasmic staining, just stromal cells staining, just tumoral cells staining, and both tumoral and stromal cells staining) was used for AR and a 3-tiered system (<1%, 1 to 50%, and >50% of tumor cell nuclei positive) was used for ER and PR. In the current study, positive was defined as stromal or/and tumoral cells staining for AR and nuclear expression in ≥1% of tumor cells for ER and PR.

Hormonally-linked risk factors and covariates

We identified 11 hormonally-linked risk factors, including physical inactivity (associated with increased estrogen[360]), recent body mass index (BMI) greater than or equal to 30 kg/m^2 (associated with hormonal imbalances[361,362]), smoking status (associated with anti-estrogenic effects[287,363]), history of ever OC use (associated with altered hormonal milieus[278,281,282,303,364]), history of pregnancy (associated with excess progesterone[354]), history of ever breastfeeding (associated with decreased estrogen[365]), age at menarche less than 13 (associated with excess estrogen[366,367]), menopause status (associated with decreased estrogen and progesterone[368-370]), history of endometriosis (associated with increase excess estrogen but reduced progesterone[286,293]), history of hysterectomy (associated which decreased estrogen[371]), and history of HRT use (associated with increased estrogen[283,355]) (**Table 4-3**). The other relevant variables from the OCAC dataset included age at diagnosis (cases) or interview (controls), race (non-white, white, or unknown), and family history of breast or ovarian cancer (no, ovarian cancer only, breast cancer only, both ovarian cancer and breast cancer). All information on the variables was self-reported.

Clinical data

Clinical data in the OTTA dataset were obtained from the combination of tumor tissue and a centralized pathology review. We obtained variables related to EOC survival, including histotypes (serous, endometrioid, mucinous, clear cell, or other), stage (stage I/II, stage III/IV, or unknown), grade (low, high, or unknown), debulking status (optimal, suboptimal, or unknown), chemotherapy (no, yes, or unknown), and primary therapy outcome (complete response/ partial response, stable disease/progressive disease, or non-applicable/ unknown). Each site in OTTA reported vital status, survival time, and follow-up information from medical record review, patient contact, linkage with state cancer registries, use of the SEER registry, and death-record databases.

Statistical analysis

Polytomous logistic regression is used to model nominal outcome variables and produces conditional odds ratios called as relative risk ratios (RRRs), which is equivalent to odds ratio when the outcome is binomial. In the current study, polytomous logistic regression was used to estimate RRRs and 95% confidence intervals (CIs) for EOC risk by tumor types as defined by the individual receptor presence and joint presence based on hormonally-linked risk factors compared to all controls controlling for study site, age at diagnosis (cases) or interview (controls), family history of breast or ovarian cancer (no, ovarian cancer only, breast cancer only, or both ovarian cancer and breast cancer), duration of OC use (0, <1, 1-4, 5-9, or 10+ years), number of pregnancies (never, 1, 2, 3, or 4+), menopause status at diagnosis or at interview (pre or post), and hormonal treatment use (no, estrogen only, combination, or others). P-values for heterogeneity of RRRs from Wald test were reported. Sensitivity analyses were conducted restricting to invasive cases only and comparing cases to all controls by adding an unknown outcome category for cases without hormonal receptor status in the polytomous logistic regression.

Kaplan-Meier curves were used to visualize survival from the time of diagnosis among all cases and histotype-specific cases by individual receptor presence and joint receptor presence. P-values from log-rank test were obtained to estimate the difference between survivor functions across tumor types defined by hormone receptor status. The Cox proportional hazard model with left truncation was used to estimate hazard ratios (HRs) and 95% CIs for the association between hormonally-linked risk factors and survival from time of diagnosis by tumor types as defined by the individual and joint presence of hormone receptors controlling for study site, age at diagnosis (cases) or interview (controls), histotypes (serous, endometrioid, mucinous, clear cell, or other), stage (stage I/II, stage III/IV, or unknown), grade (low, high, or unknown), and debulking status (optimal, suboptimal, or unknown). The interaction effects between hormonally-linked risk factors and hormone receptor status were evaluated by Wald test. We did not consider hormonally-linked risk factors of age at menarche, history of hysterectomy, and history of endometriosis due too few cases with these data. We estimated the adjusted HRs and 95% CI for the association between hormonally-linked risk factors and the histotype-specific survival by tumor types defined by the individual and joint presence of hormone receptors. Statistical analyses were performed in Stata/SE version 16.1 (StataCorp, College Station, TX), and all statistical tests were two-sided with a significance level of 5%.

4.4 Results

Hormonally-linked risk factors by tumor types defined by receptors

Characteristics of controls and cases defined by individual receptor presence are summarized in **Table 4-3**. There were 1,390 AR- cases, 563 AR+ cases, and 10,411 controls from 10 case-control studies included in the AR analyses. Compared to women with AR+ tumors, women with AR- tumors were older and less likely to report family history of breast or ovarian cancer and history of hysterectomy. We included 564 ER- cases, 1,282 ER+ cases, and 16,606 controls from 8 case-control studies in the ER analyses. Women with ER- tumors were more likely to be non-white and physically inactive compared to controls and women with ER+ tumors. Women with ER+ tumors were more likely to report family history of breast or ovarian cancer and history of hysterectomy. There were 1,528 PR- cases, 1,125 PR+ cases, and 19,851 controls from 10 case-control studies in the PR analyses. Women with PR- tumors were older and were more likely to be non-white than controls and women with PR+ tumors. Women with PR+ tumors were less likely to report HRT use compared to controls and women with PR- tumors.

The associations between hormonally-linked risk factors and EOC risk did not significantly vary by AR status (**Table 4-4**). Obesity status at adulthood was significantly associated with a higher risk of ER- tumors relative to controls (RRR 1.53, 95% CI 1.18-1.98) but not associated with ER+ tumors relative to controls (RRR 1.13, 95% CI 0.95-1.35; P for heterogeneity 0.053). Hysterectomy had a larger estimated effect for the risk of ER+ cases relative to controls (RRR 4.99, 95% CI 4.27-5.83), as compared to ER- cases relative to controls (RRR 3.67, 95% CI 2.93-4.60; P for heterogeneity 0.018). Menopause status was associated with a higher risk of PR- cases relative to controls (RRR 1.52, 95% CI 1.26-1.83) but not associated with PR+ cases relative to controls (RRR 0.98, 95% CI 0.80-1.20; P for heterogeneity 0.0008). Number of pregnancies and

duration of oral contraceptive use showed dose-response protective effects on EOC risk by individual receptor presence, except the effect of duration of oral contraceptive use on AR+ tumors (P for trend 0.1086). Duration of breastfeeding showed dose-response protective effects on EOC risk by individual AR status and ER status. Sensitivity analyses restricting to invasive cases only and comparing cases to controls from all case-control studies by adding an unknown index in the outcome did not alter the association between hormonally-linked risk factors and EOC risk by tumor types defined by individual receptor presence (**Supplemental Table. A**).

The association between hysterectomy and EOC risk differed by the joint presence of AR and ER (P for heterogeneity 0.0028; **Table 4-5 Panel A**) and by the joint presence of AR and PR (P for heterogeneity 0.0388; **Table 4-5 Panel B**) but the 95% CIs for each category of tumors overlapped. Hysterectomy is associated with a higher risk of AR-ER+ cases relative to controls (RRR 9.31, 95% CI 7.17-12.09) and with similar risks of AR-ER- (RRR 4.50), AR+ER- (RRR 6.71) and AR+ER+ (RRR 5.97). Hysterectomy is associated with higher risks of AR+PR- cases and AR+ER+ cases (RRRs 11.90 and 10.62, respectively) and with similar risks of AR-PR- cases and AR+PR+ cases (RRRs 7.40 and 7.09, respectively). Menopause status was associated with a lower risk of AR-PR+ cases relative to controls (RRR 0.65, 95 CI% 0.45-0.94), and a higher risk of AR-PR- cases relative to controls (RRR 1.74, 95% CI 1.31-2.32), but not significantly associated with AR+PR- cases and AR+PR+ cases relative to controls (P for heterogeneity 0.0002; **Table 4-5 Panel B**). Menopause status was significantly associated with a higher risk of ER+PR- cases relative to controls (RRR 2.17, 95% CI1.60-2.95) but not significantly associated with ER-PR- cases, ER-PR+ cases, and ER+PR+ cases relative to controls (P for heterogeneity 0.0004; **Table 4-5 Panel C**). Sensitivity analyses restricting to invasive cases only and comparing cases to controls from all case-control studies by adding an unknown outcome category for cases did not

alter any association (data not shown). The association of hysterectomy and menopause status with EOC risk by the joint presence of two receptors was not modified by stratifying by a third receptor (**Supplemental Table. B**). Menopause status was associated with higher risks of AR-ER+PR- cases and AR+ER+PR- cases relative to controls (RRRs 2.20 and 2.29, respectively) and lower risk of AR-ER-PR+ cases and AR-ER+PR+ cases relative to controls (RRRs 0.23 and 0.63, respectively).

Survival by tumor types defined by receptors

We included 2,552 AR- tumor cases, 1,153 AR+ tumor cases, 830 ER- tumor cases, 1,699 ER+ tumor cases, 2,640 PR- tumor cases, and 1,728 PR+ tumor cases in the survival analyses. Clinical characteristics and hormonally linked risk factors among tumor types defined by individual hormonal receptor presence are summarized in **Supplemental Table. C**. Serous cases made up a larger percentage of AR+ cases than AR- cases (73.11% vs. 58.74%) and a greater percentage of ER+ cases than ER- cases (74.63% vs. 37.11%). Endometrioid cases made up a greater percentage of PR+ cases than PR- cases (28.59% vs. 5.76%). Clear cell cases were more likely hormone receptor negative. ER+ cases were at a more advanced stage than ER- cases (60.47% vs. 36.36%). More PR- cases had high grades compared to PR+ cases (90.79% vs. 78.79%).

Women with ER- tumors had a longer survival time (median 7.26 years, 95% CI 6.12-8.66 years) compared to women with ER+ tumors (median 4.94 years, 95% CI 4.62-5.36 years). Women with PR+ tumors had a longer survival time (median 6.93 years, 95% CI 6.21-8.05 years) than women with PR- tumors (median 4.22 years, 95% CI 3.89-4.56 years). Women with AR+ and AR- tumors had similar survival times (median 5.11 years and 4.92 years, respectively). The Kaplan-Meier curves for survival from diagnosis by individual receptor presence are presented

(**Figure 4-1**). Survival did not vary by individual AR status, but did vary by ER status and PR status. We also used Kaplan-Meier curves to visualize the survival by the joint presence of hormone receptors (**Supplemental Figure A**). The curves for EOC tumors defined by the joint receptor presences crossed in all analyses.

Survival by histotype and by individual receptor presence are presented in **Supplemental Figure B**. When evaluated by individual histotype, women with PR+ HGSOC had longer survival compared to women with PR- HGSOC (P from log-rank test =0.0003). There was no noted survival difference in HGSOC by either ER or AR status. Among HGSOC cases, there was no significant difference in survival by the joint presence of AR and ER (**Figure 4-2 Panel A**), or the joint presence of AR and PR (**Figure 4-2 Panel B**). Women with ER-PR+ high grade serous tumors had the best survival compared to women with high grade serous tumors defined by the other three ER and PR subtypes (**Figure 4-2 Panel C**). There was no clear distinction among the groups defined by the three receptors' joint presence (**Figure 4-2 Panel D**). When we evaluated endometrioid cancers, women with ER+ or PR+ endometrioid tumors had a longer survival time compared to women with ER- or PR- tumors (**Supplemental Figure B)**. There was no difference in survival between those with AR- and AR+ endometrioid tumors (**Supplemental Figure B**). When examining survival based on joint presence hormone receptors, the association of ER and PR positivity and survival was not altered by the presence of AR (**Figure 4-3**). There was no difference in survival for any of the individual hormone receptors in women with mucinous cancers (**Supplemental Figure B**). Lastly, women with ER- clear cell tumors had a longer survival time than women with ER+. Survival for this histotype did not differ by ER or AR (**Supplemental Figure B**). Since the sample size of clear cell tumors was limited, we did not estimate the survival stratified by the joint presence of hormone receptors.

Hormonally-linked risk factor related to survival

When we evaluated hormonally linked risked factors by hormone receptor status across all histologic subtypes, physical inactivity was significantly associated with worse survival for ER+ cases (HR 1.47, 95% CI 1.14-1.89) and non-significantly associated with better survival for ER- cases (HR 0.75, 95% CI 0.48-1.16) (P for interaction 0.14) (**Table 4-6**). The association between physical inactivity and survival by ER status was not modified by AR or PR status (data not shown). History of pregnancy was non-significantly associated with higher hazards of death for PR- HGSOC (HR 1.20 95% CI 0.96-1.50) and with lower hazards for PR+ HGSOC (HR 0.88 95% CI 0.66-1.17) (P for interaction 0.22). HRT use was associated with improved HGSOC survival regardless of tumor types as defined by the individual receptor presence, except PR+ cases. The associations between hormonally-linked risk factors and HGOSC survival did not vary by tumor types defined by the joint presence of ER and PR (data not shown). We did not evaluate the associations on endometrioid, mucinous and clear cell cancers differed by tumor types defined by the individual or joint receptor presence due to limited sample sizes.

4.5 Discussion

In the current study, we observed differences in EOC risk and survival based on tumor hormone receptor status. We report that the association between menopause status at diagnosis and EOC risk varied by the presence of PR and is not altered by the presence of AR or ER. Specifically, post-menopausal women had higher risk of PR- ovarian tumors. We also observed the association between hysterectomy and EOC risk varied by the presence of AR, ER, and PR. However, regardless the presence of AR, ER and PR, women with a history of hysterectomy had higher EOC risk than those with no history of hysterectomy. We also confirmed and expanded previously reported data showing significant differences in EOC survival based on tumor receptor status for ER,[204] which may be modified by physical inactivity. We also confirmed previously reported survival differences based on tumor PR status.[204] In contrast, tumor AR status was not associated with survival. We further found that women with ER-PR+ HGSOC tumors have longer survival compared to women with the other three HSGOC types defined by the presence of ER and PR. Women with ER-PR- endometrioid tumors have worse survival compared to women with the other three endometrioid tumor types defined by the presence of ER and PR. Women with ER+ clear cell tumors have worse survival compared to women with ER- clear cell tumors. Collectively, our findings suggested that ER and PR potentially serve as prognostic biomarkers for HGSOC and endometrioid ovarian cancer while ER may serve as a prognostic biomarker for clear cell ovarian cancer.

Menopausal status at diagnosis was differentially associated with EOC risk based on the presence of PR. Women with post-menopausal status were more likely to develop PR-tumors compared to women with pre-menopausal status. Our finding was consistent with the results from a previous pooled study of 197 Nurses' Health Study (NHS) cases, 42 NHS II cases and 76 New

England Case-control Study (NECC) cases[372] and the study of 157 NHS cases.[373] In our study, 57.6% of all cases were PR- tumors (N=1525) and 42.4 % PR+ tumors (N=1125). The distribution of PR, overall, was similar to the NHS, NHS II and NECC study,[372] but the percentage of PR- tumors was lower than that in the NHS study. Both our study and the NHS, NHS II and NECC study considered PR+ if >=1% of cells stained positive, while the NHS study considered PR+ if >10% of cells stained positive. Thus, regardless of how PR+ was defined, the association of PR status with EOC risk appears to be modified by menopausal status. Furthermore, consistent with previous studies,[205,372-377] we observed that PR-tumors were more likely to be at advanced stage, higher grade and suboptimal debulking status and presented worse survival outcomes compare to PR+ tumors. Although the exact biologic mechanism underlying these findings are unknown, they may reflect that fact that menopause is associated with a decrease in ovarian PR expression (**Table 4-3**) and that progesterone exposure is associated with reduced EOC risk [378] and improved survival.[378,379]

When examining survival by tumors defined by individual receptor status, we recapitulated some previously reported findings, but also reported on novel results. Consistent with a Swedish cohort study,[204,205] we found that women with PR- HGSOC tumors, PR- endometrioid tumors, and ER- endometrioid tumors had worse survival. However, no prior studies have examined survival by receptor status for mucinous and clear cell cases. Notably, for these never reported on subtypes, we also found that ER+ clear cell cases were associated with worse survival and that survival did not vary by receptor status for mucinous cases. The heterogeneity on the association between the presence of hormonal receptors and survival across histotypes suggested different AR, ER, PR signaling in ovarian cancer by histotypes. Our study contrasted with a prospective population-based study with 90 serous cases from the Malmö Diet and Cancer Study (MDCS) and Malmö

Preventive Project (MPP) cohorts, which indicated AR expression alone was observed to be a favorable prognostic factor for the serous subtypes,[206] and the Swedish cohort study, which indicated AR+PR+ tumors present a better survival [205]. The reasons for the conflicting findings might be the definition of AR positive and the outcomes of interest. In the MDCS and MPP study, serous cases were not separated into HGSOC and LGSOC and the cur-off point for AR was 10% stained tumor cells.[206] The Swedish cohort study combined serous and endometrioid tumors together and also used 10% stained tumor cells as a cutoff for hormone receptor positive and negative staining.[205] We did not identify any significant interaction of hormonally-linked risk factors and the presence of hormone receptors on survival by histotypes.

Our analyses on survival by histotype and tumor types define by the presence of hormone receptors were limited by the sample size. We did not perform the Kaplan-Meier curves for patients with low-grade serous ovarian tumors defined by the presence of hormone receptors or for patients with mucinous and clear cell tumors defined by the joint presence of hormone receptors. Moreover, we only had 52 ER-PR+ HGSOC cases and the better survival of ER-PR+ HGSOC compared to the other HGSOC types defined by the presence of ER and PR could be due to chance. Despite these limitations, our study is the largest study evaluating the associations between hormonally-linked risk factors and EOC risk and survival by histotypes and by tumor types defined by the presence of three hormone receptors. Our study provided extra evidence supporting the association between menopausal status and EOC risk varies by PR status and suggested that studying the biology mechanisms underlying the association would further our knowledge of ovarian tumor development. Moreover, our study identified ER and PR as potential prognostic biomarkers for HGSOC and endometrioid ovarian cancer and ER as potential prognostic biomarkers for clear cell

ovarian cancer pooling the studies all over the world, which increased the generalizability of our findings.

In conclusion, we found that some hormonally-linked risk factors were associated with EOC tumor types defined by the presence of AR, ER, and/or PR hormone receptors. Ovarian tumors presented different aggressiveness depending on histotypes and hormone receptor status, underscoring the need to consider both histotype and hormone receptors when evaluating patient prognosis. Our findings further suggest that potential biologic mechanisms underlying the association between hormonally-linked risk factors and EOC risk and outcomes need to be studied by both histotypes and tumor types defined by hormone receptor status in order to truly illuminate the etiology of and potential prevention modalities for this highly fatal group of diseases.

4.6 Figures and tables

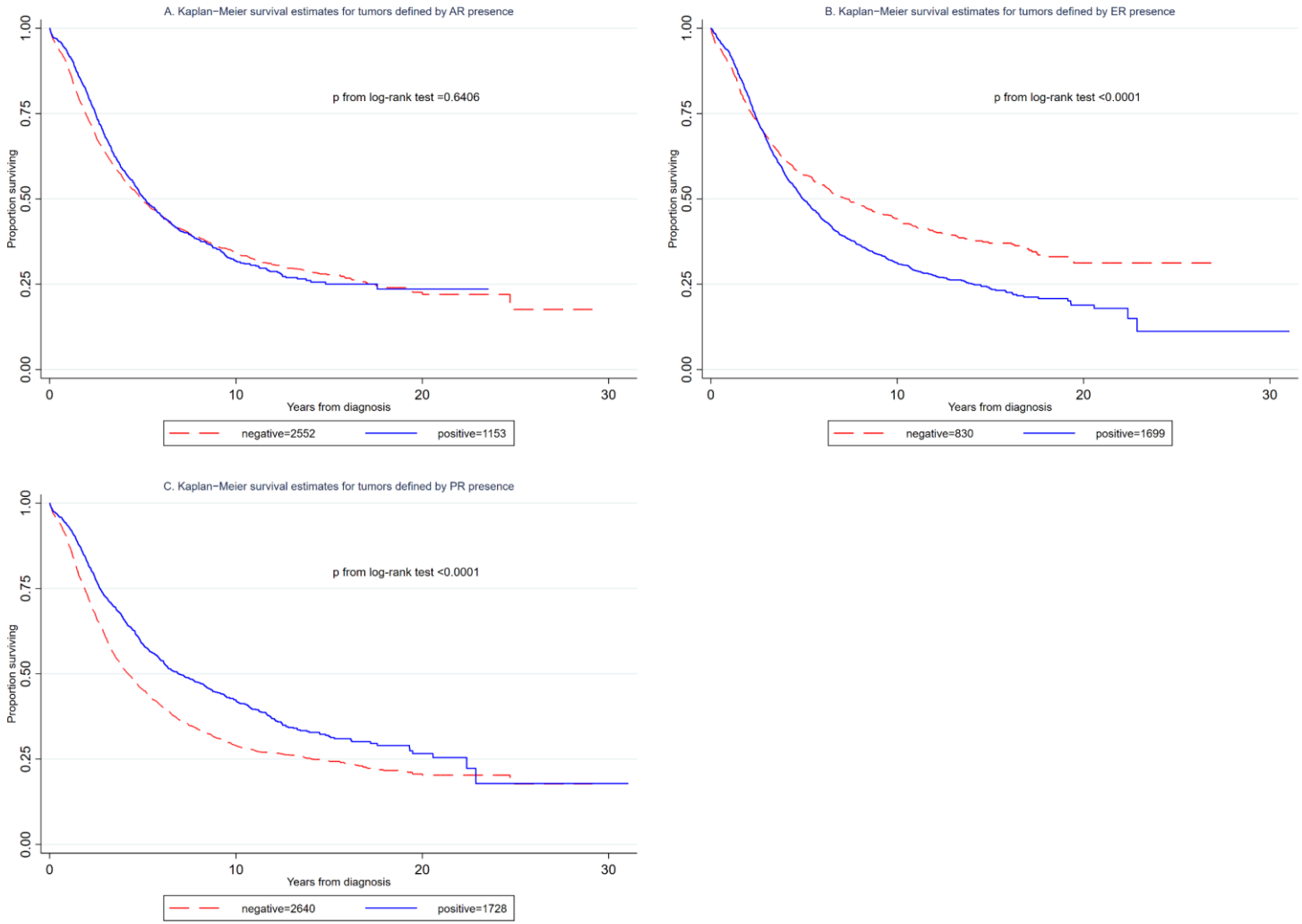


Figure 4-1 Kaplan-Meier curves for survival from the time of diagnosis of EOC by individual hormonal receptors presence

AR, androgen receptor; ER, estrogen receptor; PR, progesterone receptor.

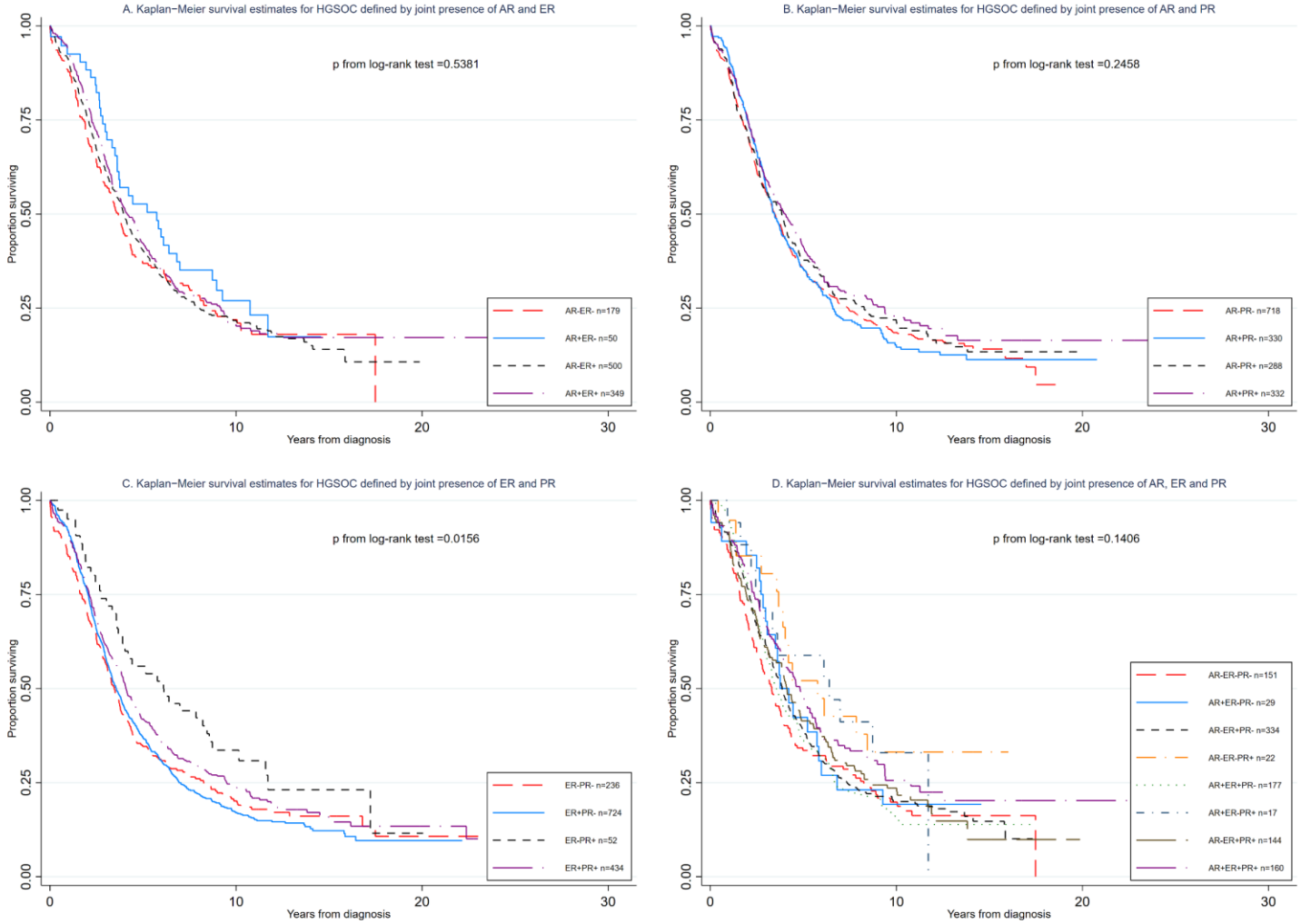


Figure 4-2 Kaplan-Meier curves for survival from the time of diagnosis of high-grade serous ovarian cancer by joint presence of hormonal receptors

AR, androgen receptor; ER, estrogen receptor; HGSOC, high-grade serous ovarian cancer; PR, progesterone receptor.

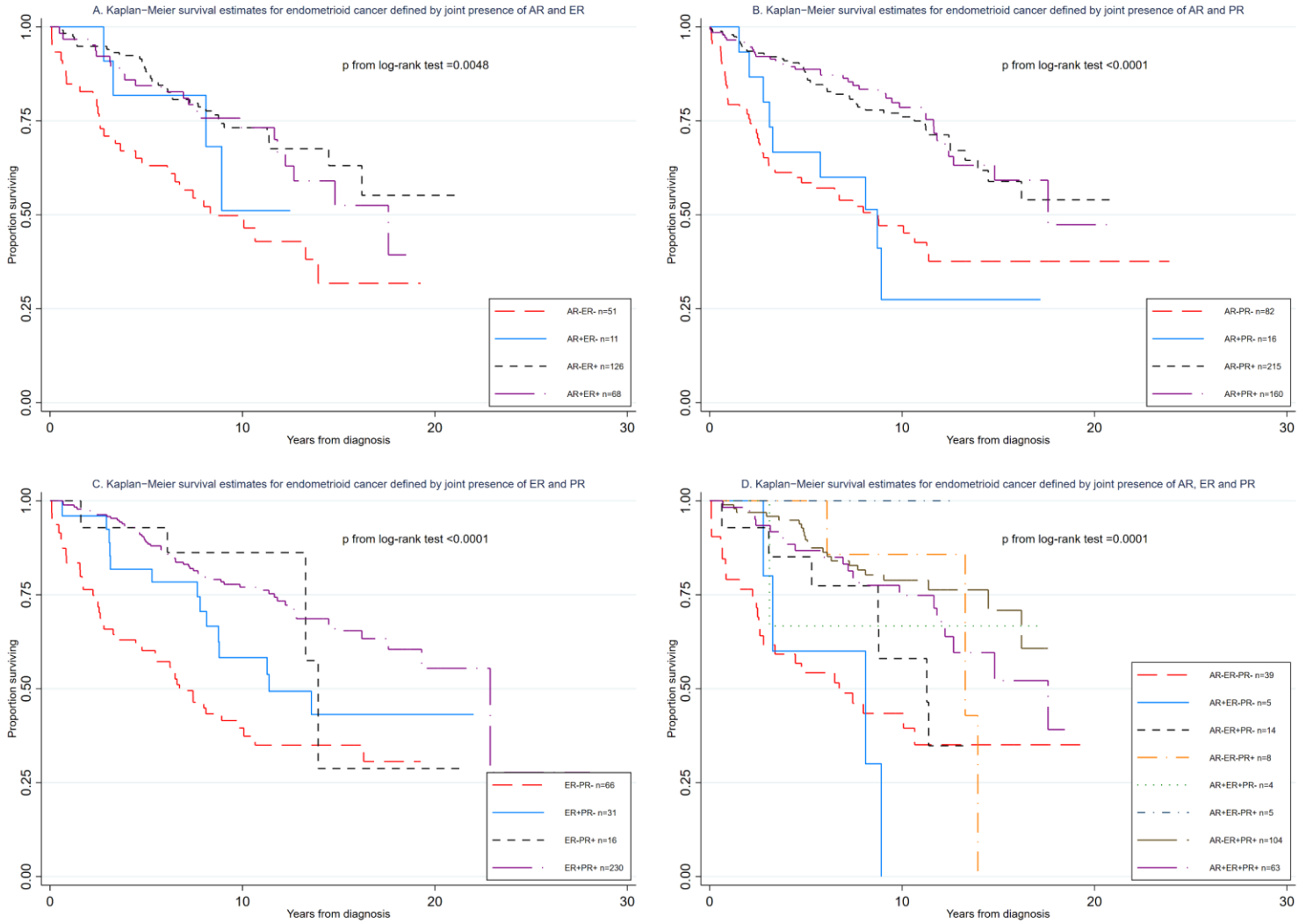


Figure 4-3 Kaplan-Meier curves for survival from the time of diagnosis of endometrioid ovarian cancer by joint presence of hormonal receptors

AR, androgen receptor; ER, estrogen receptor; PR, progesterone receptor.

Table 4-1 Characteristics of the 13 case-control studies from the Ovarian Cancer Association Consortium and the Ovarian Tumor Tissue Analysis consortium in risk analyses, conducted in Australia, Europe, and North America

Study	Region	Study Name	Study Period	Controls, n	Cases, n (%)		Cases, n (%)		Cases, n (%)	
					AR-	AR+	ER-	ER+	PR-	PR+
AUS [55]	Australia	Australian Ovarian Cancer Study	2002-2005	1506	30 (69.77)	13 (30.23)	23 (10.85)	189 (89.15)	134 (60.63)	87 (39.37)
BAV [309]	Germany	Bavarian Ovarian Cancer Cases and Controls	2002-2006	629	198 (82.16)	43 (17.84)	0	0	0	0
CNI	Spain	CNIO Ovarian Cancer Study	2002-2012	186	8 (80.00)	2 (20.00)	0	0	0	0
GER [312]	Germany	Germany Ovarian Cancer Study	1993-1996	533	62 (62.00)	38 (38.00)	0	0	50 (53.19)	44 (46.81)
HAW [313]	USA	Hawaii Ovarian Cancer Case-Control Study	1993-2008	1103	120 (90.91)	12 (9.09)	79 (64.23)	44 (35.77)	95 (76.61)	29 (23.39)
HOP [314]	USA	Hormones and Ovarian Cancer Prediction Study	2003-2008	1802	26 (56.52)	20 (43.48)	10 (22.22)	35 (77.78)	15 (32.61)	33 (68.75)
LAX	USA	Women's Cancer Program at the Samuel Oschin Comprehensive Cancer Institute	1989 - present	222	118 (73.29)	43 (26.71)	0	0	0	0
MAL [60,357]	Denmark	MALignant OVArian cancer	1994-1999	1564	61 (91.04)	6 (8.96)	63 (50.00)	63 (50.00)	99 (72.79)	37 (27.21)
MAY [316]	USA	Mayo Clinic Ovarian Cancer Case-Control Study	2000-2011	2299	518 (70.48)	217 (29.52)	101 (23.17)	335 (76.83)	534 (55.17)	434 (44.83)
OVA	Canada	Ovarian Cancer in Alberta and British Columbia	2002-present	2712	0	0	0	0	75 (49.34)	77 (50.66)
POL [323]	Poland	Polish Ovarian Cancer Case Control Study	2000-2003	1128	0	0	52 (31.14)	115 (68.86)	94 (56.97)	71 (43.03)
SEA [358]	UK	Study of Epidemiology and Risk Factors in Cancer Heredity	1998-present	6637	0	0	129 (39.69)	196 (60.31)	202 (60.84)	130 (39.16)
STA [325]	USA	Family Registry for Ovarian Cancer AND Genetic Epidemiology of Ovarian Cancer	1997-2001	567	249 (59.57)	169 (40.43)	107 (25.97)	305 (74.03)	230 (55.69)	183 (44.31)
Total	-	-	-	20888	1390 (71.17)	563 (28.83)	564 (30.55)	1282 (69.45)	1528 (57.60)	1125 (42.40)

AR, androgen receptor; ER, estrogen receptor; PR, progesterone receptor.

Table 4-2 Characteristics of the 14 case-control studies and 5 case-only studies from the Ovarian Tumor Tissue Analysis consortium in survival analyses, conducted in Australia, Europe, and North America

Study	Region	Study Name	Study Period	Study Type	AR, n (%)		ER, n (%)		PR, n (%)	
					negative	positive	negative	positive	negative	positive
AOV [359]	Canada	Alberta Ovarian Tumor Types Study	1978-2010	Case-only	295 (63.44)	170 (36.56)	0	0	268 (57.88)	195 (42.12)
AUS [55]	Australia	Australian Ovarian Cancer Study	2002-2005	Case-control	30 (69.77)	13 (30.23)	23 (10.55)	195 (89.45)	139 (61.23)	88 (38.77)
BAV [309]	Germany	Bavarian Ovarian Cancer Cases and Controls	2002-2006	Case-control	186 (83.04)	38 (16.96)	0	0	0	0
CNI	Spain	CNIO Ovarian Cancer Study	1. 2022-2012; 2. 2006-2013	1. Case-control; 2. Case -only	112 (86.15)	18 (13.85)	0	0	0	0
GER [312]	Germany	Germany Ovarian Cancer Study	1993-1996	Case-control	64 (64.65)	35 (35.35)	0	0	53 (56.99)	40 (43.01)
HAW [313]	USA	Hawaii Ovarian Cancer Case-Control Study	1993-2008	Case-control	120 (90.91)	12 (9.09)	79 (64.23)	44 (35.77)	95 (76.61)	29 (23.39)
HOP [314]	USA	Hormones and Ovarian Cancer Prediction Study	2003-2008	Case-control	26 (59.09)	18 (40.91)	9 (20.93)	34 (79.09)	14 (30.43)	32 (69.57)
LAX	USA	Women's Cancer Program at the Samuel Oschin Comprehensive Cancer Institute	1989 - present	Case-control	184 (74.19)	64 (25.81)	0	0	0	0
MAL [60,357]	Denmark	MALignant OVArian cancer	1994-1999	Case-control	61 (91.04)	6 (8.96)	63 (50.00)	63 (50.00)	99 (72.79)	37 (27.21)
MAY [316]	USA	Mayo Clinic Ovarian Cancer Case-Control Study	2000-2011	Case-control	586 (70.52)	245 (29.48)	118 (23.89)	376 (76.11)	632 (56.73)	482 (43.27)
OVA	Canada	Ovarian Cancer in Alberta and British Columbia	2002-present	Case-control	0	0	0	0	76 (49.67)	77 (50.33)
POC	Poland	Polish Ovarian Cancer Study	1998-2006	Case-control	94 (65.28)	50 (34.72)	0	0	63 (44.06)	80 (55.94)
POL [323]	Poland	Polish Ovarian Cancer Case Control Study	2000-2003	Case-control	0	0	46 (30.87)	103 (69.13)	92 (61.74)	57 (38.26)
SEA [358]	UK	Study of Epidemiology and Risk Factors in Cancer Heredity	1998-present	Case-control	0	0	120 (40.68)	175 (59.32)	193 (63.91)	109 (36.09)
STA [325]	USA	Family Registry for Ovarian Cancer AND	1997-2001	Case-control	200 (62.89)	118 (37.11)	88 (28.12)	225 (71.88)	207 (65.91)	109 (36.09)

SWE	Sweden	Genetic Epidemiology of Ovarian Cancer Sweden Western Region Ovarian Cancer Study	2002-present	Case-only	0	0	0	0	105 (58.01)	76 (41.99)
VAN	Canada	OVCARE	2003-present	Case-only	446 (58.45)	317 (41.55)	284 (36.98)	48 4(63.02)	466 (66.01)	240 (33.99)
WMH	Australia	Westmead Hospital: Molecular Biology of Gynecologic Disease	1992- 2012	Case-only	148 (75.13)	49 (24.87)	0	0	138 (63.59)	79 (36.41)
Total					2552 (68.88)	1153 (31.12)	830 (32.82)	1699 (67.18)	2640 (60.44)	1728 (39.56)

AR, androgen receptor; ER, estrogen receptor; PR, progesterone receptor.

Table 4-3 Characteristics of participants used to estimate the association with EOC risk by individual receptor presence[1]

	Controls (N=10,411), n (%)	AR- (N=1,390), n (%)	AR+ (N=563), n (%)	Controls (N=16,606), n (%)	ER- (N=564), n (%)	ER+ (N=1,282), n (%)	Controls (N=19,851), n (%)	PR- (N=1,528), n (%)	PR+ (N=1,125), n (%)
Age, years, mean (SD)	56.82 (13.26)	58.38 (12.73)	56.24 (12.33)	56.88 (11.53)	56.02 (11.92)	56.22 (11.57)	56.81 (11.32)	58.84 (11.36)	55.75 (11.86)
Race									
Non - White	1066 (10.27)	180 (13.10)	61 (10.93)	1077 (6.50)	111 (19.68)	108 (8.48)	1337 (6.80)	161 (10.65)	85 (7.66)
White	9315 (89.73)	1194 (86.90)	497 (89.07)	15501 (93.50)	453 (80.32)	1166 (91.52)	18327 (93.20)	1351 (89.35)	1025 (92.34)
Unknown	30	16	5	28	0	8	187	16	15
Family history of breast or ovarian cancer in first-relative									
No	7206 (92.14)	780 (87.64)	377 (84.53)	7623 (91.41)	409 (91.50)	901 (85.40)	8132 (89.99)	1047 (86.96)	747 (85.08)
Yes, ovarian cancer only	63 (0.80)	17 (1.91)	10 (2.24)	82 (0.98)	9 (2.10)	21 (1.99)	82 (0.91)	21 (1.74)	17 (1.94)
Yes, breast cancer only	397 (5.08)	63 (7.08)	38 (8.52)	405 (4.86)	20 (4.47)	79 (7.49)	542 (6.00)	97 (8.06)	67 (7.63)
Yes, both ovarian cancer and breast cancer	155 (1.98)	30 (3.37)	21 (4.71)	229 (2.75)	9 (2.01)	54 (5.12)	281 (3.11)	39 (3.24)	47 (5.35)
Unknown	2590	500	117	8267	117	227	10814	324	247
Hormonally-link risk factors									
Physical inactivity									
Active	5290 (77.01)	358 (76.33)	104 (71.72)	5290 (77.01)	146 (69.52)	335 (76.14)	5290 (77.01)	381 (73.55)	213 (76.62)
Inactive	1579 (22.99)	111 (23.67)	41 (28.28)	1579 (22.99)	64 (30.48)	105 (23.86)	1579 (22.99)	137 (26.45)	65 (23.38)
Unknown	3542	921	418	9737	354	842	12982	1010	847
Obesity status at adulthood									
underweight/normal	3951 (48.71)	344 (44.73)	115 (41.37)	3951 (48.71)	113 (43.63)	267 (44.76)	3951 (48.71)	347 (43.65)	228 (40.35)
overweight/obese	4161 (51.29)	425 (55.27)	163 (58.63)	4161 (51.29)	146 (56.37)	332 (55.24)	4161 (51.29)	448 (56.35)	337 (59.65)
Unknown	2299	621	285	8494	305	681	11739	733	560
Smoking status									
Never Smoker	5399 (51.26)	661 (60.09)	310 (62.50)	5853 (55.46)	300 (55.97)	699 (56.74)	7506 (54.40)	836 (57.54)	621 (57.82)
Current Smoker	1522 (15.86)	129 (11.73)	59 (11.90)	1692 (16.03)	102 (19.03)	180 (14.61)	1999 (14.49)	214 (14.73)	132 (12.29)

Former Smoker	2675 (27.88)	310 (28.18)	127 (25.60)	3009 (28.51)	134 (25.00)	353 (28.65)	4294 (31.12)	403 (27.74)	321 (29.89)
Unknown	815	290	67	6052	28	50	6052	75	51
Duration of oral contraceptive use, years									
0	3031 (32.69)	464 (44.92)	195 (42.21)	6344 (39.74)	274 (50.93)	563 (46.03)	7286 (37.99)	679 (46.86)	457 (42.87)
<1	1099 (11.85)	153 (14.81)	81 (17.53)	1733 (10.85)	70 (13.01)	189 (15.45)	1945 (10.14)	191 (13.18)	155 (14.54)
1-4	1486 (16.03)	169 (16.36)	65 (14.07)	2250 (14.09)	75 (13.94)	174 (14.23)	2879 (15.01)	235 (16.22)	159 (14.92)
5-9	2047 (22.08)	160 (15.49)	78 (16.88)	3208 (20.09)	80 (14.87)	190 (15.54)	4060 (21.17)	226 (15.60)	186 (17.45)
10+	1609 (17.35)	87 (8.42)	43 (9.31)	2430 (15.22)	39 (7.25)	107 (8.75)	3010 (15.69)	118 (8.14)	109 (10.23)
Unknown	1139	357	101	641	26	59	671	79	59
Number of pregnancies									
Never	1079 (11.22)	228 (17.47)	98 (18.42)	1855 (11.28)	109 (20.07)	208 (16.81)	2233 (11.34)	250 (17.01)	200 (18.60)
1	1018 (10.58)	189 (14.48)	73 (13.72)	1689 (10.27)	83 (14.29)	179 (14.47)	2062 (10.47)	197 (13.40)	151 (14.05)
2	1468 (25.66)	326 (24.98)	127 (23.87)	4907 (29.83)	122 (22.47)	308 (24.90)	5973 (30.33)	354 (24.08)	274 (25.49)
3	2261 (23.51)	271 (20.77)	114 (21.43)	3887 (23.63)	110 (20.26)	273 (22.07)	4604 (23.38)	301 (20.48)	237 (22.05)
4+	2792 (29.51)	291 (22.30)	120 (22.56)	4114 (25.01)	119 (21.92)	269 (21.75)	4822 (24.48)	368 (25.03)	213 (19.81)
Unknown	793	85	31	154	21	45	157	58	50
Breastfeeding									
No	2543 (34.56)	360 (55.99)	156 (54.17)	4516 (32.51)	214 (48.97)	419 (47.24)	5568 (32.59)	440 (46.81)	305 (46.49)
Yes	4815 (65.44)	283 (44.01)	132 (45.83)	9377 (67.49)	223 (51.03)	468 (52.76)	11517 (67.41)	500 (53.19)	351 (53.51)
Unknown	3053	747	275	2713	127	395	2766	588	469
Duration of breastfeeding									
0	2543 (34.66)	360 (56.60)	156 (54.36)	4516 (32.52)	214 (49.08)	419 (47.40)	5568 (33.61)	440 (47.01)	305 (46.49)
<6 months	1871 (25.50)	119 (18.71)	55 (19.16)	4255 (30.64)	113 (25.92)	196 (22.17)	4900 (29.58)	233 (24.89)	159 (24.24)
6-12 months	1196 (16.30)	78 (12.26)	26 (9.06)	2203 (15.86)	47 (10.78)	124 (14.03)	2566 (15.49)	118 (12.61)	88 (13.41)
>12 months	1727 (13.54)	79 (12.42)	50 (17.42)	2912 (20.97)	62 (14.22)	145 (16.40)	3532 (21.32)	145 (15.49)	104 (15.85)
Unknown	3074	754	276	2720	128	398	3285	592	469
Age at menarche									
<=13 years	6297 (66.38)	777 (67.51)	365 (72.85)	9225 (64.81)	355 (68.40)	799 (68.29)	11516 (66.07)	958 (68.33)	743 (71.65)

>13 years	3189 (33.62)	374 (32.49)	136 (27.15)	5009 (35.19)	164 (31.60)	371 (31.71)	5915 (33.93)	444 (31.67)	294 (28.35)
Unknown	925	239	62	2372	45	112	2420	126	88
Menopause status									
pre	3109 (32.04)	335 (26.01)	166 (31.50)	4278 (29.45)	168 (31.40)	369 (30.52)	5250 (29.57)	325 (22.48)	372 (35.00)
post	6594 (67.96)	953 (73.99)	361 (68.50)	10250 (70.55)	367 (68.60)	840 (69.48)	12502 (70.43)	1121 (77.52)	691 (65.00)
Unknown	708	102	36	2078	29	73	2099	82	62
Endometriosis									
No	8226 (94.22)	594 (91.53)	244 (92.08)	7629 (92.95)	247 (90.15)	573 (91.53)	8154 (93.28)	804 (92.84)	553 (89.77)
Yes	505 (5.78)	55 (8.47)	21 (7.92)	579 (7.05)	27 (9.85)	53 (8.47)	587 (6.72)	62 (7.16)	63 (10.23)
Unknown	1680	741	298	8398	290	656	11110	662	509
Hysterectomy									
No	8089 (84.06)	667 (59.39)	283 (55.17)	13751 (83.94)	366 (70.52)	720 (62.72)	16217 (82.64)	770 (55.16)	549 (53.98)
Yes	1534 (15.94)	456 (40.61)	230 (44.83)	2630 (16.06)	153 (29.48)	428 (37.28)	3407 (17.36)	626 (44.84)	468 (46.02)
Unknown	788	267	50	225	45	134	227	132	108
Hormonal treatment use									
No	6145 (64.39)	702 (67.31)	318 (67.52)	10593 (65.87)	335 (65.69)	734 (64.61)	12822 (66.34)	880 (63.54)	704 (69.50)
Estrogen only	705 (7.39)	49 (4.70)	14 (2.97)	665 (4.14)	21 (4.12)	27 (2.38)	1164 (6.02)	62 (4.48)	46 (4.54)
Combination	1525 (15.98)	140 (13.42)	65 (13.80)	1589 (9.88)	41 (8.04)	123 (10.83)	1991 (10.30)	194 (14.01)	129 (12.73)
Others	1169 (12.25)	152 (14.57)	74 (15.71)	3235 (20.12)	113 (20.16)	252 (22.18)	3350 (17.33)	249 (17.98)	134 (13.23)
Unknown	869	347	92	524	54	146	524	143	112

AR, androgen receptor; ER, estrogen receptor; PR, progesterone receptor.
1 Including AUS, BAV, CNI, GER, HAW, HOP, LAX, MAL, MAY, STA for tumor defined by AR status; AUS, HAW, HOP, MAL, MAY, POL, SEA, STA for tumor defined by ER status; AUS, GER, HAW, HOP, MAL, MAY, OVA, POL, SEA, STA for tumor defined by PR status.

Table 4-4 Pooled relative risk ratios for the association between hormonally linked risk factors and epithelial ovarian cancer by individual hormonal receptor presence compared to all controls[1,2]

	AR+, AR- compared to controls (N=10,411)			ER+, ER- compared to controls (N=16,606)			PR+, PR- compared to controls (N=8,852)		
	RRR (95% CI)			RRR (95% CI)			RRR (95% CI)		
	AR- N=1390	AR+ N=563	P for heter	ER- N=564	ER+ N=1282	P for heter	PR- N=1,528	PR+ N=1,125	P for heter
Physical inactivity									
Active	ref	ref	0.120	ref	ref	0.137	ref	ref	0.735
Inactive	1.26 (0.98, 1.61)	1.77 (1.20, 2.61)		1.68 (1.20, 2.36)	1.24 (0.97, 1.58)		1.36 (1.09, 1.70)	1.28 (0.95, 1.73)	
Obesity status at adulthood									
underweight/normal	ref	ref	0.523	**ref**	**ref**	**0.053**	ref	ref	0.402
overweight/obese	1.07 (0.91, 1.27)	1.18 (0.91, 1.52)		**1.53 (1.18, 1.98)**	**1.13 (0.95, 1.35)**		1.21 (1.04, 1.42)	1.34 (1.11, 1.60)	
Smoking status									
Never Smoker	ref	ref	0.439	ref	ref	0.355	ref	ref	0.096
Current Smoker	1.08 (0.86, 1.34)	1.11 (0.81, 1.51)		1.40 (1.09, 1.79)	1.21 (1.00, 1.47)		1.35 (1.13, 1.61)	1.10 (0.89, 1.36)	
Former Smoker	1.08 (0.92, 1.26)	0.92 (0.74, 1.16)		0.96 (0.77, 1.19)	1.06 (0.91, 1.22)		1.00 (0.87, 1.14)	1.10 (0.95, 1.27)	
Duration of oral contraceptive use, years									
0	ref	ref	0.381	ref	ref	0.740	ref	ref	0.406
<1	1.00 (0.80, 1.26)	1.01 (0.75, 1.36)		0.87 (0.64, 1.16)	1.00 (0.82, 1.22)		1.04 (0.86, 1.25)	1.08 (0.87, 1.33)	
1-4	0.73 (0.59, 0.91)	0.52 (0.38, 0.72)		0.66 (0.50, 0.89)	0.63 (0.52, 0.78)		0.82 (0.68, 0.97)	0.67 (0.54, 0.82)	
5-9	0.50 (0.41, 0.63)	0.46 (0.34, 0.61)		0.57 (0.43, 0.75)	0.50 (0.41, 0.61)		0.57 (0.47, 0.68)	0.54 (0.44, 0.65)	
10+	0.39 (0.30, 0.51)	0.35 (0.25, 0.51)		0.36 (0.25, 0.52)	0.35 (0.28, 0.45)		0.39 (0.31, 0.48)	0.41 (0.33, 0.52)	
P for trend[3]	0.0002	0.1086		0.0502	0.0002		0.0009	0.0007	

Number of pregnancies									
Never	ref	ref	0.893	ref	ref	0.356	ref	ref	0.209
1	1.02 (0.80, 1.29)	0.98 (0.70, 1.37)		0.85 (0.62, 1.16)	0.98 (0.78, 1.24)		0.89 (0.72, 1.11)	0.93 (0.74, 1.18)	
2	0.75 (0.61, 0.93)	0.79 (0.59, 1.06)		0.54 (0.41, 0.72)	0.70 (0.58, 0.86)		0.64 (0.53, 0.77)	0.67 (0.55, 0.83)	
3	0.6 (0.54, 0.84)	0.75 (0.56, 1.02)		0.61 (0.45, 0.81)	0.71 (0.58, 0.88)		0.62 (0.51, 0.75)	0.69 (0.55, 0.85)	
4+	0.56 (0.45, 0.69)	0.62 (0.46, 0.84)		0.58 (0.44, 0.78)	0.57 (0.46, 0.70)		0.61 (0.51, 0.74)	0.51 (0.41, 0.64)	
P for trend[3]	<0.0001	<0.0001		<0.0001	<0.0001		<0.0001	<0.0001	
Duration of breastfeeding									
0	ref	ref	0.074	ref	ref	0.650	ref	ref	0.666
<6 months	0.61 (0.48, 0.79)	0.85 (0.59, 1.21)		0.75 (0.57, 0.99)	0.67 (0.54, 0.82)		0.83 (0.61, 0.89)	0.81 (0.65, 1.01)	
6-12 months	0.57 (0.43, 0.76)	0.47 (0.30, 0.75)		0.53 (0.37, 0.76)	0.61 (0.48, 0.78)		0.60 (0.47, 0.75)	0.72 (0.55, 0.95)	
>12 months	0.45 (0.34, 0.60)	0.69 (0.47, 1.00)		0.53 (0.38, 0.73)	0.51 (0.40, 0.64)		0.53 (0.42, 0.66)	0.61 (0.47, 0.79)	
P for trend[3]	<0.0001	0.0227		0.0109	<0.0001		0.2175	0.3540	
Age at menarche									
<=13 years	ref	ref	0.201	ref	ref		ref	ref	0.271
>13 years	0.91 (0.79, 1.06)	0.78 (0.63, 0.97)		0.87 (0.71, 1.06)	0.92 (0.80, 1.06)	0.648	0.88 (0.78, 1.00)	0.80 (0.70, 0.92)	
Menopause status at diagnosis									
pre	ref	ref	0.809	ref	ref	0.793	**ref**	**ref**	**0.0008**
post	1.41 (1.14, 1.75)	1.36 (1.00, 1.83)		1.22 (0.92, 1.62)	1.28 (1.04, 1.56)		**1.52 (1.26, 1.83)**	**0.98 (0.80, 1.20)**	
Endometriosis									
No	ref	ref	0.715	ref	ref	0.508	ref	ref	0.109
Yes	1.34 (0.98, 1.83)	1.21 (0.76, 1.95)		1.34 (0.87, 2.08)	1.13 (0.82, 1.55)		1.01 (0.76, 1.35)	1.38 (1.03, 1.85)	
Hysterectomy									
No	ref	ref	**0.067**	**ref**	**ref**	**0.018**	ref	ref	**0.057**
Yes	5.80	7.33		**3.67**	**4.99**		5.10	6.11	

	(4.90, 6.86)	(5.82, 9.24)		**(2.93, 4.60)**	**(4.27, 5.83)**		(4.45, 5.83)	(5.22, 7.15)	
Hormonal treatment use									
No	ref	ref	0.406	ref	ref	0.120	ref	ref	0.806
Estrogen only	0.74 (0.53, 1.01)	0.56 (0.32, 0.98)		0.94 (0.58, 1.54)	0.57 (0.38, 0.86)		0.67 (0.51, 0.89)	0.79 (0.57, 1.09)	
Combination	0.91 (0.73, 1.12)	1.07 (0.79, 1.44)		0.72 (0.50, 1.04)	0.92 (0.74, 1.15)		0.93 (0.77, 1.11)	0.97 (0.78, 1.20)	
Others	0.72 (0.57, 0.90)	0.87 (0.63, 1.21)		1.31 (1.01, 1.70)	1.55 (1.29, 1.87)		1.31 (1.10, 1.57)	1.23 (0.98, 1.54)	

AR, androgen receptor; CI, confidence interval; ER, estrogen receptor; heter, heterogeneity; PR, progesterone receptor; RRR, relative risk ratio.

1 Including AUS, BAV, CNI, GER, HAW, HOP, LAX, MAL, MAY, STA for tumor defined by AR status; AUS, HAW, HOP, MAL, MAY, POL, SEA, STA for tumor defined by ER status; AUS, GER, HAW, HOP, MAL, MAY, OVA, POL, SEA, STA for tumor defined by PR status.

2 adjusted for study site, age (continuous), family history of breast or ovarian cancer in first-relative (no, ovarian cancer only, breast cancer only, both ovarian cancer and breast cancer), duration of OC use (0, <1, 1-4, 5-9, or 10+ years), number of pregnancies (never, 1, 2, 3, or 4+), menopause status at diagnosis (pre or post), and hormonal treatment use (no, estrogen only, combination, or others). Models treated unknown groups as indexes. Estimates for unknown groups were not reported in the table.

3 P for trend was from Wald test.

Table 4-5 Pooled relative risk ratios for the association between hormonally linked risk factors and epithelial ovarian cancer by joint hormonal receptor presence compared eto all controls[1,2]

	RRR (95% CI)				
PANEL A Control (N=8841)	**AR- ER- N=292**	**AR+ ER- N=44**	**AR- ER+ N=498**	**AR+ ER+ N=244**	**P for heter**
Physical inactivity					
Active	ref	ref	ref	ref	0.7755
Inactive	1.61 (1.09, 2.38)	0.88 (0.22, 3.50)	1.36 (0.95, 1.93)	1.25 (0.68, 2.27)	
Obesity status at adulthood					
underweight/ normal	ref	ref	ref	ref	0.7038
overweight/ obese	1.27 (0.94, 1.71)	1.47 (0.56, 3.89)	1.04 (0.81, 1.33)	1.12 (0.73, 1.71)	
Smoking status					
Never Smoker	ref	ref	ref	ref	0.1698
Current Smoker	1.40 (0.98, 2.01)	1.69 (0.77, 3.70)	0.96 (0.67, 1.38)	1.38 (0.90, 2.09)	
Former Smoker	1.03 (0.76, 1.39)	0.58 (0.25, 1.38)	1.22 (0.97, 1.52)	1.03 (0.75, 1.41)	
Duration of oral contraceptive use, years					
0	ref	ref	ref	ref	0.2414
<1	0.75 (0.51, 1.12)	1.67 (0.70, 4.01)	1.17 (0.86, 1.59)	1.14 (0.77, 1.69)	
1-4	0.55 (0.37, 0.80)	0.91 (0.36, 2.29)	0.73 (0.54, 0.99)	0.42 (0.27, 0.66)	
5-9	0.46 (0.32, 0.68)	0.47 (0.17, 1.38)	0.47 (0.34, 0.65)	0.50 (0.34, 0.75)	
10+	0.23 (0.13, 0.41)	0.44 (0.12, 1.60)	0.48 (0.66, 0.68)	0.36 (0.22, 0.60)	
Number of pregnancies					
Never	ref	ref	ref	ref	0.6034
1	0.90 (0.59, 1.38)	0.98 (0.32, 3.01)	1.12 (0.77, 1.63)	0.83 (0.52, 1.35)	
2	0.62 (0.42, 0.92)	0.44 (0.14, 1.44)	0.78 (0.56, 1.09)	0.75 (0.49, 1.14)	
3	0.52 (0.34, 0.78)	1.08 (0.41, 2.89)	0.83 (0.59, 1.15)	0.61 (0.39, 0.95)	
4+	0.46 (0.31, 0.68)	0.81 (0.30, 2.18)	0.64 (0.46, 0.89)	0.43 (0.28, 0.68)	
Duration of breastfeeding					
0	ref	ref	ref	ref	0.5856
<6 months	0.57 (0.38, 0.87)	0.98 (0.37, 2.60)	0.66 (0.44, 0.99)	0.86 (0.52, 1.43)	
6-12 months	0.52 (0.32, 0.84)	0.45 (0.12, 1.65)	0.54 (0.35, 0.85)	0.48 (0.27, 0.86)	
>12 months	0.40 (0.25, 0.64)	0.64 (0.24, 1.71)	0.43 (0.28, 0.65)	0.75 (0.48, 1.20)	
Age at menarche					
<=13 years	ref	ref	ref	ref	0.1661
>13 years	0.82 (0.61, 1.09)	0.59 (0.27, 1.29)	0.98 (0.78, 1.23)	0.65 (0.47, 0.92)	
Menopause status at diagnosis					
pre	ref	ref	ref	ref	0.9959

post	1.16 (0.77, 1.74)	1.08 (0.41, 2.85)	1.13 (0.82, 1.56)	1.19 (0.77, 1.86)	
Endometriosis					
No	ref	ref	ref	ref	0.3156
Yes	1.44 (0.82, 2.52)	4.19 (1.12, 15.62)	1.18 (0.74, 1.89)	1.08 (0.49, 2.38)	
Hysterectomy					
No	ref	ref	ref	ref	**0.0028**
Yes	4.50 (3.25, 6.24)	6.71 (2.89, 15.57)	9.31 (7.17, 12.09)	5.97 (4.15, 8.59)	
Hormonal treatment use					
No	ref	ref	ref	ref	0.9251
Yes	1.13 (0.83, 1.53)	0.86 (0.36, 2.04)	1.03 (0.80, 1.32)	1.09 (0.76, 1.57)	
PANEL B Control (N=9374)	**AR- PR- N=669**	**AR+ PR- N=180**	**AR- PR+ N=319**	**AR+ PR+ N=272**	**P for heter**
Physical inactivity					
Active	ref	ref	ref	ref	0.8774
Inactive	1.36 (1.01, 1.82)	1.66 (0.91, 3.01)	1.29 (0.81, 2.06)	1.58 (0.92, 2.70)	
Obesity status at adulthood, kg/m^2					
underweight/ normal	ref	ref	ref	ref	0.8927
overweight/ obese	1.09 (0.88, 1.34)	1.28 (0.84, 1.97)	1.18 (0.87, 1.59)	1.16 (0.82, 1.66)	
Smoking status					
Never Smoker	ref	ref	ref	ref	0.2309
Current Smoker	1.18 (0.90, 1.56)	1.04 (0.61, 1.76)	0.93 (0.60, 1.43)	1.31 (0.88, 1.94)	
Former Smoker	1.11 (0.91, 1.35)	0.80 (0.55, 1.15)	1.32 (1.01, 1.72)	0.99 (0.73, 1.34)	
Duration of oral contraceptive use, years					
0	ref	ref	ref	ref	0.3873
<1	1.08 (0.83, 1.42)	0.80 (0.48, 1.34)	0.91 (0.62, 1.34)	1.25 (0.86, 1.81)	
1-4	0.79 (0.61, 1.02)	0.71 (0.45, 1.13)	0.75 (0.53, 1.07)	0.45 (0.30, 0.70)	
5-9	0.52 (.40, 0.68)	0.55 (0.35, 0.88)	0.49 (0.34, 0.70)	0.42 (0.29, 0.63)	
10+	0.38 (0.27, 0.53)	0.33 (0.18, 0.61)	0.42 (0.27, 0.64)	0.33 (0.20, 0.53)	
Number of pregnancies					
Never	ref	ref	ref	ref	0.2907
1	0.89 (0.65, 1.22)	1.06 (0.59, 1.93)	1.44 (0.95, 2.18)	0.96 (0.62, 1.50)	
2	0.71 (0.54, 0.94)	0.91 (0.54, 1.53)	0.80 (0.54, 1.19)	0.63 (0.42, 0.94)	
3	0.58 (0.44, 0.78)	0.83 (0.49, 1.41)	0.97 (0.66, 1.42)	0.74 (0.49, 1.10)	
4+	0.57 (0.43, 0.75)	0.82 (.49, 1.35)	0.58 (0.39, 0.88)	0.48 (0.32, 0.73)	
Duration of breastfeeding					
0	ref	ref	ref	ref	0.4118
<6 months	0.61 (0.45, 0.84)	0.77 (0.41, 1.44)	0.80 (0.50, 1.27)	0.96 (0.60, 1.53)	
6-12 months	0.58 (0.40, 0.83)	0.61 (0.30, 1.23)	0.76 (0.45, 1.28)	0.46 (0.24, 0.88)	

>12 months	0.41 (0.28, 0.59)	0.74 (0.41, 1.34)	0.54 (0.32, 0.90)	0.71 (0.44, 1.17)	
Age at menarche					
<=13 years	ref	ref	ref	ref	0.2315
>13 years	0.87 (0.71, 1.05)	0.79 (0.55, 1.12)	0.93 (0.71, 1.22)	0.63 (0.46, 0.86)	
Menopause status at diagnosis					
pre	ref	ref	ref	ref	**0.0002**
post	**1.74 (1.31, 2.32)**	1.58 (0.94, 2.68)	**0.65 (0.45, 0.94)**	1.15 (0.77, 1.73)	
Endometriosis					
No	ref	ref	ref	ref	0.5887
Yes	1.14 (0.76, 1.71)	1.26 (0.60, 2.67)	1.68 (1.03, 2.73)	1.06 (0.55, 2.06)	
Hysterectomy					
No	ref	ref	ref	ref	**0.0388**
Yes	7.40 (5.98, 9.17)	11.90 (8.05, 17.58)	10.62 (7.70, 14.65)	7.09 (5.10, 9.85)	
Hormonal treatment use					
No	ref	ref	ref	ref	0.8071
Yes	0.97 (0.79, 1.19)	1.02 (0.71, 1.46)	0.92 (0.67, 1.26)	0.83 (0.60, 1.15)	

PANEL C Control (N=16606)	**ER- PR- N=495**	**ER+ PR- N=583**	**ER- PR+ N=58**	**ER+ PR+ N=665**	**P for heter**
Physical inactivity					
Active	ref	ref	ref	ref	0.5642
Inactive	1.61 (1.12, 2.30)	1.28 (0.92, 1.79)	2.02 (0.62, 6.56)	1.18 (0.83, 1.68)	
Obesity status at adulthood					
underweight/ normal	ref	ref	ref	ref	0.1145
overweight/ obese	1.57 (1.19, 2.07)	1.01 (0.79, 1.29)	1.47 (0.65, 3.12)	1.31 (1.02, 1.67)	
Smoking status					
Never Smoker	ref	ref	ref	ref	0.2370
Current Smoker	1.43 (1.10, 1.86)	1.19 (0.90, 1.56)	0.74 (0.30, 1.83)	1.19 (0.93, 1.54)	
Former Smoker	0.94 (0.75, 1.18)	0.93 (0.76, 1.15)	1.06 (0.57, 1.94)	1.19 (0.98, 1.44)	
Duration of oral contraceptive use, years					
0	ref	ref	ref	ref	0.6718
<1	0.93 (0.68, 1.27)	1.04 (0.78, 1.38)	0.59 (0.21, 1.60)	1.00 (0.77, 1.29)	
1-4	0.70 (0.52, 0.96)	0.82 (0.62, 1.08)	0.51 (0.20, 1.31)	0.52 (0.39, 0.69)	
5-9	0.55 (0.41, 0.75)	0.56 (0.43, 0.74)	0.65 (0.29, 1.46)	0.47 (0.36, 0.61)	
10+	0.36 (0.25, 0.53)	0.39 (0.27, 0.54)	0.28 (0.08, 0.96)	0.33 (0.24, 0.46)	
Number of pregnancies					
Never	ref	ref	ref	ref	0.2669
1	0.86 (0.62, 1.20)	0.85 (0.60, 1.20)	0.84 (0.28, 2.47)	1.07 (0.80, 1.43)	
2	0.49 (0.36, 0.67)	0.73 (0.55, 0.98)	1.08 (0.45, 2.58)	0.66 (0.50, 0.86)	

3	0.59 (0.43, 0.80)	0.71 (0.52, 0.96)	0.92 (0.36, 2.33)	0.73 (0.56, 0.96)	
4+	0.57 (0.42, 0.77)	0.64 (0.47, 0.85)	0.81 (0.32, 2.07)	0.50 (0.38, 0.66)	
Duration of breastfeeding					
0	ref	ref	ref	ref	0.9719
<6 months	0.73 (0.55, 0.98)	0.65 (0.48, 0.88)	1.06 (0.47, 2.39)	0.72 (0.55, 0.94)	
6-12 months	0.51 (0.35, 0.75)	0.61 (0.44, 0.86)	0.69 (0.23, 2.03)	0.63 (0.45, 0.86)	
>12 months	0.53 (.37, 0.75)	0.49 (0.36, 0.68)	0.51 (0.17, 1.52)	0.54 (0.40, 0.73)	
Age at menarche					
<=13 years	ref	ref	ref	ref	0.5368
>13 years	0.90 (0.73, 1.11)	0.95 (0.79, 1.16)	0.66 (0.36, 1.21)	0.82 (0.68, 0.99)	
Menopause status at diagnosis					
pre	ref	ref	ref	ref	**0.0004**
post	**1.27 (0.94, 1.73)**	**2.17 (1.60, 2.95)**	**0.81 (0.35, 1.84)**	**0.97 (0.75, 1.26)**	
Endometriosis					
No	ref	ref	ref	ref	0.1506
Yes	1.17 (0.71, 1.91)	0.84 (0.52, 1.36)	2.66 (1.06, 6.70)	1.29 (0.86, 1.94)	
Hysterectomy					
No	ref	ref	ref	ref	0.1068
Yes	3.27 (2.58, 4.14)	4.11 (3.36, 5.03)	4.10 (2.19, 7.66)	4.76 (3.87, 5.86)	
Hormonal treatment use					
No	ref	ref	ref	ref	0.4960
Yes	1.04 (0.83, 1.30)	1.21 (0.99, 1.48)	1.59 (0.86, 2.95)	1.09 (0.88, 1.34)	

AR, androgen receptor; CI, confidence interval; ER, estrogen receptor; heter, heterogeneity; PR, progesterone receptor; RRR, relative risk ratio.
1 Including AUS, HAW, HOP, MAL, MAY, and STA for tumor defined by AR and ER status; AUS, GER, HAW, HOP, MAL, MAY, and STA for tumor defined by AR and PR status; HAW, HOP, MAL, MAY, POL, SEA, and STA for tumor defined by ER and PR status.
2 adjusted for study site, age (continuous), family history of breast or ovarian cancer in first-relative (yes or no), duration of OC use (0, <1, 1-4, 5-9 or 10+ years), number of pregnancies (never, 1, 2, 3, or 4+), menopause status at diagnosis (pre or post), and hormonal treatment use (yes, or no). Models treated unknown groups as indexes. Estimates for unknown groups are not reported in the table.

Table 4-6 Hazard ratios for the association of clinical variables and hormonally linked risk factors with survival from time of diagnosis for epithelial invasive ovarian tumor defined by individual receptor presence[1]

	AR- (N=2552)		AR+ (N=1153)		ER- (N=830)		ER+ (N=1699)		PR- (N=2640)		PR+ (N=1728)	
	HR (95% CI) Model 1[2]	HR (95% CI) Model 2[3]	HR (95% CI) Model 1[2]	HR (95% CI) Model 2[3]	HR (95% CI) Model 1[2]	HR (95% CI) Model 2[3]	HR (95% CI) Model 1[2]	HR (95% CI) Model 2[3]	HR (95% CI) Model 1[2]	HR (95% CI) Model 2[3]	HR (95% CI) Model 1[2]	HR (95% CI) Model 2[3]
Tumor characteristics												
Histotypes												
Serous	ref		ref		ref		ref		ref		ref	
Endometrioid	0.77 (0.61, 0.96)		0.61 (0.43, 0.87)		1.02 (0.72, 1.46)		0.44 (0.33, 0.57)		1.05 (0.81, 1.35)		0.49 (0.38, 0.63)	
Mucinous	1.32 (1.02, 1.71)		1.10 (0.65, 1.85)		0.91 (0.62, 1.33)		0.61 (0.28, 1.29)		0.92 (0.71, 1.18)		0.68 (0.34, 1.35)	
Clear cell	1.15 (0.93, 1.42)		0.53 (0.31, 0.93)		0.70 (0.52, 0.93)		0.86 (0.57, 1.29)		0.86 (0.69, 1.06)		0.75 (0.43, 1.29)	
Other	0.9 (0.66, 1.30)		0.73 (0.42, 1.29)		1.33 (0.84, 2.10)		0.42 (0.29, 0.62)		1.13 (0.86, 1.49)		0.41 (0.26, 0.64)	
Stage												
Stage I/II	ref		ref		ref		ref		ref		ref	
Stage III/IV	3.70 (3.13, 4.38)		3.17 (2.50, 4.02)		3.05 (2.32, 4.01)		2.44 (2.03, 2.92)		3.27 (2.79, 3.85)		3.38 (2.76, 4.14)	
Grade												
Low	ref		ref		ref		ref		ref		ref	
High	1.36 (1.09, 1.69)		1.79 (1.28, 2.50)		1.20 (0.83, 1.74)		1.22 (0.95, 1.56)		1.29 (1.02, 1.64)		1.44 (1.12, 1.84)	
Debulking status												
Optimal	ref		ref		ref		ref		ref		ref	
Suboptimal	1.77 (1.44, 2.17)		1.72 (1.20, 2.46)		2.61 (1.39, 4.91)		2.05 (1.55, 2.70)		1.86 (1.52, 2.27)		1.65 (1.25, 2.18)	
Hormonally-linked risk factors												
Physical inactivity												
Active		ref		ref		**ref**		**ref**		ref		ref
Inactive		1.02 (0.78, 1.35)		1.71 (1.14, 2.56)		**0.75 (0.48, 1.16)**		**1.47 (1.14, 1.89)**		1.16 (0.91, 1.48)		1.42 (1.02, 1.99)
Obesity status at adulthood												
No		ref		ref		ref		ref		ref		ref
Yes		0.94 (0.79, 1.12)		1.48 (1.16, 2.14)		0.92 (0.66, 1.27)		1.12 (0.92, 1.36)		1.01 (0.85, 1.19)		1.33 (1.05, 1.68)
Smoking Status												
Never Smoker		ref		ref		ref		ref		ref		ref
Current Smoker		1.19 (0.96, 1.49)		1.06 (0.75, 1.51)		1.32 (0.93, 1.89)		1.19 (0.96, 1.49)		1.12 (0.92, 1.35)		1.08 (0.83, 1.42)

Former Smoker	1.05 (0.89, 1.23)	0.89 (0.69, 1.15)	1.18 (0.89, 1.57)	1.01 (0.86, 1.20)	1.07 (0.93, 1.24)	1.02 (0.84, 1.24)
Duration of oral contraceptive use, years						
0	ref	ref	ref	ref	ref	ref
<1	1.09 (0.86, 1.38)	1.09 (0.75, 1.59)	1.14 (0.76, 1.73)	1.06 (0.85, 1.32)	1.02 (0.82, 1.26)	1.07 (0.82, 1.41)
1-4	0.94 (0.74, 1.20)	0.90 (0.60, 1.34)	0.99 (0.66, 1.50)	0.89 (0.71, 1.12)	0.83 (0.68, 1.02)	0.96 (0.73, 1.27)
5-9	1.04 (0.82, 1.33)	1.10 (0.78, 1.55)	1.00 (0.69, 1.45)	0.97 (0.78, 1.21)	0.95 (0.78, 1.16)	1.01 (0.78, 1.32)
10+	0.72 (0.51, 1.01)	0.99 (0.63, 1.55)	1.08 (0.61, 1.93)	0.78 (0.58, 1.04)	0.96 (0.74, 1.26)	0.78 (0.55, 1.09)
Number of full-term pregnancies						
Never	ref	ref	ref	ref	ref	ref
1	0.84 (0.66, 1.06)	0.93 (0.61, 1.41)	1.19 (0.78, 1.81)	0.98 (0.73, 1.31)	0.99 (0.79, 1.25)	0.93 (0.67, 1.29)
2	0.88 (0.71, 1.07)	1.04 (0.74, 1.47)	0.65 (0.43, 0.97)	1.18 (0.93, 1.51)	1.08 (0.89, 1.32)	0.89 (0.67, 1.18)
3	0.79 (0.63, 0.98)	1.05 (0.75, 1.47)	0.80 (0.53, 1.20)	0.98 (0.77, 1.26)	0.87 (0.71, 1.07)	0.94 (0.71, 1.23)
4+	0.79 (0.64, 0.98)	1.07 (0.77, 1.49)	0.92 (0.62, 1.35)	1.06 (0.83, 1.36)	0.99 (0.82, 1.21)	1.04 (0.79, 1.37)
Duration of breastfeeding, months						
0	ref	ref	ref	ref	ref	ref
<=6	0.79 (0.58, 1.06)	0.50 (0.31, 0.82)	1.14 (0.80, 1.64)	1.18 (0.93, 1.48)	1.09 (0.88, 1.34)	1.01 (0.75, 1.38)
>6, <=12	0.62 (0.43, 0.89)	0.95 (0.56, 1.61)	0.88 (0.54, 1.43)	1.14 (0.88, 1.49)	0.93 (0.71, 1.21)	1.04 (0.72, 1.52)
>12	0.79 (0.56, 1.12)	1.00 (0.63, 1.59)	1.06 (0.69, 1.61)	1.11 (0.83, 1.44)	1.13 (0.89, 1.44)	1.07 (0.76, 1.52)
Menopausal status at diagnosis						
Pre	ref	ref	ref	ref	ref	ref
Post	0.86 (0.71, 1.05)	0.75 (0.56, 1.01)	0.83 (0.59, 1.18)	0.83 0.68, 1.03)	0.99 (0.82, 1.20)	0.74 (0.59, 0.94)
Hormonal treatment use						
No	ref	ref	ref	ref	ref	ref
Yes	0.79 (0.67, 0.94)	0.73 (0.56, 0.94)	0.86 (0.65, 1.14)	0.76 (0.65, 0.90)	0.79 (0.69, 0.92)	0.94 (0.77, 1.15)

AR, androgen receptor; CI, confidence interval; ER, estrogen receptor; HR, hazard ratio; PR, progesterone receptor.
1 Including AOV, AUS, BAV, CNI, GER, HAW, HOP, LAX, MAL, MAY, POC, STA, VAN, and WMH for tumor defined by AR status; AUS, HAW, HOP, MAL, MAY, POL, SEA, STA, and VAN for tumor defined by ER status; AOV, AUS, GER, HAW, HOP, MAL, MAY, OVA, POC, POL, SEA, STA, SWE, VAN and WMH for tumor defined by PR status.
2 One multivariable model included age, histotypes, stage, grade, and debulking status. Models treated unknown groups as indexes. Estimates for unknown groups are not reported in the table.
3 Separated multivariable models included the variable of interest adjusting for age, histotypes, stage, grade, and debulking status. Models treated unknown groups as indexes. Estimates for unknown groups are not reported in the table.

5.0 Paper III: Feature identification for epithelial ovarian cancer survival using machine learning techniques

5.1 Abstract

Introduction: Ovarian cancer is the most lethal gynecologic cancer, but little progress has been made in identifying factors predicting survival. Machine learning (ML) techniques may address this concern. The aim of the current study is to evaluate several ML techniques in order to develop a prediction model for survival in epithelial ovarian cancer (EOC)patients and identify the most important clinical and tumor marker features.

Method: We included 5803 patients diagnosed with EOC from 22 studies with data on at least 7 immunohistochemistry biomarkers from a set of 9 immunohistochemistry markers: androgen receptor (AR), estrogen receptor alpha (ER), progesterone receptor (PR), myeloid differentiation primary response gene 88 (MyD88), toll-like receptor 4 (TLR4), folate receptor 1 (FOLR1), CD8+ tumor-infiltrating lymphocytes (CD8+ TILs), p16, and phosphatase and tensin homolog (PTEN). The dataset was split into the training set to conduct model selection and the external test set to perform feature identification. The best model was selected based on C-index from seven prediction models built by Cox proportional hazard models (Cox), random survival forest (RSF), boosting in Cox regression (boostCox), support vector machine for survival (SVMsur), deep neural networks for survival analysis using pseudo values (DNNSurv), and deep neural networks for survival analysis based on the partial likelihood from a Cox proportional hazards model (deepsurv). The top 5, 10, and 15 features, and the whole set of features from the best model were refit into the training set. Feature identification was based on the C-index from

the external test set. Hazard Ratios (HRs) and 95% confidence intervals (CIs) of each feature in the boostCox models with the best performance were obtained to indicate the direction of effects of each feature on EOC survival.

Results: The boostCox model presented the best performance with Harrell's C index of 71.73% and Uno's C index of 72.01% among all seven models. The boostCox models with the top 10 features, top 15 features, and the whole set of features presented similar performance. For application in the clinical settings, the boostCox model with the top 10 features, including stage, age, grade, CD8, histotype, debulking status, AR, PR, race, and p16, was selected as the final prediction model.

Conclusion: ML techniques can be applied to predict EOC survival. In our case, the boostCox model presented the best performance. Our prediction model indicated that CD8, AR, PR and p16 play important roles in the prediction of EOC survival. Understanding the biologic mechanisms behind these observations can provide insight into future treatments targeting these biomarkers.

5.2 Introduction

According to the American Cancer Society, about 13,770 women will die from ovarian cancer in 2021 in the U.S., more than any other gynecologic cancer.[1,380] Due to its low survival rate, the mortality trend of ovarian cancer mirrors the incidence trend.[381] Epithelial ovarian cancer (EOC) accounts for nearly 90% of malignant ovarian cancer.[2] The most common histotypes of EOC include high-grade and low-grade serous (60%), endometrioid (10%), clear cell (6%), and mucinous (6%).[2] Among ovarian cancer cases at the distant stage, the 5-year overall survival ranged from 13.9% with mucinous histotype to 54.2% with low-grade serous histotype of the distant stage.[12] There is a need to better understand features that impact survival outside of the specific histologic subtypes and stage.

Previous studies have suggested that clinical variables, such as histotype, tumor stage, surgical debulking status, grade and BRCA mutations impact EOC survival.[1,382-387] Tumor-specific features, such as hormone receptor expression,[204-206] may also be associated with prognosis. In addition to hormone receptor expression, the Ovarian Tumor Tissue Analysis Consortium (OTTA) reported that other tumor markers, such as myeloid differentiation primary response gene 88 (MyD88), toll-like receptor 4 (TLR4), folate receptor 1 (FOLR1), CD8+ tumor-infiltrating lymphocytes (CD8+ TILs), p16, and phosphatase and tensin homolog (PTEN), are associated with survival in histotype-specific ways.[207-211] To date, no prediction model for EOC survival has been developed to identify the relative importance of features from these reported prognostic clinical variables and biomarkers.

Machine learning (ML) techniques, such as support vector machines, decision tress, and artificial neural networks, have been widely applied in cancer research[388] and have shown that the accuracy of predicting cancer susceptibility, recurrence, and morality can be improved from 15%

to 25% [389]. To date, only one study employed classification for predicting the EOC survival, showing that using gradient boosting improved the area under the curve from 0.597 by Cox proportional hazard models to 0.843 in the test set.[390]

The aim of the current study is to develop a prediction model for EOC patient survival by pooling cases from 22 studies and identifying the most important features from clinical variables and nine biomarkers related to EOC survival based on the performances of seven models built by Cox proportional hazard model and ML techniques.

5.3 Method

Patients and clinical variables

The OTTA was formed in 2010 to validate prognostic markers for EOC by histotypes.[356] We included 5803 patients diagnosed with EOC from 22 OTTA studies with data on at least 7 IHC biomarkers. Characteristics of these 22 OTTA studies are summarized in **Table 5-1**.[55,60,209,309,312-314,316,325,329,357,358,391,392] All studies received local Institutional Review Board approvals. We obtained follow-up data, IHC data, and clinical variables that impact survival, including age at diagnosis, tumor stage (stage I/II, stage III/IV, or unknown), histotypes (high grade serous, low grade serous, endometrioid, mucinous, or clear cell), grade (low, high, or unknown), behavior (invasive or discordant), debulking status (optimal, suboptimal, or unknown), and BRCA 1/2 mutation status (wild type, pathogenic, unclassified variant, or unknown/untested) from the OTTA data coordinating center.

Immunohistochemistry

Data on staining of the nine IHC biomarkers (androgen receptor (AR), estrogen receptor alpha (ER), progesterone receptor (PR), MyD88, TLR4, FOLR1, CD8+ TILs, p16, and PTEN) were obtained from the OTTA coordinating center. IHC analyses were performed at Genetic Pathology Evaluation Centre (Vancouver, BC, Canada) for ER and PR,[204] Ventana Medical Systems Inc. (Tucson, AZ, USA) for AR,[211] at the Mayo Clinic (Rochester, Minnesota) for MyD88, TLR4 and CD8+ TILs,[207,208] at Leica Microsystems (Wetzlar, Germany) for FOLR1,[209] at Cell Signaling (Danvers, MA, USA) for PTEN,[211] and at two institutions (Genetic Pathology Evaluation, Centre, University of British Columbia, and Calgary Laboratory Services, University of Calgary, Canada) for p16.[210] AR was scored into a 5-tiered system (no tumoral tissue, necrosis or hemorrhage, no staining in tumoral cells or just cytoplasmic staining, just stromal cells staining, just tumoral cells staining,

and both tumoral and stromal cells staining); ER and PR were scored into a 3-tiered system (<1%, 1 to 50%, and >50% of tumor cell nuclei positive); p16 expression was classified into a 3- tiered system was used (<1%, 1 to 75%, and >75% of tumor cell nuclei positive); MyD88, TLR4 and PTEN were scored into a 4-tiered system (negative, week, moderate and strong expression); CD8+ TILs were scored into a 4-tiered system (none, 1-2 IEL/40 x HPF, 3-19 IEL/40 x HPF, and >=20 IEL/40 x HPF); and FOLR1 was scored into a 6-tiered system (absent, weak, 1-50% irrespective of subcellular localization, >50% with membranous localization, 50-95% with cytoplasmic staining and >95% with cytoplasmic staining). We labeled the missing values of each IHC biomarker as "untested/uninterpretable". An index for patients with an untested/uninterpretable value was added to each biomarker. The missing data patterns for IHC biomarkers by site are presented in **Supplemental Table I**.

Model selection

Patients were randomly split into a training set (70%) for model selection and an external test set (30%) for feature identification. The training set was further randomly split into a training set (70%) and test set (30%) for model selection. A flowchart for the construction of a prediction model for EOC survival is shown in **Figure 5-1**. In addition to Cox proportional hazard models (Cox) (R package *Survival*) dealing with right-censored data fitting with age, stage and histotypes (basic Cox) and fitting with all variables (full Cox), we evaluated five ML techniques, including random survival forest (RSF) (R package *randomForestSRC*),[393] boosting in Cox regression (boostCox) (R package *mboost*),[394] support vector machine for survival (SVMsur) (R package *survivalsvm*),[395] deep neural networks for survival analysis using pseudo values (DNNSurv) (R package *survivalmodels*) [396] and deep neural networks for survival analysis based on the partial likelihood from a Cox proportional hazards model (deepsurv) (R package *survivalmodels*)[397] to build the prediction models for EOC survival using the training set (N=2843). The detailed

description of the features of each of these models is shown in **Supplemental Table II**. To evaluate model performance, Harrell's C index[398] and Uno's C index dealing with censored survival[399] data were calculated for each model in the test set (N=1219; R package *Hmisc* and *survAUC*).

Feature identification

To identify important features, the best performing model based on the C-index was selected. It was then refit with the top 5, 10 and 15 features, and the full set of features using the entire training set (N=4062). Uno's C indices at the discrete time point (at the first, third, fifth, tenth and fifteenth years after the diagnosis) were calculated using the external test set (N=1741) to estimate the performances of the best performing model fit with four different feature sets. Hazard Ratios (HRs) and 95% confidence intervals (CIs) of each feature in the models with the best performances were obtained from a Cox model using the entire dataset (N=5803) to indicate the direction of effects of each feature on EOC survival. All statistical analysis were performed using R Studio (R version 4.1.0).

5.4 Results

Description of participants

We included 5803 EOC cases in the current analysis (**Table 5-2**). There were 3588 fatal cases (61.93%) and 2215 censored cases (38.17%) in the analysis dataset. The median survival time was 1890 days (5.2 years). There were 3800 cases of high grade serous histotype (65.48%), 784 cases of endometrioid histotype (13.51%), 667 cases of clear cell histotype (11.49%), 359 cases of mucinous histotype (6.19%) and 193 cases of low grade serous histotype (3.33%). Nealy 60% of cases were diagnosed at stage III/IV. There were 2665 cases with optimal debulking status (45.92%) and 427 cases with suboptimal debulking status (7.36%). The majority of cases had negative AR expression (56.54%), untested or uninterpretable ER expression (58.09%) or PR expression (59.16%), moderate intensity of TLR4 (42.65%) or MyD88 (38.46%), untested or uninterpretable FOLR1 (55.99%), weak intensity of PTEN (40.10%), 3-19 IEL/40 x HPF of CD8 (34.98%) and 1 to 75% of tumor cell nuclei positive expression of p16 (41.98%).

Model selection

The overall Harrell's and Uno's C indexes to evaluate each model's performances using the test set are summarized in **Table 5-3**. The boostCox model performed best with Harrell's C index of 71.73% and Uno's C index of 72.01%. The full Cox model had the second highest Harrell's C index (71.08%) and forth highest Uno's C index 7(0.54%). The basic Cox model had the second highest Uno's C index (71.16%) and forth highest Harrell's C index (71.16%). The RSF model had the third highest Harrell's C index of 71.03% and the third highest Uno's C index of 70.98%. We further evaluated each model's performance at one, three, five, ten and fifteen years after diagnosis (**Supplemental Table III**). The boostCox model presented the best performance followed by the full Cox model and the RSF model at all time points.

Feature identification

The variable importance in the boostCox model is presented in **Figure 5-2**. The top fifteen features based on the variable importance were stage, age, grade, CD8, histotypes, debulking status, AR, PR, race, p16, BRCA1/2 mutation status, ER, FOLR1, MyD88, TLR4. Uno's C indexes were calculated at one, three, five, ten and fifteen years after diagnosis for the boostCox models with the top 5, 10, 15 features and the whole set of features (**Table 5-4**). The boostCox models with the top 10 features, top 15 features and the whole set of features had similar performance. Therefore, the boostCox model with the top 10 features (the most parsimonious model) was selected as the final prediction model. The features identified by the final prediction model include stage, age, grade, CD8, histotypes, debulking status, AR, PR, race and p16 expression. The refitted Cox model with these ten variables indicated that CD8 was significantly negatively associated with hazard of EOC death (HR for 20 or more IEL/40 x HPF, 3-19 IEL/40 x HPF and 1-2 IEL/40 x HPF compared to no IEL 0.89, 0.76. 0.60, respectively). Larger than 75% of tumor cells positive expression of p16 had a borderline significant association with worse survival compared to negative p16 expression (HR 1.16, 95% CI 1.00-1.34). Although AR and PR expression were important indicators in the prediction model, they were not significantly associated with EOC survival in the refitted Cox model.

5.5 Discussion

In the current study, we applied five ML techniques to build prediction models for EOC survival. The boostCox model had the best performance among all five ML models, plus the Cox model with age stage and histotypes, and the Cox model with the full set of features. The boostCox models with the top 10, 15 important features and the full set of features presented similar performance based on Uno's C-indexes. The features identified by our final prediction model include stage, age, grade, CD8, histotypes, debulking status, AR, PR, race and p16 expression.

To date, there have been two studies that applied ML techniques in the field of EOC survival.[385,400] Both studies performed clustering based on tumor features and then identified significant differences across the clusters. To our knowledge, there have been no previous ML-based studies to predict time-to-event among ovarian cancer patients directly. In the current study, we applied RSF, boostCox, SVMsur, DNNSurv and deepsurv to build a prediction model for EOC survival. RSF and boostCox are tree-based methods, which have a built-in function to determine the importance of features. SVMsur is a popular alternative approach to the Cox model when the proportional hazards assumption cannot be easily checked. DNNSurv and deepsurv are two deep neural network models that are widely used in big data. However, the last three techniques do not allow feature identification. The boostCox with importance values assigned to each variable performed best in terms of Harrells' C index and Uno's C index. The boostCox technique obtains statistical model estimates via gradient descent, and carries out feature identification.[401] The strengths of the boostCox technique are that the results can be interpreted similar to those from the classic Cox model, and it identifies specific features from the set of potential predicators (ie, it is not "black box"). However, the magnitudes and the direction of the associations between predictors and outcomes cannot be directly quantified the boostCox technique. Unexpectedly, the

two deep neural network models, DNNSurv and deepsurv did not perform as well as other models. This could be due to the small number of predictors in the current dataset, which could induce overfitting. These Thechiniques may be more suitable for building a prediction model when using datasets with a large number of predictors.

CD8+ TILs, AR, ER and p16 are the four biomarkers in the top ten features identified by the boostCox model. CD8+ TILs plays an important role for immune defense against intracellular pathogens and for tumor surveillance.[402] Activation of CD8+ T cells triggers TILs to fill tumor cells.[224] Higher CD8+ TILs in tumors was associated with better survival in the OTTA study[208] and a meta-analysis including 8 studies.[403] A prospective population-based study with 90 serous cases indicated AR expression alone was observed to be a favorable prognostic factor for the serous subtypes,[206] and the Swedish cohort study with 118 serous and endometrioid cases indicated AR+PR+ tumors present a better survival.[205] A meta-analysis polling 26 studies indicated that patients with PR- tumors presented worse survival compared to patients with PR+ tumors[377] and the OTTA study indicated patients with PR- HGSOC and PR- endometrioid ovarian cancer presented worse survivals compared to patients with PR+ HGSOC and PR- endometrioid ovarian cancer.[204] Although AR and PR were identified by the boostCox model, the results obtained from fitting a standard Cox regression using the entire dataset indicated that AR and PR were non-significantly associated with EOC survival. Together with previous studies,[204-206,377] our data suggests that AR and PR may impact survival in a histotype-specific way and that the biological mechanisms for AR and PR on EOC survival should be studied by histotypes. p16 is a tumor suppressor, which regulates the progression of the cell cycle from the G1 phase to the S phase.[226] Our results indicated that p16 expression in >75% of tumor cells was associated with worse survival of EOC compared to p16 expression in <1% of tumor cells. The OTTA study showed that

absent p16 expression was associated with worse survival of LGSOC compared to heterogeneous p16 expression while block p16 expression was associated with worse survival of endometrioid and clear cell ovarian cancer compared to heterogeneous p16 expression.[210] Thus, p16 could be a potential histotype-specific treatment target.

There are a few limitations in our study. First, we included missing values by creating an index for each feature. The percentage of missing values ranged from 2.77% to 61.24% (**Table 5-2**), with BRCA1/2 mutation status, PR, and FOLR1 each having more than 50% missing values. We chose not to conduct imputation in order to make the prediction model applicable to real-world data, where missing values may be common. Moreover, the missing value patterns were heterogenous by site. For example, ER, PR and FOLR1 status were all missing from two sites (BRZ, LZX). While we could have included site in our analyses as either a stratum or co-variate, this would have limited the generalizability of our model by impacting feature identification. The second limitation was that some potential risk factors related to survival, such as cancer antigen125 level,[404-406] types of chemotherapy,[167,407] response to chemotherapy,[408] body mass index,[237,409] hormone replacement therapy use,[233,237,240] age at menopause and menarche,[233] physical activity,[252] and smoking,[237,253] were not available through the OTTA and thus were not included in our analyses. The third limitation was that the tunning parameters might not be fully optimized. Refining the tuning parameters was beyond the scope of this paper which was intended to identify the best type of model and the important predictive features; however, we recommended that future studies aim to optimize the models using cross-validation or the bootstrap.

Despite these limitations, our study has several strengths, including the large sample size by pooling multiple study sites all over the world, applying the novel ML techniques to predict EOC survival directly, and identifying the important biomarkers associated with EOC survival.

Importantly, our study showed that ML techniques can accurately identify prognostic features and predict survival outcomes from a modest sized, real-world data set with substantial missing data. We suggest systematically collecting more thorough data, including clinical clinical variables (e.g., type of chemotherapy, response to chemotherapy) and biomarkers (e.g., CA-125) relevant to EOC outcomes to validate the method. Future studies with more comprehensive clinical, lifestyle, and biological data can address this study's limitations and provide more accurate prediction models and feature identification.

In conclusion, ML techniques were successfully applied to predict survival outcomes in EOC patients. The biomarkers identified by our final prediction model include CD8, AR, PR, and p16 expression. Understanding the biological mechanisms behind these observations provides insight into potential treatment strategies that could be used to target these biomarkers.

5.6 Figures and tables

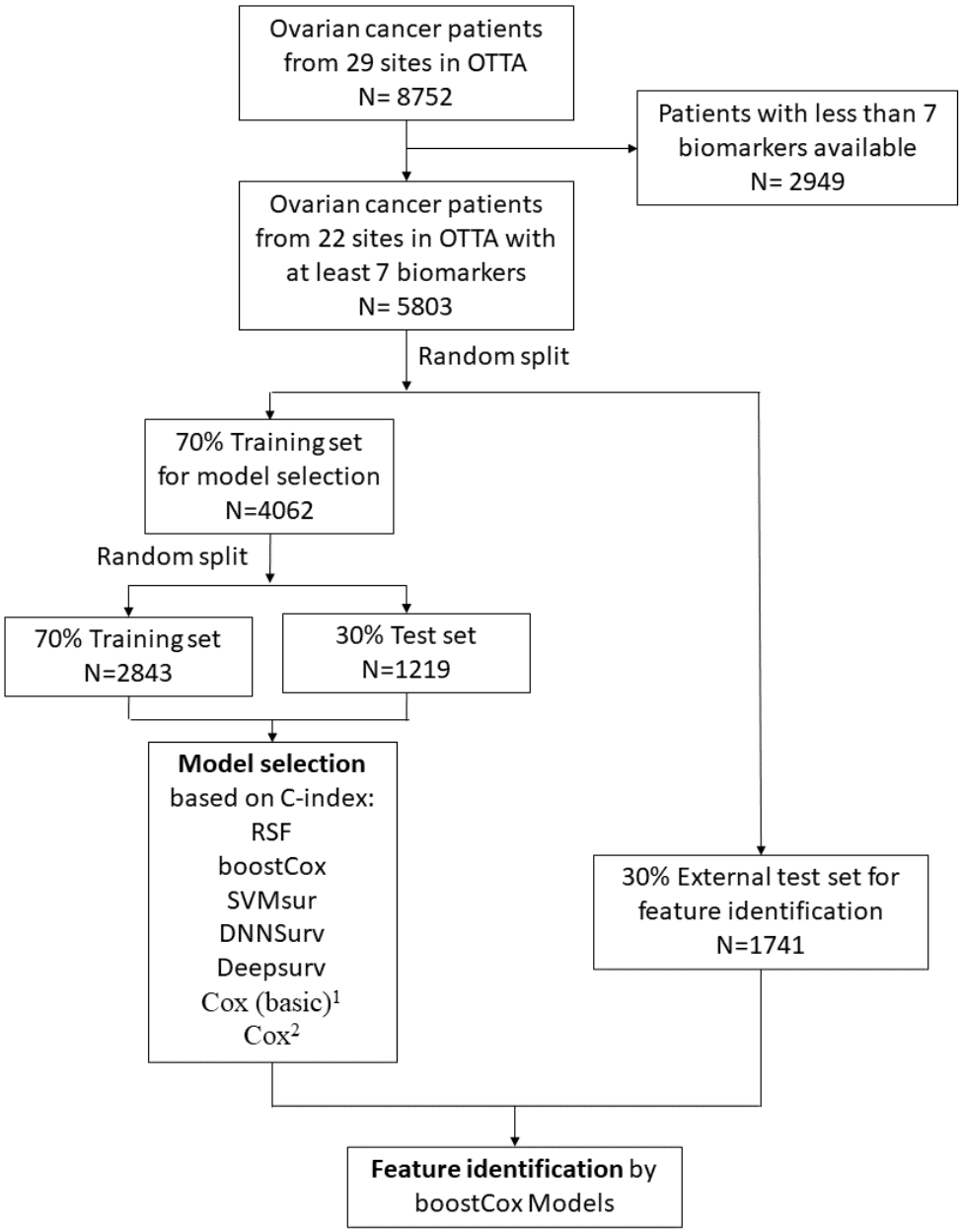


Figure 5-1 Flow chart of the development of the prediction model for ovarian cancer surviva

boostCox, boosting in Cox regression; Cox, Cox proportional hazards model; deepsurv, deep neural networks for survival analysis based on the partial likelihood from a Cox proportional hazards model; DNNSurv, deep neural networks for survival analysis using pseudo values; RSF, random survival forest; SVMsur, support vector machine for survival.
1 Model included age, stage and histotypes.
2 Model included age, race, stage, histotypes, behavior, grade, debulking status, BRCA1/2 mutation status and nine biomarkers

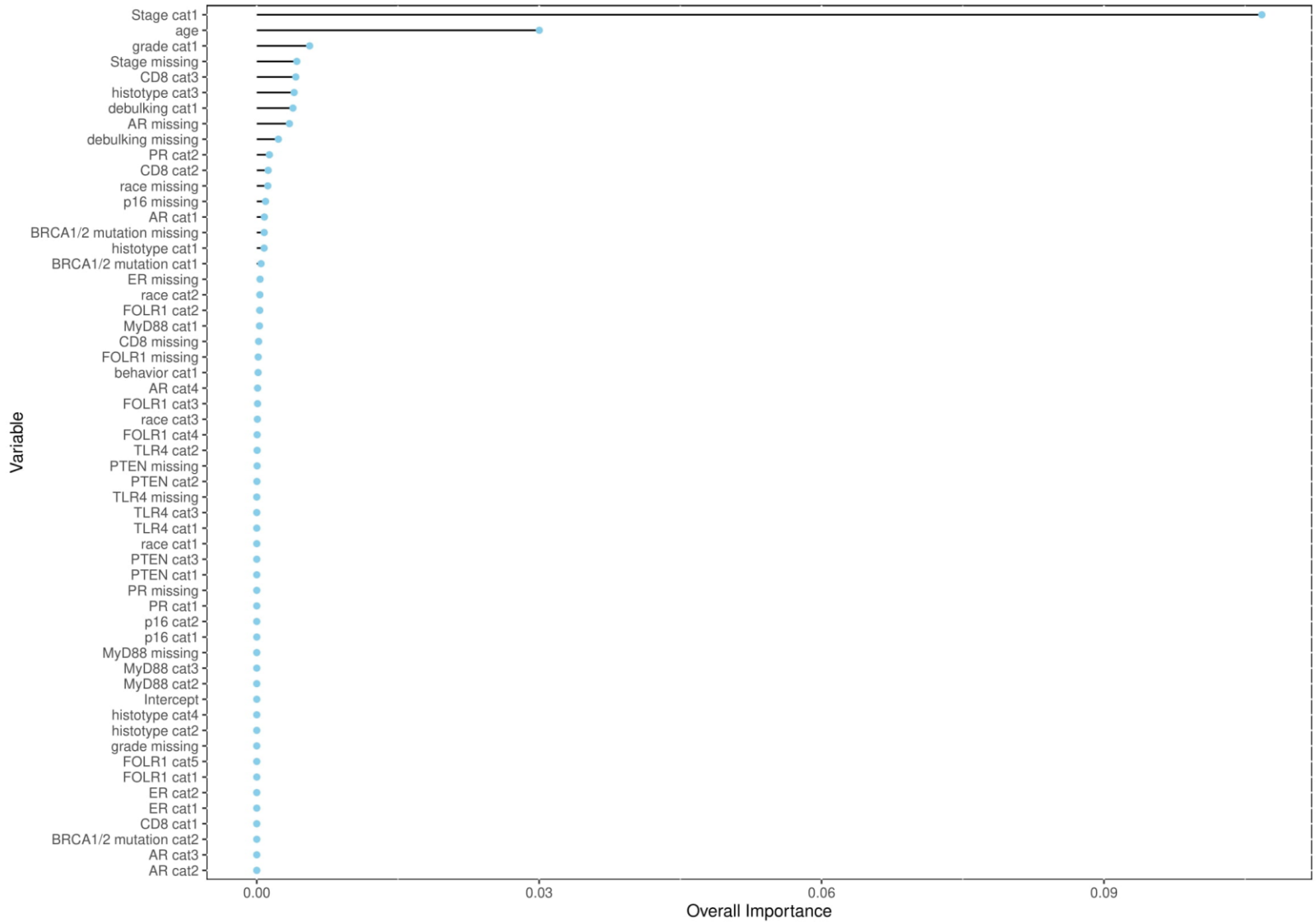


Figure 5-2 Importance of variables in the full boostCox model

AR, Androgen Receptor; cat, categorical level; CD8, Cluster of differentiation 8; ER, Estrogen Receptor; FOLR1, Folate receptor alpha; MyD88, Myeloid differentiation primary response 88; PR, Progesterone Receptor; PTEN, Phosphatase and tensin homolog; TLR4, Toll-like receptor 4.

Table 5-1 Characteristics of studies from the Ovarian Tumor Tissue Analysis consortium

Site	Region	Study Name	Study Period	Total Cases, n	Censored, n (%)	Uncensored, n (%)
AOC [55]	Australia	Australian Ovarian Cancer Study	2002-2006	163	23 (14.1)	140 (85.9)
AOV [209]	Canada	Alberta Ovarian Tumor Types Study	1978-2010	461	257 (55.7)	204 (44.3)
BAV [309]	Germany	Bavarian Ovarian Cancer Cases and Controls	2002-2006	227	70 (30.8)	157 (69.2)
BRZ	Brazil	Brazil Gynecologic Tumor Bank Study	1987-2010	107	54 (50.5)	53 (49.5)
CAL[410]	Canada	Calgary Serous Carcinoma Study	2003- 2007	106	28 (26.4)	78 (73.6)
CNI[411]	Spain	CNIO Ovarian Cancer Study	1. 2022-2012 2. 2006-2013	121	85 (70.2)	36 (29.8)
GER [312]	Germany	Germany Ovarian Cancer Study	1993-1996	88	21 (23.9)	67 (76.1)
HAW [313]	USA	Hawaii Ovarian Cancer Case-Control Study	1993-2008	124	57 (46.0)	67 (54.0)
HOP [314]	USA	Hormones and Ovarian Cancer Prediction Study	2003-2008	38	20 (52.06)	18 (47.4)
LAX [412]	USA	Women's Cancer Program at the Samuel Oschin Comprehensive Cancer Institute	1989 - present	263	79 (30.0)	184 (70.0)
MAL [60,357]	Denmark	MALignant OVArian cancer	1994-1999	114	23 (20.2)	91 (79.8)
MAY [316]	USA	Mayo Clinic Ovarian Cancer Case-Control Study	2000-2011	805	220 (27.3)	585 (72.7)
NOT [392]	UK	Nottingham Study	1991-2011	460	182 (39.6)	578 (60.4)
POC[323]	Poland	Polish Ovarian Cancer Study	1998-2006	129	69 (53.5)	60 (46.5)
SEA [358]	UK	Study of Epidemiology and Risk Factors in Cancer Heredity	1998-present	502	224 (44.6)	278 (55.4)
SOC [391]	UK	Southampton Ovarian Cancer Study	1993-1998	51	12 (23.5)	39 (76.5)
STA [325]	USA	Family Registry for Ovarian Cancer AND Genetic Epidemiology of Ovarian Cancer	1997-2001	302	129 (42.7)	173 (57.3)
TUE	Germany	Tuebingen University Hospital	1999-2008	201	77 (38.3)	124 (61.7)
TVA[413]	Canada	Ovarian Cancer in Alberta	2005-2011	148	83 (56.1)	65 (43.9)
UKO [329]	UK	United Kingdom Ovarian cancer Population Study	2006-2010	104	48 (46.2)	56 (53.8)
VAN [414,415]	Canada	Vancouver Ovarian Cancer Study	1984-2000	1056	396 (37.5)	660 (62.5)
WMH[416]	Australia	Westmead Hospital: Molecular Biology of Gynecologic Disease	1992- 2012	233	58 (24.9)	175 (75.1)
Total				5803	2215 (38.2)	3588 (61.8)

Table 5-2 Comparison of training set and validation set

Potential Prognostic variable	Training Set	Test Set	External Test Set	Total
N	**2843**	**1219**	**1741**	**5803**
Age(year), mean (SD)	58.77 (12.34)	58.36 (11.99)	58.86 (12.16)	58.71 (12.21)
Race				
White	1605 (56.45)	678 (55.62)	923 (53.02)	3206 (55.25)
Black	11 (0.39)	3 (0.25)	13 (0.75)	27 (0.47)
Asian	68 (2.39)	31 (2.54)	55 (3.16)	154 (2.65)
Other	51 (1.79)	23 (1.89)	31 (1.78)	105 (1.81)
missing	1108 (38.97)	484 (39.70)	719 (41.30)	2311 (39.82)
Histology				
High Grade Serous	1886 (66.34)	753 (61.77)	1161 (66.69)	3800 (65.48)
Low Grade Serous	83 (2.92)	59 (4.84)	51 (2.93)	193 (3.33)
Mucinous	181 (6.37)	77 (6.32)	101 (5.80)	359 (6.19)
Endometrioid	381 (13.40)	175 (14.36)	228 (13.10)	784 (13.51)
Clear cell	312 (10.97)	155 (12.72)	200 (11.49)	667 (11.49)
Stage				
Stage I/II	1055 (37.11)	473 (38.80)	662 (38.02)	2190 (37.74)
Stage III/IV	1715 (60.32)	709 (58.16)	1028 (59.05)	3452 (59.49)
missing	73 (2.57)	37 (3.04)	51 (2.93)	161 (2.77)
Behavior				
Invasive	2839 (99.86)	1211 (99.34)	1737 (99.77)	5787 (99.72)
Discordant	4 (0.14)	8 (0.66)	4 (0.23)	16 (0.28)
Grade				
Low	325 (11.43)	167 (13.70)	218 (12.52)	710 (12.24)
High	2378 (83.64)	978 (80.23)	1444 (82.94)	4800 (82.72)
Unknown	140 (4.92)	74 (6.07)	79 (4.54)	293 (5.05)
Debulking Status				
Optimal	1306 (45.94)	549 (45.04)	810 (46.52)	2665 (45.92)
Suboptimal	212 (7.46)	87 (7.14)	128 (7.35)	427 (7.36)
Unknown	1325 (46.61)	583 (47.83)	803 (46.12)	2711 (46.72)
BRCA1/2 mutation status				
Wild type	905 (31.83)	397 (32.57)	562 (32.28)	1864 (32.12)
Pathogenic	135 (4.75)	47 (3.86)	88 (5.05)	270 (4.65)
Unclassified variant	66 (2.32)	16 (1.31)	33 (1.90)	115 (1.98)
Unknown/Untested	1737 (61.10)	759 (62.26)	1058 (60.77)	3554 (61.24)
Immunohistochemistry				
Androgen Receptor				
No Tissue, Non-tumoural tissue, Necrosis, Hemorrhage	67 (2.36)	30 (2.46)	40 (2.30)	137 (2.36)

No staining in tumoral cells or just cytoplasmic staining (Negative)	1567 (55.12)	725 (59.47)	989 (56.81)	3281 (56.54)
Just stromal cells staining (Positive)	70 (2.46)	30 (2.46)	36 (2.07)	136 (2.34)
Just tumoral (epithelial)cells staining (Positive)	655 (23.04)	241 (19.77)	398 (22.86)	1294 (22.30)
Both tumoural and stromal cells staining(Positive)	47 (1.65)	13 (1.07)	26 (1.49)	86 (1.48)
Untested / uninterpretable	437 (15.37)	180 (14.77)	252 (14.47)	869 (14.98)
Estrogen Receptor				
Negative (<1% of tumor cells)	424 (14.91)	192 (15.75)	222 (12.75)	838 (14.44)
1 to 50% of tumor cell nuclei positive	224 (7.88)	74 (6.07)	137 (7.87)	435 (7.50)
> 50% of tumor cells positive	543 (19.10)	251 (20.59)	365 (20.96)	1159 (19.97)
Untested / uninterpretable	1652 (8.11)	702 (57.59)	1017 (58.41)	3371 (58.09)
Progesterone Receptor				
Negative (<1% of tumor cells)	763 (26.84)	337 (27.65)	453 (26.02)	1553 (26.76)
1 to 50% of tumor cell nuclei positive	246 (8.65)	97 (7.96)	157 (9.02)	500 (8.62)
> 50% of tumor cells positive	150 (5.28)	69 (5.66)	98 (5.63)	317 (5.46)
Untested / uninterpretable	1684 (59.23)	716 (58.74)	1033 (59.33)	3433 (59.16)
Toll-like receptor 4, TLR4				
Negative intensity	300 (10.55)	125 (10.25)	162 (9.30)	587 (10.12)
Weak intensity	390 (13.72)	179 (14.68)	237 (13.61)	806 (13.89)
Moderate intensity	1241 (43.65)	514 (42.17)	778 (44.69)	2533 (43.65)
Strong intensity	158 (5.56)	74 (6.07)	99 (5.69)	331 (5.70)
Untested / uninterpretable	754 (26.52)	327 (26.83)	465 (26.71)	1546 (26.64)
Myeloid differentiation primary response 88, MyD88				
Negative intensity	324 (11.40)	143 (11.73)	198 (11.37)	665 (11.46)
Weak intensity	343 (12.06)	173 (14.19)	205 (11.77)	721 (12.42)
Moderate intensity	1101 (38.73)	461 (37.82)	670 (38.48)	2232 (38.46)
Strong intensity	618 (21.74)	251 (20.59)	354 (20.33)	1223 (21.08)
Untested / uninterpretable	457 (16.07)	191 (15.67)	314 (18.04)	962 (16.58)
Folate receptor alpha, FOLR1				
Absent staining	340 (11.96)	153 (12.55)	198 (11.37)	691 (11.91)
Weak staining	197 (6.93)	102 (8.37)	140 (8.04)	439 (7.57)
Strong 1–50%	270 (9.50)	107 (8.78)	161 (9.25)	538 (9.27)
Strong membranous 50%	165 (5.80)	80 (6.56)	104 (5.97)	349 (6.01)
Strong cytoplasmic 50–95%	202 (7.11)	80 (6.56)	113 (6.49)	395 (6.81)
Strong cytoplasmic 95%	76 (2.67)	27 (2.21)	39 (2.24)	142 (2.45)
Untested / uninterpretable	1593 (56.03)	670 (54.96)	986 (56.63)	3249 (55.99)
Phosphatase and tensin homolog, PTEN				
Negative intensity	560 (19.70)	226 (18.54)	336 (19.30)	1122 (19.33)
Weak intensity	1136 (39.96)	508 (41.67)	683 (39.23)	2327 (40.10)

Moderate intensity	561 (19.73)	256 (21.00)	368 (21.14)	1185 (20.42)
Strong intensity	117 (4.12)	48 (3.94)	80 (4.60)	245 (4.22)
Untested / uninterpretable	469 (16.50)	181 (14.85)	274 (15.74)	924 (15.92)
Cluster of differentiation 8, CD8				
No IEL	638 (22.44)	282 (23.13)	373 (21.42)	1293 (22.28)
1-2 IEL/40 x HPF	486 (17.09)	187 (15.34)	280 (16.08)	953 (16.42)
3-19 IEL/40 x HPF	982 (34.54)	415 (34.04)	633 (36.36)	2030 (34.98)
20 or more IEL/40 x HPF	467 (16.43)	201 (16.49)	286 (16.43)	954 (16.44)
Untested / uninterpretable	270 (9.50)	134 (10.99)	169 (9.71)	573 (9.87)
p16				
Negative (<1% of tumor cells)	249 (8.76)	121 (9.93)	178 (10.22)	548 (9.44)
1 to 75% of tumor cell nuclei positive	1172 (41.22)	547 (44.87)	717 (41.18)	2436 (41.98)
> 75% of tumor cells positive	934 (32.85)	356 (29.20)	522 (29.98)	1812 (31.23)
Untested / uninterpretable	488 (17.16)	195 (16.00)	324 (18.61)	1007 (17.35)
Overall Survival				
Censored status				
Censored	1071 (37.67)	483 (39.62)	661 (37.97)	2215 (38.17)
Uncensored	1772 (62.33)	736 (60.38)	1080 (62.03)	3588 (61.83)
Survival Time, days				
Median (25th, 75th centiles)	1824 (810, 6289)	2017 (833, 6999)	1923 (839, 6389)	1890 (821, 6389)

IEL, intraepithelial lymphocytes

Table 5-3 Summary of model performances in terms of C-index

Model	Harrell's C in %	Uno's C in %
RSF	71.03	70.98
boostCox	**71.73**	**72.01**
SVMsur	61.34	62.62
DNNSurv	59.83	63.03
deepsurv	61.12	63.55
Cox (basic)[1]	69.49	71.16
Cox[2]	71.08	70.54

boostCox, boosting in Cox regression; Cox, Cox proportional hazards model; deepsurv, deep neural networks for survival analysis based on the partial likelihood from a Cox proportional hazards model; DNNSurv, deep neural networks for survival analysis using pseudo values; RSF, random survival forest; SVMsur, support vector machine for survival.

1 Model included age, stage and histotypes.

2 Model included age, race, stage, histotypes, behavior, grade, debulking status, VRCA1/2 mutation status and nine biomarkers.

Table 5-4 Summary of model performances using the External Test Set for boostCox models with identified features based on variable importance

Model	Features included	Uno's C-index in %					
		at 1st year	**at 3rd year**	**at 5th year**	**at 10th year**	**at 15th year**	**Maximum time**
Full model	age, race, stage, histotypes, behavior, grade, debulking status, BRCA1/2 mutation status and nine biomarkers	71.23	71.52	71.98	70.58	67.36	70.43
Model 1 (15 variables)	stage, age, grade, CD8, histotypes, debulking status, AR, PR, race, p16, BRCA1/2 mutation status, ER, FOLR1, MyD88, TLR4	71.26	71.54	71.98	70.58	67.36	70.43
Model 2 (10 variables)	**stage, age, grade, CD8, histotypes, debulking status, AR, PR, race, p16**	**71.20**	**71.25**	**71.79**	**70.52**	**67.49**	**70.51**
Model 3 (5 variables)	stage, age, grade, CD8, histotypes	69.64	69.22	70.10	69.56	67.48	70.25

AR, Androgen Receptor; CD8, Cluster of differentiation 8; ER, Estrogen Receptor; FOLR1, Folate receptor alpha; MyD88, Myeloid differentiation primary response 88; PR, Progesterone Receptor; TLR4, Toll-like receptor 4.

Table 5-5 Hazard ratio of ten features fitting in boostCox

Features	Hazard Ratio (95% confidence intervals)
Stage	
Stage I/II	ref
Stage III/IV	3.14 (2.83, 3.47)
missing	2.44 (1.95, 3.06)
Age per year	1.024 (1.020, 1.027)
Grade	
Low	ref
High	1.46 (1.20, 1.79)
Unknown	1.50 (1.14, 1.98)
Cluster of differentiation 8, CD8	
No IEL	ref
1-2 IEL/40 x HPF	0.89 (0.80, 0.99)
3-19 IEL/40 x HPF	0.76 (0.69, 0.83)
20 or more IEL/40 x HPF	0.60 (0.53, 0.67)
Untested / uninterpretable	0.83 (0.73, 0.95)
Histology	
High Grade Serous	ref
Low Grade Serous	0.89 (0.66, 1.18)
Mucinous	1.09 (0.89, 1.33)
Endometrioid	0.71 (0.60, 0.83)
Clear cell	0.89 (0.76, 1.04)
Debulking Status	
Optimal	ref
Suboptimal	1.52 (1.35, 1.72)
Unknown	1.28 (1.18, 1.38)
Androgen Receptor	
No Tissue, Non-tumoral tissue, Necrosis, Hemorrhage	ref
No staining in tumoral cells or just cytoplasmic staining (Negative)	1.24 (0.98, 1.56)
Just stromal cells staining (Positive)	1.15 (0.83, 1.61)
Just tumoral (epithelial)cells staining (Positive)	1.12 (0.88, 1.43)
Both tumoral and stromal cells staining (Positive)	0.92 (0.63, 1.33)
Untested / uninterpretable	0.83 (0.65, 1.07)
Progesterone Receptor	
Negative (<1% of tumor cells)	ref
1 to 50% of tumor cell nuclei positive	1.03 (0.90, 1.16)
> 50% of tumor cells positive	0.86 (0.72, 1.03)
Untested / uninterpretable	1.06 (0.98, 1.15)
Race	
White	ref
Black	1.09 (0.71, 1.68)
Asian	0.71 (0.56, 0.91)
Other	0.89 (0.68, 1.16)
missing	1.16 (1.08, 1.25)
p16	
Negative (<1% of tumor cells)	ref
1 to 75% of tumor cell nuclei positive	1.08 (0.94, 1.24)
> 75% of tumor cells positive	1.16 (1.00, 1.34)
Untested / uninterpretable	1.28 (1.09, 1.49)

6.0 Discussion

6.1 Summary and Novelty

Epithelial ovarian cancer continues to have high mortality due to lack of early diagnosis and high recurrence of disease after primary treatment. EOC is a heterogeneous disease made up of molecularly distinct histotypes. Even with these differences, it has been consistently reported that the development of EOC is a hormone driven process. Based on this knowledge, this dissertation reported the heterogeneity of the histotype-specific associations with LOYs and with the individual components of LOYs. It further described different risk and prognostic profiles in EOC patients with tumor types defined by hormone receptor status overall and based on tumor histotypes. Moreover, ML techniques were successfully utilized to build a prediction model for EOC survival and identified CD8, AR, PR, and p16 as crucial factors for predicting EOC survival.

EOC is relatively rare, affecting only 1% of population, and this creates challenges for researchers aiming to improve the diagnosis and treatment of EOC. The small number of cases in individual studies necessitates pooling resources to increase the power of analyses to identify prognostic factors. Our approach in the first and second paper was pooling data from more than 20 case-control studies which allowed us to estimate the histotype-specific associations. This approach is innovative because it combines data across studies to evaluate risk factors by histotype as no single study has such a large sample size to adequately assess histotype-specific associations. We found substantially different risk-factor profiles by histotypes and conclude that one must include histotype to accurately predict risk and take appropriate action to prevent EOC. Moreover, we conducted interaction analyses and stratification analyses to identify whether hormone status

modifies the association between risk factors and EOC risk or the association between risk factors survival. We found that the association between menopause status at diagnosis and EOC risk varied by the presence of PR. These types of analyses can be conducted only when very large, pooled datasets are available.

One of the strengths of this work is utilizing data from 20 studies to draw clinically meaningful conclusions. All three papers take advantage of access to a diverse and large dataset created by pooling existing multicenter studies. Besides increasing the sample size and the power for identifying risk factors, pooling data from multiple studies also increases the diversity of the population. For example, we pooled two studies from Australia, one from Japan, one from China, two from Germany, one from Netherlands, one from Poland, one from UK, three from Canada and thirteen from USA in the first paper. Among the overall 47471 cases and controls, we included 86.9% white, 2.16% black, 6.8% Asian and 3.1% population with other races in the first paper. The greater diversity improves the generalizability of our study results to broader populations in the United States and other countries.

Adding to the generalizability is the real-world collection of variables, which means contending with missing variables. Missing data is a shortcoming of this work. Nonetheless, missing data is common in general medical practice. Building a model that is based on real-world data and incorporates missing data as a feature in the model facilitates translation of the model results into practice since clinical datasets are not perfect. In this dissertation, I used several strategies to deal with missing data – using multiple imputation by chained equation imputation (Paper I), sensitivity analysis excluding missing data (Paper II), creating index for missing data (Paper III). The other challenge I encountered when pooling multi-center datasets is harmonizing the definition and coding of variables. For example, age at last mensural period (LMP) is only

available in 7 study sites. I assigned the age at LMP by comparing age at diagnosis or interview, age at hysterectomy, age at first hormone replacement therapy use and the published average age at menopause by country. To assure the accuracy of estimating the association between LOY and EOC risk, I compared the imputed values and the raw data. The estimated LOY-EOC associations were not altered by imputed age at LMP. Rigorous harmonization of variables provided sufficient power to estimate the hisototype-specific association without sacrificing the accuracy.

The application of ML techniques in the third paper overcomes some of the shortcoming of standard statistical practices and opens the door to building a more accurate prediction model for EOC survival. The standard analytic method to assess factors associated with EOC survival is to conduct a CoxPHR. CoxPHR is a semi-parametric model containing the baseline hazard (the non-parametric component) and the covariate vector (the parametric component). CoxPHR replies on several assumptions most notably the assumption of proportional hazards, which is that the ratio of the hazards for any two strata is constant overtime. Violations of the proportional hazard assumption and inaccurate specification of the parametric function could reduce the power of CoxPHR to identify important risk factors. Our innovative approach using ML techniques better fit survival data with nonlinear log-risk functions and increases the accuracy in predicting cancer survival without specifying the parametric function or requiring the proportional hazard assumption.

A frequently cited disadvantage of using ML techniques is that the resulting algorithm is a non-interpretable "black box." Some ML techniques have the ability to identify the critical features for predicting a given outcome. Supplying the "critical features" for predicting a given outcome overcomes the black-box limitation of many ML techniques and offer clinical investigators insight to better interpret the model results. The successful completion of our project improves the

accuracy of predicting ovarian cancer survival and provides potential treatment targets for future research.

6.2 Public health relevance and future study

The results of this dissertation further our understanding of EOC development and survival by exploring the roles of ovulation, hormone-related conditions, and hormone receptors. In the first paper, we found that an increasing LOY is associated with increased overall risk of EOC, risk of HGSOC, endometrioid ovarian cancer, and clear cell ovarian cancer. The associations of the individual components of LOY and ovarian cancer risk also varied by histotypes such that age at menarche was associated with a significant increased risk of mucinous but not with other histotypes. Our results supported that mucinous histotype develop via different causal mechanisms than other histotypes. We recommend examining the biological mechanisms by LOY component and histotypes. A better assessment of each LOY component in future studies is required in order to achieve this goal.

In the second paper, EOC tumor types defined by hormone receptor status have varying risk and prognostic profiles in general and based on histotypes. In particular, the association between menopause status at diagnosis and EOC risk varied by the presence of PR. We also confirmed previously reported data showing significant differences in EOC survival based on tumor receptor status for ER, which may be modified by physical inactivity; and previously reported survival differences based on tumor PR status. We further found that women with ER-PR+ HGSOC tumors have longer survival compared to women with the other three HSGOC types defined by the presence of ER and PR. Women with ER-PR- endometrioid tumors have worse survival compared to women with the other three endometrioid tumor types defined by the presence of ER and PR. Women with ER+ clear cell tumors have worse survival compared to women with ER- clear cell tumors. Our findings suggests that ER and PR potentially serve as prognostic biomarkers for HGSOC and endometrioid ovarian cancer while ER may serve as a

prognostic biomarker for clear cell ovarian cancer. Our results imply that it is essential to analyze the associations of hormonally-linked risk factors and EOC risk and outcomes by histotypes and by hormone receptor status in order to fully understand the potential biological mechanisms underlying these relationships.

We suggest creating a validated prognostic score for EOC patients using the features identified in the second and third paper associated with EOC survival. The second paper observed that the survival in EOC patients differed by histotypes and by tumors defined by hormone receptor status. The third paper identified CD8 (a transmembrane glycoprotein involving in immune defense), AR (androgen receptors), PR (progesterone receptor), and p16 (a tumor suppressor) expression from the prediction model built using ML techniques. A novel prognostic score including these features can be developed and refined to improve the accuracy of prediction for EOC survival. Clinicians can use the novel prognostic score to make more specific decisions for patients with a high prognostic score and improve patients' outcomes. A number of these risk factors, such as CD8 and p16, may not be available in the medical record and thus not easily available for research studies. Moreover, some of the components that are needed to create an accurate LOY estimate are not generally available in the medical record. However, if clinicians were convinced that a predictor model has clinical utility, the components LOY are obtainable by taking a detailed patient history, and some biomarkers can be measured.

The successful application of ML techniques and the bright prospect of developing a reliable and valid prognostic score should drive clinicians to collect more comprehensive data. We suggest systematically collecting more thorough data, including clinical variables (e.g., type of chemotherapy, response to chemotherapy) and biomarkers (e.g., CA-125) relevant to EOC outcomes to validate the method and improve the prediction's accuracy.

Overall, these findings support revisiting the hypotheses of ovarian carcinogenesis by histotypes and provide important information about the future direction of EOC prevention and treatment.

Appendix A Supplemental Tables for Paper I

Supplemental Table 1 Algorithms to calculate lifetime ovulatory years

Algorithms #	Number of sites included	Sites included	Variables included in LOY algorithms								LOY algorithms[4]
			Age at last menstrual period	Age at menarche	Number of Pregnancies, regardless of outcome	Total number of months of being pregnant, regardless of outcome(s)	Total number of full-term births	Use, months Duration of Oral Contraceptive	Total months of breastfeeding	Average cycle length	
The first class of algorithms											
A	25	AUS, BAV, CON, DOV, GER, HAW, HOP, JPN, MAY, MCC, NCO, NEC, NJO, NTH, OVA, POL, SON, STA, SWH, TBO, TOR, UCI, UKO, USC, VTL	X	X	X						Menstrual span – number of pregs *0.75
B	23	AUS, CON, DOV, GER, HAW, HOP, JPN, MCC, NCO, NEC, NJO, NTH, OVA, POL, SON, STA, SWH, TBO, TOR, UCI, UKO, USC, VTL	X	X			X				Menstrual span – number of full-term births *0.75
C	23	AUS, CON, DOV, GER, HAW, HOP, JPN, MCC, NCO, NEC, NJO, NTH, OVA, POL, SON, STA, SWH, TBO, TOR, UCI, UKO, USC, VTL	X	X	X		X				Menstrual span – number of full-term births *0.75 - (number of pregs – number of full-term births) *0.25
D	12	AUS, DOV, GER, HAW, MCC, NCO, NJO, OVA, POL, STA, UCI, USC	X	X		X					Menstrual span –(months of being pregnant)/12
The second class of algorithms											
E	24	AUS, CON, DOV, GER, HAW, HOP, JPN, MAY, MCC, NCO, NEC, NJO, NTH, OVA, POL, SON, STA, SWH, TBO, TOR, UCI, UKO, USC, VTL	X	X	X			X			Algorithm A – (months of oral contraceptive use)/12
F[1]	22	AUS, CON, DOV, GER, HAW, HOP, JPN, NCO, NEC, NJO, NTH, OVA,	X	X			X	X			Algorithm B - months of oral contraceptive use/12

		POL, SON, STA, SWH, TBO, TOR, UCI, UKO, USC, VTL										
G[1]	22	AUS, CON, DOV, GER, HAW, HOP, JPN, NCO, NEC, NJO, NTH, OVA, POL, SON, STA, SWH, TBO, TOR, UCI, UKO, USC, VTL	X	X	X		X	X			Algorithm C - months of oral contraceptive use/12
H[1]	11	AUS, DOV, GER, HAW, NCO, NJO, OVA, POL, STA, UCI, USC	X	X		X		X			Algorithm D - months of oral contraceptive use/12
The third class of algorithms												
I[2]	16	AUS, CON, DOV, GER, HAW, HOP, JPN, NCO, NEC, NJO, POL, SON, STA, SWH, TOR, USC	X	X	X			X	X		Algorithm E - months of oral contraceptive use/12
J[3]	16	AUS, CON, DOV, GER, HAW, HOP, JPN, NCO, NEC, NJO, POL, SON, STA, TBO, TOR, USC	X	X			X	X	X		Algorithm F - months of oral contraceptive use/12
K[3]	16	AUS, CON, DOV, GER, HAW, HOP, JPN, NCO, NEC, NJO, POL, SON, STA, TBO, TOR, USC	X	X	X		X	X	X		Algorithm G - months of oral contraceptive use/12
L	9	AUS, DOV, GER, HAW, NCO, NJO, POL, STA, USC	X	X		X		X	X		Algorithm H -months of oral contraceptive use/12
The fourth class of algorithms												
M	10	AUS, CON, DOV, HAW, NCO, NEC, NJO, SON, TOR, USC	X	X			X	X	X	X	Algorithm J * (365.25/Average cycle length in days)/13
N	10	AUS, CON, DOV, HAW, NCO, NEC, NJO, SON, TOR, USC	X	X	X		X	X	X	X	Algorithm K* (365.25/Average cycle length in days)/13
O	6	AUS, DOV, HAW, NCO, NJO, USC	X	X		X		X	X	X	Algorithm L* (365.25/Average cycle length in days)/13

[1] MCC was excluded due to limited numbers within site to impute missing values.
[2] NTH was excluded due to fail to converge on observed data.
[3] NTH was excluded due to limited numbers within site to impute missing values.
[4] The menstrual span is defined as age at last menstrual period minus age at menarche

Supplemental Table 2 Comparison of observed and assigned values of age at last menstrual period

Site	Imputation Method	Overall						Pre/peri-menopausal				Post-menopausal			
		Observed		Imputed		Combined		Observed		Imputed		Observed		Imputed	
		Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases
	N	**7185**	**5997**	**1131**	**884**	**8316**	**6881**	**2801**	**1814**	**42**	**20**	**4226**	**4077**	**1051**	**851**
CON, DOV, HOP, NEC, POL, SON, TOR[1]	Assigned based on average age at menopause by country, age at hysterectomy, age at first HRT use	48.42 (5.95)	48.59 (6.40)	51.10 (3.23)	50.66 (3.31)	48.78 (5.73)	48.86 (6.21)	43.70 (6.48)	43.37 (6.95)	49.64 (2.05)	47.55 (6.25)	51.55 (2.71)	50.92 (4.58)	51.28 (3.14)	50.77 (4.21)
CON, DOV, HOP, NEC, POL, SON, TOR[1]	Kept raw age at menopause at age at LMP; Re-assigned observations with age at baseline >=51, and raw age at menopause < 40, and <=age at hysterectomy or age at first HRT use	47.17 (6.22)	47.07 (6.32)	50.39 (2.15)	49.97 (3.36)	47.61 (5.94)	47.44 (6.10)	44.02 (6.93)	43.75 (7.49)	49.64 (2.05)	47.55 (6.25)	49.24 (4.74)	48.52 (5.14)	50.51 (1.95)	50.05 (3.22)
	N			**17888**	**14386**	**17888**	**14386**			**5363**	**3941**			**11472**	**9494**
Others[2]	Assigned based on average age at menopause by country, age at hysterectomy, age at first HRT use	NA	NA	48.77 (6.16)	48.84 (6.52)	48.77 (6.16)	48.84 (6.52)	NA	NA	43.00 (7.20)	42.5 (7.70)	NA	NA	51.45 (3.19)	51.43 (3.70)

NA, not applicable.

1 There are 314 participants without menopause status in the OCAC core dataset.

2 There are 2005 participants without menopause status in the OCAC core dataset.

Supplemental Table 3 Percentage of missing values in components of lifetime ovulatory years calculation by OCAC site

study	Age at menarche		Hysterectomy		Age at hysterectomy (among women with hysterectomy)		HTR use (no matter what type)		First age using HRT (among women with HRT)		Age at last menstrual period	
	controls	cases	controls	cases	controls	cases	controls	cases	controls	cases	controls	cases
AUS	3.72	7.16	1.13	5.04	1.03	1.82	0	5.24	3.57	16.59	100	100
BAV	46.9	36.7	41.34	55.85	59.09	6.45	48.17	46.78	100	100	100	100
CON[1]	0	0	0	0	3.19	5.43	100	100	-	-	0.73	1.21
DOV[1]	0	0.06	0	0	0	0	0	0	0.12	0	34.23	30.03
GER	1.13	2.71	0	0	0	0	0	0	0	1.85	100	100
HAW	0	0.11	0	0	0	0	0	0	0	0	100	100
HOP	0	0	0	0	0	0	1.94	1.91	0.16	0.39	5.33	4.43
JPN	4.72	0	0	0.66	100	100	2.58	0.66	100	54.55	100	100
MAY	6.57	17.44	100	22.59	100	100	5.22	22.54	11.51	10.38	100	100
MCC	16.14	41.62	4.48	100	-	-	100	100	-	-	100	100
NCO	0.28	0.5	0.09	0.17	1.2	1.26	0.09	0.17	0	0	100	100
NEC	0.38	0.39	0	0	0	0	0	0	6.37	4.45	3	2.94
NJO	0.66	0.84	0	100	-	-	0	0	0.73	8.62	100	100
NTH	0.83	13.96	0.5	2.26	3.53	0.56	21.17	1.51	44	13.64	100	100
OVA	1.78	2.5	0.07	0.12	2.67	4.99	0	0	3.21	5.74	100	100
POL	1.6	1.02	0	0.34	1.69	0	5.67	6.8	1.94	2.94	1.42	3.40
SON	0	0	0	0	0	0	0	0	0.98	1.2	0.18	0.44
STA	0	2.11	0	0.6	1.61	1.27	0	0.3	0	0	100	100
SWH	0.1	0	0	0	0	0	100	100	-	-	100	100
TBO	41.46	12.28	92.2	45.96	6.67	2.86	100	100	-	-	100	100
TOR	0.31	0.09	0	0.43	0	0	0	0	100	100	0.31	0.51
UCI	7.82	6.76	7.17	6.29	0.63	4.55	11.89	7.7	1.5	0.86	100	100
UKO	11	20.62	11.93	23.36	3.83	5.47	10.07	12.51	4.44	6.49	100	100
USC	0.04	0.13	0	0	0	0	0	0	0	0	100	100
VTL	2.42	3.88	0	0	100	100	100	100	-	-	100	100

1 CON and DOV used average cycle length at age 18 in 20s as average cycle length.

Supplemental Table 3 (cont'd)

study	Number of Pregnancies, regardless of outcome		Total number of months of being pregnant, regardless of outcome(s)		Total number of full-term births		Total months of breastfeeding		Duration of Oral Contraceptive Use, months		Average cycle length	
	controls	**cases**	**controls**	**cases**	**controls**	**cases**	**controls**	**cases**	**controls**	**cases**	**controls**	**cases**
AUS	0	5.19	4.05	22.38	0	4.79	12.42	25.5	0.46	5.85	16.87	34.48
BAV	45.31	32.6	91.41	88.45	91.41	88.45	57.87	80.56	86.96	87.72	100	100
CON[1]	0	0	100	100	0	0	10.53	14.89	0	0	1.81	6.24
DOV[1]	0.05	0.13	0.59	0.64	0	0.19	10.55	17.03	0	0.19	3.03	3.07
GER	0	0	0	0	0	0	15.01	20.16	1.13	1.16	100	100
HAW	0	0	0	0	0	0	11.33	22.57	0	0	1	1.01
HOP	0	0	90.73	81.58	0	0	9.27	18.54	0	0.12	100	100
JPN	2.15	1.97	87.55	80.26	2.15	0.66	16.31	22.37	2.15	1.97	100	100
MAY	4.35	10.4	100	100	100	100	100	100	7.18	12.89	100	100
MCC	16.35	41.62	16.35	42.2	16.35	42.2	37.15	65.9	18.05	43.93	100	100
NCO	0	0.08	0.37	0.5	0	0.08	9.22	16.15	3.23	4.44	13.18	14.73
NEC	0	0	86.81	75.28	0	0	13.19	24.72	0.05	0.19	7.76	8.19
NJO	0	0.42	0.44	0.42	0	0.42	10.48	25.32	2.18	3.38	6.99	7.17
NTH	17.5	1.13	99.67	2.26	16.5	1.13	18.33	25.28	2.33	20	100	100
OVA	0.11	0.06	27.06	42.33	0.04	0.12	31.54	50.95	0.89	1.1	100	100
POL	0	0.34	0.09	0.68	0	0.34	27.57	39.12	1.68	2.04	69.95	96.94
SON	0	0.22	100	100	0	0	9.75	19.33	0	0	2.66	1.56
STA	0	0	0	0	0	0	23.99	38.95	0	0.75	100	100
SWH	0	0	100	100	0	0	2.33	3.95	0.1	0	100	100
TBO	0.49	0.7	49.27	49.12	1.95	2.81	54.15	28.07	44.88	15.44	100	100
TOR	0	0	93.17	80.89	0	0	0	0	0	0	0.31	0
UCI	6.68	6.13	6.68	6.13	6.68	6.13	55.05	24.53	7	6.76	52.12	11.48
UKO	12.18	21.69	91.29	82.72	12.18	21.69	37.39	52.44	16.5	26.7	100	100
USC	0	0	0	0.04	0	0	39	39.29	0.19	0.13	19.54	17.98
VTL	10.48	11.65	100	100	100	100	100	100	1.61	3.88	100	100

1 CON and DOV used average cycle length at age 18 in 20s as average cycle length.

Supplemental Table 4 Distribution of lifetime ovulatory years calculated from 15 algorithms among participants with complete data

Algorithms #	Number of sites included	Cases	Controls	mean	standard deviation	median	25th, 75th percentile
A	25	25081 (55.58)	20046 (44.42)	34.00	6.29	35.25	32.00, 37.50
B	23	22519 (55.56)	18013 (44.44)	34.40	6.23	35.75	32.50, 37.75
C	23	22509 (55.56)	18003 (44.44)	34.26	6.25	35.50	32.25, 37.50
D	12	13596 (56.28)	10561 (43.72)	34.25	6.51	35.75	32.25, 37.75
E	24	24480 (55.89)	19323 (44.11)	30.21	8.58	32.42	26.00, 35.92
F	22	21931 (55.37)	17676 (44.63)	30.71	8.47	32.92	26.50, 36.33
G	22	21921 (55.37)	17666 (44.64)	30.56	8.48	32.75	26.50, 36.25
H	11	13111 (55.86)	10362 (44.14)	30.39	8.71	32.58	25.95, 36.25
I	16	14424 (56.32)	11189 (43.68)	29.62	8.25	31.5	25.25, 35.25
J	16	14426 (56.30)	11199 (43.70)	30.14	8.18	32.17	26.00, 35.58
K	16	14424 (56.32)	11189 (43.68)	29.97	8.19	32	25.75, 35.50
L	9	8473 (56.60)	6498 (43.40)	29.81	8.54	31.83	25.17, 35.50
M	10	9134 (51.71)	8530 (48.29)	30.06	8.87	31.76	25.19, 35.81
N	10	9133 (51.71)	8529 (48.29)	29.89	8.88	31.61	25.00, 35.62
O	6	6132 (54.37)	5147 (45.63)	29.71	8.95	31.36	24.67, 35.62

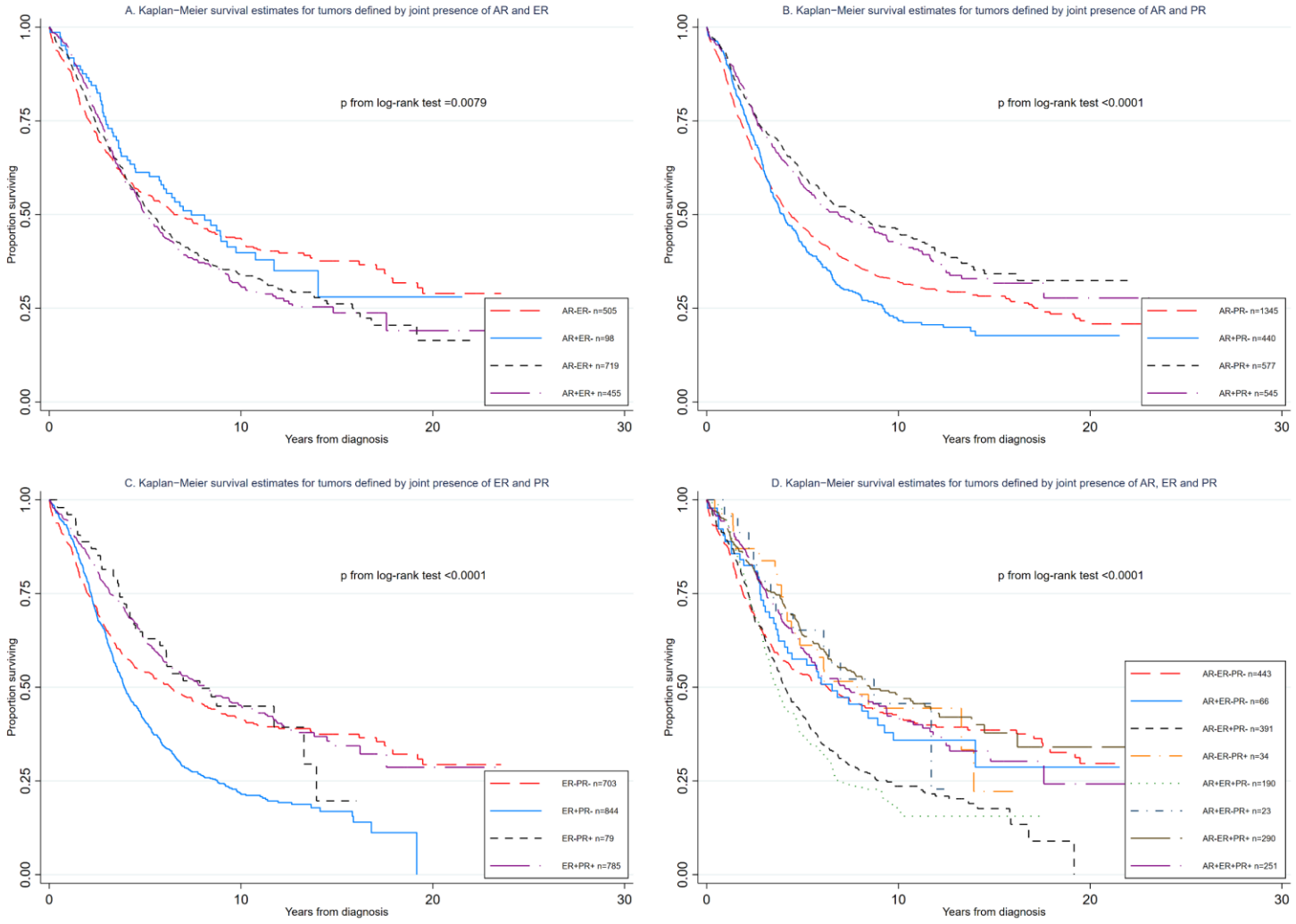
Supplemental Table 5 Pairwise correlations of lifetime ovulatory years calculated from 15 algorithms using complete data

Algorithms	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
A	1.0000														
B	0.9928	1.0000													
C	0.9968	0.9992	1.0000												
D	0.9836	0.9867	0.9871	1.0000											
E	0.7648	0.7706	0.7733	0.7697	1.0000										
F	0.7656	0.7720	0.7711	0.7693	0.9960	1.0000									
G	0.7694	0.7722	0.7725	0.7701	0.9982	0.9996	1.0000								
H	0.7731	0.7760	0.7762	0.7839	0.9906	0.9924	0.9926	1.0000							
I	0.7651	0.7598	0.7631	0.7523	0.9901	0.9849	0.9876	0.9795	1.0000						
J	0.7526	0.7602	0.7590	0.7500	0.9857	0.9899	0.9895	0.9822	0.9954	1.0000					
K	0.7575	0.7608	0.7613	0.7515	0.9882	0.9892	0.9899	0.9823	0.9980	0.9995	1.0000				
L	0.7543	0.7583	0.7584	0.7685	0.9781	0.9799	0.9803	0.9901	0.9889	0.9912	0.9914	1.0000			
M	0.6864	0.6910	0.6909	0.7066	0.8738	0.8771	0.8771	0.9074	0.8832	0.8869	0.8867	0.9185	1.0000		
N	0.6918	0.6927	0.6938	0.7088	0.8778	0.8784	0.8792	0.9086	0.8873	0.8884	0.8889	0.9198	0.9996	1.0000	
O	0.7058	0.7071	0.7081	0.7083	0.9064	0.9073	0.9080	0.9083	0.9174	0.9188	0.9193	0.9196	0.9996	0.9999	1.0000

Supplemental Table 6 Correlations between individual components and the corresponding lifetime ovulatory years from 15 algorithms using complete data

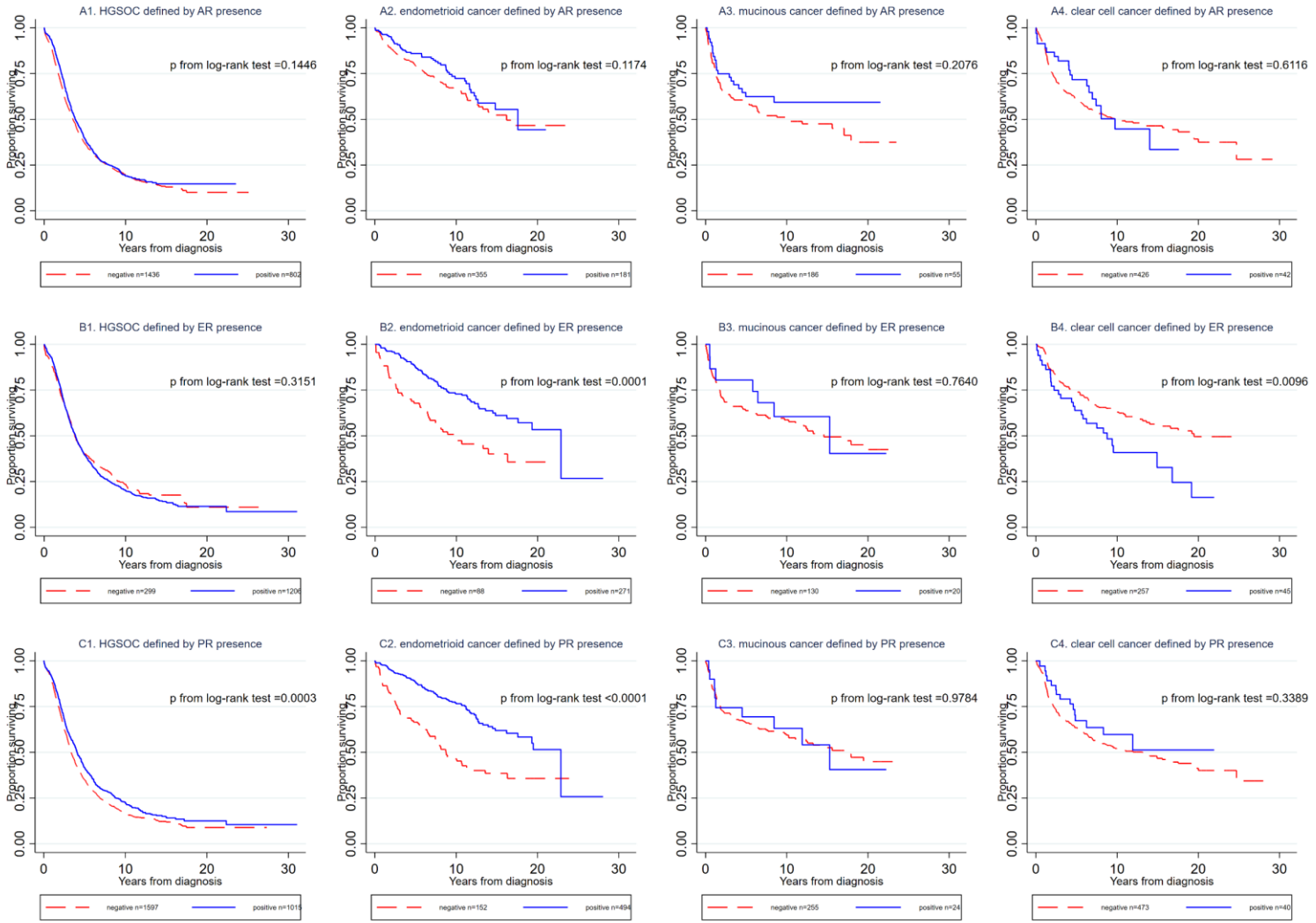
Components	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
Age at last menstrual period	0.9381	0.9465	0.9453	0.9370	0.7389	0.7514	0.7512	0.7514	0.7320	0.7308	0.7319	0.7290	0.6613	0.6635	0.6753
Age at menarche	-0.2322	-0.2327	-0.2326	-0.2009	-0.1407	-0.1410	-0.1413	-0.1298	-0.1597	-0.1616	-0.1614	-0.1399	-0.1542	-0.1535	-0.1590
Number of pregnancies, regardless of outcome	-0.0423	NA	0.0032	NA	0.0198	NA	0.0527	NA	-0.0428	NA	-0.0061	NA	NA	-0.0033	NA
Total number of months of being pregnant, regardless of outcome(s)	NA	NA	NA	-0.0644	NA	NA	NA	-0.0102	NA	NA	NA	-0.0713	NA	NA	0.0286
Total number of full-term births	NA	0.0543	0.0521	NA	NA	0.0988	0.0972	NA	NA	0.0481	0.0504	NA	0.0590	0.0611	NA
Total months of breastfeeding	NA	NA	NA	NA	NA	NA	NA	NA	-0.2062	-0.2035	-0.2045	-0.2041	-0.1916	-0.1927	-0.2070
Duration of oral contraceptive use, months	NA	NA	NA	NA	-0.6810	-0.6761	-0.6752	-0.6538	-0.6753	-0.6827	-0.6809	-0.6702	-0.5913	-0.5915	-0.6059
Average cycle length	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	-0.3252	-0.3231	-0.3164

Appendix B Supplemental Figures and Tables for Paper II



Supplemental Figure A Kaplan-Meier curves for survival from the time of diagnosis of EOC by joint presence of hormonal receptors

AR, androgen receptor; ER, estrogen receptor; PR, progesterone receptor.



Supplemental Figure B Kaplan-Meier curves for survival after diagnosis of EOC by histotypes by individual hormonal receptors presence

AR, androgen receptor; ER, estrogen receptor; HGSOC, high-grade serous ovarian cancer; PR, progesterone receptor.

Supplemental Table. A Pooled relative risk ratios for the association between hormonally linked risk factors and epithelial ovarian cancer by individual hormonal receptor presence compared to all controls[1]

	AR+, AR- compared to controls (N=20,888)					ER+, ER- compared to controls (N=20,888)					PR+, PR- compared to controls (N=20,888)				
	RRR (95% CI)					RRR (95% CI)					RRR (95% CI)				
	AR- N=1390	AR+ N=563	AR unknown N=1816	P for positive vs. negative heter	P for overall heter	ER- N=564	ER+ N=1282	ER unknown N=1923	P for positive vs. negative heter	P for overall heter	PR- N=1528	PR+ N=1125	PR unknown N=1116	P for positive vs. negative heter	P for overall heter
Physical inactivity															
Active	ref	ref	ref	0.125	0.110	ref	ref	ref	0.105	0.014	ref	ref	ref	0.752	0.094
Inactive	1.26 (0.98, 1.61)	1.77 (1.20, 2.60)	1.12 (0.92, 1.36)			1.73 (1.23, 2.42)	1.24 (0.97, 1.58)	0.99 (0.82, 1.21)			1.37 (1.10, 1.72)	1.30 (0.96, 1.75)	0.99 (0.79, 1.24)		
Obesity status at adulthood															
underweight/ normal	ref	ref	ref	0.578	0.489	ref	ref	ref	**0.046**	0.123	ref	ref	ref	0.410	0.238
overweight/ obese	1.07 (0.90, 1.26)	1.16 (0.90, 1.49)	1.21 (1.05, 1.40)			1.51 (1.17, 1.96)	1.11 (0.93, 1.32)	1.16 (1.01, 1.34)			1.21 (1.03, 1.41)	1.32 (1.10, 1.59)	1.06 (0.88, 1.28)		
Smoking status															
Never Smoker	ref	ref	ref	0.450	0.604	ref	ref	ref	0.2889	0.280	ref	ref	ref	0.090	0.086
Current Smoker	1.04 (0.84, 1.30)	1.07 (0.78, 1.45)	1.19 (1.02, 1.40)			1.36 (1.06, 1.74)	1.16 (0.96, 1.41)	1.02 (0.86, 1.22)			1.32 (1.11, 1.58)	1.08 (0.87, 1.33)	0.97 (0.78, 1.21)		
Former Smoker	1.07 (0.92, 1.25)	0.92 (0.73, 1.15)	1.06 (0.93, 1.20)			0.95 (0.77, 1.18)	1.06 (0.92, 1.22)	1.00 (0.88, 1.14)			0.99 (0.87, 1.13)	1.09 (0.94, 1.27)	0.94 (0.77, 1.15)		
Duration of oral contraceptive use, years															
0	ref	ref	ref	0.380	0.415	ref	ref	ref	0.747	0.563	ref	ref	ref	0.421	0.571
<1	1.03 (0.82, 1.29)	1.04 (0.77, 1.40)	1.07 (0.89, 1.29)			0.88 (0.65, 1.18)	1.01 (0.83, 1.24)	1.12 (0.91, 1.36)			1.03 (0.76, 1.25)	1.08 (0.87, 1.33)	1.02 (0.77, 1.35)		
1-4	0.73 (0.59, 0.91)	0.52 (0.38, 0.71)	0.79 (0.66, 0.95)			0.66 (0.50, 0.89)	0.63 (0.52, 0.77)	0.82 (0.68, 0.99)			0.81 (0.68, 0.97)	0.66 (0.54, 0.82)	0.58 (0.42, 0.80)		
5-9	0.51 (0.41, 0.63)	0.46 (0.34, 0.62)	0.61 (0.52, 0.73)			0.57 (0.43, 0.75)	0.50 (0.41, 0.61)	0.59 (0.50, 0.71)			0.56 (0.47, 0.67)	0.53 (0.44, 0.65)	0.58 (0.44, 0.76)		

10+	0.39 (0.30, 0.51)	0.35 (0.25, 0.51)	0.42 (0.34,			0.37 (0.25, 0.52)	0.36 (0.28, 0.45)	0.44 (0.35,			0.38 (0.31, 0.48)	0.41 (0.33, 0.52)	0.40 (0.29,		
Number of pregnancies															
Never	ref	ref	ref	0.919	0.001	ref	ref	ref	0.358	0.100	ref	ref	ref	0.214	0.009
1	1.02 (0.81, 1.29)	0.96 (0.69, 1.34)	0.63 (0.51, 0.77)			0.87 (0.64, 1.18)	1.00 (0.79, 1.25)	0.79 (0.64, 0.98)			0.91 (0.73, 1.12)	0.94 (0.74, 1.18)	0.68 (0.50, 0.92)		
2	0.75 (0.61, 0.93)	0.77 (0.57, 1.03)	0.46 (0.38, 0.54)			0.56 (0.42, 0.74)	0.71 (0.58, 0.86)	0.65 (0.55, 0.78)			0.64 (0.53, 0.77)	0.68 (0.55, 0.83)	0.59 (0.45, 0.76)		
3	0.68 (0.55, 0.85)	0.74 (0.55, 1.00)	0.39 (0.32, 0.46)			0.62 (0.46, 0.83)	0.71 (0.58, 0.88)	0.51 (0.42, 0.61)			0.62 (0.52, 0.75)	0.68 (0.55, 0.84)	0.39 (0.30 0.52)		
4+	0.55 (0.44, 0.68)	0.60 (0.44, 0.81)	0.38 (0.32, 0.46)			0.59 (0.44, 0.79)	0.56 (0.45, 0.69)	0.50 (0.41, 0.60)			0.62 (0.51, 0.74)	0.51 (0.41, 0.64)	0.41 (0.31, 0.53)		
Duration of breastfeeding															
0	ref	ref	ref	0.076	0.280	ref	ref	ref	0.620	0.778	ref	ref	ref	0.721	0.001
<6 months	0.62 (0.48, 0.79)	0.85 (0.59, 1.21)	0.73 (0.62, 0.87)			0.80 (0.61, 1.05)	0.69 (0.56, 0.85)	0.65 (0.53, 0.79)			0.76 (0.63, 0.92)	0.83 (0.66, 1.04)	0.41 (0.32, 0.53)		
6-12 months	0.57 (0.43, 0.77)	0.48 (0.30, 0.76)	0.62 (0.51, 0.77)			0.57 (0.40, 0.81)	0.64 (0.50, 0.81)	0.54 (0.42, 0.69)			0.62 (0.49, 0.78)	0.74 (0.56, 0.96)	0.35 (0.26, 0.47)		
>12 months	0.46 (0.34, 0.61)	0.70 (0.48, 1.02)	0.56 (0.46, 0.69)			0.56 (0.40, 0.77)	0.53 (0.42, 0.66)	0.54 (0.43, 0.68)			0.55 (0.44, 0.68)	0.62 (0.48, 0.80)	0.35 (0.26, 0.48)		
Age at menarche															
<=13 years	ref	ref	ref	0.204	0.405	ref	ref	ref	0.625	0.720	ref	ref	ref	0.266	0.177
>13 years	0.91 (0.79, 1.05)	0.79 (0.63, 0.96)	0.90 (0.81, 1.01)			0.88 (0.72, 1.07)	0.93 (0.81, 1.07)	0.87 (0.77, 0.98)			0.88 (0.78, 1.00)	0.80 (0.69, 0.92)	0.98 (0.83, 1.15)		
Menopause status at diagnosis															
pri	ref	ref	ref	0.847	0.688	ref	ref	ref	0.818	0.254	**ref**	**ref**	ref	**0.001**	<0.001
post	1.39 (1.13, 1.71)	1.34 (1.00, 1.81)	1.53 (1.28, 1.82)			1.22 (0.92, 1.62)	1.27 (1.04, 1.55)	1.53 (1.27, 1.83)			**1.53 (1.26, 1.84)**	**0.98 (0.81, 1.20)**	1.94 (1.50, 2.51)		
Endometriosis															
No	ref	ref	ref	0.714	0.464	ref	ref	ref	0.618	0.628	ref	ref	ref	0.110	0.023
Yes	1.30 (0.96, 1.76)	1.18 (0.73, 1.88)	1.01 (0.76, 1.35)			1.31 (0.85, 2.03)	1.15 (0.84, 1.58)	1.39 (1.05, 1.85)			1.02 (0.76, 1.36)	1.38 (1.03, 1.85)	2.02 (1.30, 3.13)		

Hysterectomy															
No	ref	ref	ref	0.092	<0.001	ref	ref	ref	**0.035**	0.045	ref	ref	ref	0.057	<0.001
Yes	5.08 (4.30, 5.99)	6.31 (5.01, 7.94)	3.65 (3.21, 4.15)			3.25 (2.60, 4.06)	4.27 (3.66, 4.98)	4.44 (3.89, 5.08)			4.81 (4.20, 5.49)	5.76 (4.93, 6.73)	1.92 (1.56, 2.37)		
Hormonal treatment use															
No	ref	ref	ref	0.410	0.005	ref	ref	ref	0.122	<0.001	ref	ref	ref	0.786	0.002
Estrogen only	0.73 (0.53, 1.00)	0.55 (0.31, 0.96)	0.60 (0.44, 0.82)			0.92 (0.57, 1.50)	0.56 (0.38, 0.85)	0.63 (0.48, 0.83)			0.66 (0.50, 0.87)	0.78 (0.56, 1.08)	0.38 (0.18, 0.83)		
Combination	0.91 (0.74, 1.12)	1.06 (0.78, 1.44)	0.82 (0.67, 1.00)			0.70 (0.49, 1.01)	0.90 (0.72, 1.12)	0.89 (0.74, 1.07)			0.90 (0.75, 1.09)	0.94 (0.76, 1.17)	0.64 (0.43, 0.97)		
Others	0.75 (0.60, 0.94)	0.91 (0.66, 1.26)	1.23 (1.06, 1.43)			1.34 (1.04, 1.74)	1.59 (1.32, 1.92)	0.77 (0.65, 0.92)			1.33 (1.12, 1.60)	1.25 (1.00, 1.56)	0.81 (0.67, 0.98)		

AR, androgen receptor; CI, confidence interval; ER, estrogen receptor; heter, heterogeneity; PR, progesterone receptor; RRR, relative risk ratio.
1 adjusted for study site, age (continuous), family history of breast or ovarian cancer in first-relative (no, ovarian cancer only, breast cancer only, both ovarian cancer and breast cancer), duration of OC use (0, <1, 1-4, 5-9, or10+ years), number of pregnancies (never, 1, 2, 3, or 4+), menopause status at diagnosis (pre or post), and hormonal treatment use (no, estrogen only, combination, or others). Models treated unknown groups as indexes. Estimates for unknown group are not reported in the table.

Supplemental Table. B Association of menopause status and hysterectomy with EOC risk by joint presence of androgen receptor, estrogen receptor, and progesterone receptor compared to all controls[1]

Tumor types	Number of cases	Menopause status RRR[2] (95% CI)	Hysterectomy RRR[3] (95% CI)
AE-ER-PR-	265	1.34 (0.88, 2.06)	**4.21 (2.98, 5.94)**
AR-ER+PR-	254	**2.20 (1.40, 3.46)**	**8.74 (6.28, 12.18)**
AR+ER+PR-	72	**2.29 (1.00, 5.24)**	**7.81 (4.44, 13.93)**
AR-ER-PR+	22	**0.23 (0.05, 0.99)**	**6.08 (1.99, 18.59)**
AR-ER+PR+	227	**0.63 (0.41, 0.99)**	**10.20 (6.89, 15.10)**
AR+ER-PR-	34	0.81 (0.26, 2.56)	**7.14 (2.71, 18.81)**
AR+ER-PR+	8	2.34 (0.24, 22.88)	2.73 (0.24, 30.56)
AR+ER+PR+	167	0.97 (0.57, 1.63)	**5.08 (3.24, 7.97)**

AR, androgen receptor; CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor; RRR, relative risk ratio.
1 Including AUS, HAW, HOP, MAL, MAY, and STA.
2 adjusted for study site, age (continuous), family history of breast or ovarian cancer in first-relative (no, ovarian cancer only, breast cancer only, both ovarian cancer and breast cancer), duration of OC use (0, <1, 1-4, 5-9, or10+ years), number of pregnancies (never, 1, 2, 3, or 4+), and hormonal treatment use (no, estrogen only, combination, or others). Models treated unknown groups as indexes. Estimates for unknown groups are not reported in the table.
3 further adjusted for menopause status at diagnosis (pre or post). Models treated unknown groups as indexes. Estimates for unknown groups are not reported in the table.

Supplemental Table. C Characteristics of participants in survival analyses by individual hormonal receptor presence

	AR- N=2552	AR+ N=1153	P[1]	ER- N=830	ER+ N=1699	P[1]	PR- N=2640	PR+ N=1728	P[1]
Outcome									
Survival time, median (95% CI)	4.92 (4.63, 5.32)	5.11 (4.71, 5.66)		7.26 (6.12, 8.66)	4.94 (4.62, 5.36)		4.22 (3.89, 4.56)	6.93 (6.21, 8.05)	
2-year OS	74.51%	80.06%		78.42%	78.57%		73.31%	82.63%	
5-year OS	50.18%	50.39%		60.22%	49.98%		46.60%	59.25%	
10-year OS	35.05%	32.08%		47.47%	32.10%		30.78%	43.06%	
Tumor characteristics and clinical variables									
Histotypes									
Serous	1499 (58.74)	843 (73.11)	<0.001	308 (37.11)	1268 (74.63)	<0.001	1651 (62.54)	1085 (62.79)	<0.001
Endometrioid	355 (13.91)	181 (15.70)		88 (10.60)	271 (15.95)		152 (5.76)	494 (28.59)	
Mucinous	186 (7.29)	55 (4.77)		130 (15.66)	20 (1.18)		255 (9.66)	24 (1.39)	
Clear cell	426 (16.69)	42 (3.64)		257 (30.96)	45 (2.65)		473 (17.92)	40 (2.31)	
Other	86 (3.37)	32 (2.78)		47 (5.66)	95 (5.59)		109 (4.13)	85 (4.92)	
Stage									
Stage I/II	988 (40.08)	420 (37.53)	0.148	525 (63.64)	663 (39.53)	<0.001	1030 (40.23)	752 (45.30)	0.001
Stage III/IV	1477 (59.92)	699 (62.47)		300 (36.36)	1014 (60.47)		1530 (59.77)	908 (54.70)	
Unknown	87	34		5	22		80	68	
Grade									
Low	341 (14.33)	175 (15.60)	0.323	106 (13.40)	206 (12.28)	0.436	221 (9.21)	353 (21.21)	<0.001
High	2039 (85.67)	947 (84.40)		685 (86.60)	1471 (87.72)		2179 (90.79)	1311 (78.79)	
Unknown	172	31		39	22		240	64	
Debulking Status									
Optimal	1450 (89.95)	618 (91.56)	0.234	426 (97.04)	753 (91.49)	<0.001	1152 (86.88)	798 (90.68)	0.006
Suboptimal	162 (10.05)	57 (8.44)		13 (2.96)	70 (8.51)		174 (13.12)	82 (9.32)	
Unknown	940	478		391	876		1314	848	
Chemotherapy or other systemic treatment as part of primary treatment									
No	102 (11.40)	60 (14.39)	0.125	34 (21.25)	6 (1.54)	<0.001	113 (12.31)	61 (8.85)	0.027
Yes	793 (88.60)	357 (85.61)		126 (78.75)	383 (98.46)		805 (87.69)	628 (91.15)	
Unknown	1657	736		670	1310		1722	1039	
Primary therapy outcome									
Complete response/ Partial response	177 (86.73)	212 (88.70)	0.443	103 (83.74)	453 (86.45)	0.436	638 (85.98)	532 (89.86)	0.032

Stable disease/ Progressive disease	73 (13.27)	27 (11.30)		20 (16.26)	71 (13.55)		104 (14.02)	60 (10.14)	
Unknown	2002	914		707	1175		1898	1186	
Demographic									
Age, years, mean (SD)	58.53 (12.51)	58.77 (12.27)	0.5809	57.20 (11.88)	58.21 (11.60)	0.0405	59.56 (11.64)	57.13 (11.89)	<0.001
Race									
non-white	213 (11.96)	72 (10.29)	0.239	103 (18.86)	87 (7.24)	<0.001	190 (10.71)	92 (7.53)	0.003
white	1568 (88.04)	628 (89.71)		443 (81.14)	1114 (92.76)		1584 (89.29)	1130 (92.47)	
unknown	771	453		284	498		866	506	
BRCA1/2 mutation status									
wild type	779 (76.98)	318 (74.82)	0.1	333 (90.49)	765 (83.33)	0.001	945 (84.45)	600 (80.97)	0.125
pathogenic	138 (13.64)	75 (17.65)		16 (4.35)	98 (10.68)		102 (9.12)	87 (11.74)	
unclassified variant	95 (9.39)	32 (7.53)		19 (5.16)	55 (5.99)		72 (6.43)	54 (7.29)	
unknown	1540	728		462	781		1521	987	
Family history of breast/ovarian cancer									
No	771 (87.02)	344 (83.50)	0.089	396 (91.88)	827 (84.82)	<0.001	1073 (86.60)	682 (84.62)	0.208
Yes	115 (12.98)	68 (16.50)		35 (8.12)	148 (15.18)		166 (13.40)	124 (15.38)	
Unknown	1666	741		399	724		1401	922	
Hormonally-liked risk factors									
Physical inactivity									
Active	358 (76.33)	104 (71.72)	0.261	146 (69.52)	335 (76.14)	0.072	381 (73.55)	213 (76.62)	0.343
Inactive	111 (23.67)	41 (28.28)		64 (30.48)	105 (23.86)		137 (26.45)	65 (23.38)	
Unknown	2083	1008		620	1259		2122	1450	
Obesity status at adulthood									
No	344 (44.73)	114 (41.30)	0.325	113 (43.80)	268 (44.67)	0.814	347 (43.70)	227 (40.25)	0.204
Yes	425 (55.27)	162 (58.70)		145 (56.20)	332 (55.33)		447 (56.30)	337 (59.75)	
Unknown	1783	877		572	1099		1846	1164	
Smoking Status									
Never Smoker	778 (59.89)	374 (63.18)	0.372	282 (56.06)	640 (57.40)	0.11	941 (57.13)	674 (59.23)	0.024
Current Smoker	165 (12.70)	66 (11.15)		91 (18.09)	158 (14.17)		249 (15.12)	131 (11.51)	
Former Smoker	356 (27.41)	152 (25.68)		130 (25.84)	317 (28.43)		457 (27.75)	333 (29.26)	
Unknown	1253	561		327	584		993	590	
Duration of oral contraceptive Use, years									
0	448 (45.85)	175 (43.53)	0.3267	262 (52.09)	519 (46.93)	0.0756	668 (47.38)	410 (43.29)	0.022
<1	145 (14.84)	64 (15.92)		65 (12.92)	167 (15.10)		184 (13.05)	135 (14.26)	

1-4	157 (16.07)	54 (13.43)		67 (13.32)	156 (14.10)		227 (16.10)	138 (14.57)	
5-9	149 (15.25)	74 (18.41)		76 (15.11)	171 (15.46)		221 (15.67)	168 (17.74)	
10+	78 (7.98)	35 (8.71)		33 (6.56)	93 (8.41)		110 (7.80)	96 (10.14)	
Unknown	1575	751		327	593		1230	781	
Number of full-term pregnancies									
Never	229 (19.75)	116 (18.50)	0.0461	99 (19.49)	181 (16.15)	0.1114	306 (18.18)	231 (20.23)	0.088
1	224 (14.80)	77 (12.28)		79 (15.55)	154 (13.74)		233 (13.84)	154 (13.49)	
2	378 (24.97)	148 (23.60)		117 (23.03)	280 (24.98)		410 (24.36)	281 (24.61)	
3	298 (19.68)	138 (22.01)		102 (20.08)	254 (22.66)		334 (19.85)	245 (21.45)	
4+	315 (20.81)	148 (23.60)		111 (21.85)	252 (22.48)		400 (23.77)	231 (20.23)	
Unknown	1038	526		322	578		957	586	
Duration of breastfeeding, months									
0	316 (55.15)	121 (53.78)	0.5094	194 (48.14)	355 (46.04)	0.2353	414 (46.10)	244 (45.10)	0.651
<=6	113 (19.72)	43 (19.11)		106 (26.30)	179 (23.22)		228 (25.39)	137 (25.32)	
>6, <=12	69 (12.04)	22 (9.78)		43 (10.67)	108 (14.01)		115 (12.81)	71 (13.12)	
>12	75 (13.09)	39 (17.33)		60 (14.89)	129 (16.73)		141 (15.70)	89 (16.45)	
Unknown	1979	928		427	928		1742	1187	
Menopausal status at diagnosis									
Pri	378 (25.73)	172 (28.15)	0.255	147 (29.40)	298 (27.14)	0.35	365 (22.34)	369 (33.15)	<0.001
Post	1091 (74.27)	439 (71.85)		353 (70.60)	800 (72.86)		1269 (77.66)	744 (66.85)	
Unknown	1083	542		330	601		1006	615	
Hormonal treatment use									
No	649 (66.36)	266 (65.20)	0.677	309 (65.05)	642 (63.00)	0.443	852 (63.30)	610 (68.23)	0.016
Yes	329 (33.64)	142 (34.80)		166 (34.95)	377 (37.00)		494 (36.70)	284 (31.77)	
Unknown	1574	745		355	680		1294	834	

AR, androgen receptor; ER, estrogen receptor; PR, progesterone receptor.

1 P values were calculated using Fisher exact test, except for the ordinal variables number of pregnancies and oral contraceptive use where the Mann-Whitney test was used.

Appendix C Supplemental Figures and Tables for Paper II

Supplemental Table I Missing value pattern for each immunohistochemistry biomarker by site[1]

Site	Androgen Receptor	Estrogen Receptor	Progesterone Receptor	Toll-like receptor 4, TLR4	Myeloid differentiation primary response 88, MyD88	Folate receptor alpha, FOLR1	Phosphatase and tensin homolog, PTEN	Cluster of differentiation 8, CD8	p16
AOC	345/588	380/588	379/588	504/588	495/588	498/588	495/588	502/588	286/588
AOV	0/462	462/462	3/462	4/462	1/462	240/462	1/462	1/462	6/462
BAV	0/233	233/233	233/233	25/233	7/233	10/233	9/233	25/233	12/233
BRZ	0/114	114/114	114/114	24/114	21/114	114/114	6/114	20/114	8/114
CAL	0/107	107/107	107/107	7/107	4/107	36/107	1/107	7/107	2/107
CNI	0/138	138/138	138/138	27/138	18/138	138/138	21/138	24/138	18/138
GER	0/89	89/89	7/89	11/89	12/89	89/89	2/89	12/89	5/89
HAW	0/126	8/126	8/126	6/126	4/126	126/126	2/126	5/126	4/126
HOP	0/38	3/38	0/38	2/38	2/38	3/38	1/38	2/38	0/38
LAX	0/271	271/271	271/271	64/271	81/271	271/271	27/271	26/271	25/271
MAL	450/516	390/516	380/516	460/516	458/516	266/516	450/516	462/516	452/516
MAY	328/1179	704/1179	106/1179	887/1179	879/1179	713/1179	617/1179	440/1179	504/1179
NOT	0/517	321/517	320/517	326/517	91/517	341/517	144/517	121/517	84/517
POC	0/130	130/130	2/130	7/130	5/130	130/130	1/130	14/130	4/130
SEA	566/566	281/566	275/566	198/566	92/566	162/566	71/566	124/566	66/566
SOC	0/65	65/65	65/65	28/65	13/65	65/65	65/65	19/65	65/65
STA	0/305	6/305	7/305	24/305	3/305	305/305	3/305	22/305	305/305
TUE	0/208	208/208	208/208	13/208	14/208	208/208	8/208	12/208	14/208
TVA	150/150	150/150	2/150	150/150	6/150	150/150	1/150	16/150	5/150
UKO	0/107	8/107	13/107	13/107	12/107	5/107	4/107	6/107	6/107
VAN	0/1077	323/1077	382/1077	129/1077	94/1077	403/1077	122/1077	97/1077	277/1077
WMH	50/261	261/261	40/261	72/261	75/261	261/261	261/261	30/261	9/261

1 Presented as number of missing values / total number of cases in the site.

Supplemental Table II Comparisons of machine learning techniques with Cox proportional hazards mode[l]

	random survival forest	**boosting in Cox regression**	**support vector machine for survival**	**deep neural networks for survival analysis using pseudo values**	**deep neural networks for survival analysis based on the partial likelihood from a Cox proportional hazards model**	**Cox proportional hazards model**
Abbreviation in the paper	RSF	boostCox	SVMsur	DNNSurv	deepsurv	Cox
R package	randomForestSRC	mboost	survivalsvm	Survivalmodels	Survivalmodels	Survival
Assumption	No	Proportional hazards	No	No	No	Proportional hazards
Output	Death indicators and survival time	Log hazard ratio	Risk ranks	Survival probability or risk ranks	Survival probability or risk ranks	Log hazard ratio
Function for estimation / Cost function	The log-rank test and the log-rank score test	The model-based boosting methods using the partial likelihood	The ranking approach and regression approach based on the support vector regression	Sum of square errors	The partial likelihood	The partial likelihood
Censored data	Inverse probability of censoring weights	The partial likelihood	Penalization on survival predictions lower than the censoring time	Pseudo-value method	The partial likelihood	The partial likelihood

Supplemental Table III Summary of model performances at different time points in terms of Uno's C-index

Model	Uno's C-index in %				
	at 1st year	**at 3rd year**	**at 5th year**	**at 10th year**	**at 15th year**
RSF	72.26	70.57	71.09	70.85	71.02
boostCox	74.47	71.57	71.76	71.20	71.95
SVMsur	64.28	60.12	61.08	62.13	62.93
DNNSurv	65.37	60.47	58.88	59.54	60.96
deepsurv	67.61	61.21	60.39	60.8	62.19
Cox (basic)[1]	71.57	68.31	68.71	68.94	70.29
Cox[2]	73.89	71	71.02	70.57	70.77

boostCox, boosting in Cox regression; Cox, Cox proportional hazards model; deepsurv, deep neural networks for survival analysis based on the partial likelihood from a Cox proportional hazards model; DNNSurv, deep neural networks for survival analysis using pseudo values; RSF, random survival forest; SVMsur, support vector machine for survival.

1 Model included age, stage and histotypes.

2 Model included age, race, stage, histotypes, behavior, grade, debulking status, VRCA1/2 mutation status and nine biomarkers

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