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의학석사 학위논문

한국형 난소암 연구 (Ko-EVE)에서의

난소암과 위험 요인의 연관성 연구

**Association between risk factors and
ovarian cancer in the Korean
Epithelial Ovarian Cancer Study (Ko-EVE)**

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서울대학교 대학원

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Introduction

Ovarian cancer is the seventh leading cause of cancer-death in women. It has been reported that risk factors related to ovarian cancer globally. However, even though there were a few researches about risk factors of ovarian cancer, most of them are the studies of Europe. In Korea, observational study of ovarian cancer risk profiling has been never reported. Therefore, this study is to verify the association between ovarian cancer and various factors such as reproductive, hormonal treatment, lifestyle, and family history in Korea.

Methods

A total of 530 ovarian cancer cases in the Korean Epithelial Ovarian Cancer Study (Ko-EVE) and 80,979 controls in the Health Examinee (HEXA) study were primary selected. Eligible criteria of cases were incident cases diagnosed as primary ovarian cancer and confirmed histologically as epithelial ovarian carcinoma and stages one to three. We did restriction of age and enrollment year and frequency matching of enrollment year and household income to minimize selection bias and to regulate the distribution of potential confounders. To calculate odds ratios (ORs) and 95% confidence intervals (CIs), we used the multivariate logistic regression models in restricted design, conditional logistic regression models in matched design.

Results

As a result of our study, early age at menarche (OR=1.48, 95% CI=1.05-2.09), late age of the last childbirth (OR=1.68, 95% CI=1.07-2.64), past cigarette smoking (OR=3.69, 95% CI=1.75-7.78), smoking pack-year \geq 10 pack-years (OR=3.14, 95% CI=1.32-7.44), past drinking (OR=11.20, 95% CI=6.75-18.59), BMI $<$ 18.5 Kg/m² (OR=1.80, 95% CI=1.04-3.13), family history of breast cancer (OR=3.92, 95% CI=2.47-6.21), and family history of ovarian cancer (OR=33.65, 95% CI=9.67-117.13) were shown as definite risk factors of epithelial ovarian cancer.

On the other hand, parity (OR=0.24, 95% CI=0.16-0.37), number of parity \geq 2 (OR=0.23, 95% CI=0.15-0.35), artificial abortion (OR=0.66, 95% CI=0.48-0.91), HRT (OR=0.51, 95% CI=0.32-0.80), tubal ligation (OR=0.17, 95% CI=0.10-0.31), OC use (OR=0.59, 95% CI=0.41-0.87), oral contraceptives (OC) use duration \geq 10 months (OR=0.59, 95% CI=0.41-0.87), hysterectomy (OR=0.34, 95% CI=0.19-0.62), regular exercise \geq 1.5 hour/time (OR=0.60, 95% CI=0.41-0.86), regular exercise \geq 5 times/week (OR=0.41, 95% CI=0.28-0.60), regular exercise \geq 2

hours/week (OR=0.47, 95% CI=0.35-0.61) were shown as protective factors definitely for epithelial ovarian cancer. In the case of postmenopausal hormone replacement therapy (HRT), it was shown as a protective factor (OR=0.51, 95% CI=0.32-0.80). However, it cannot be said it is a definite protective factor because the information on HRT was not clear.

Conclusions

According to the result of the first observational study of profiling ovarian cancer risk in Korea, we suggest that parity, artificial abortion, OC use, tubal ligation, hysterectomy, and regular exercise may have a protective effect for ovarian cancer. Moreover, especially for parity, the duration of OC use and regular exercise, increase in the number of parity, longer duration of OC use, and more and longer hours of regular exercise have more preventive effects for ovarian cancer. We also propose that early age at menarche, late age of last childbirth, cigarette smoking, alcohol drinking, BMI <18.5 kg/m², and family history of breast cancer and ovarian cancer are risk factors for ovarian cancer. Especially for cigarette smoking, a smoking pack-year of 10 pack-years or more has a higher risk for ovarian cancer. In the case of postmenopausal replacement therapy, we have to investigate further to include hormones.

Keywords

Ovarian neoplasms, Reproductive factor, Risk factor, Frequency matching, Case-control study, Logistic regression, Epidemiology, Korea

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I. Introduction

1. Ovarian cancer

Ovarian cancer is cancer of ovaries, which is an organ of the female reproductive tract related to producing and releasing eggs and producing the hormones estrogens and progesterone. There is a pair of ovaries, which lean behind the uterus and in front of the sacroiliac articulation. Of all the different types of ovarian cancers, 90% are epithelial ovarian cancer. (1) Because of the anatomical position of the ovaries, it is hard to detect in early stage and new patients visit the hospital with an advanced stage of ovarian cancer. Therefore, ovarian cancer has a poor prognosis. Ovarian cancer is one of the most common cancers in women and the seventh leading cause of cancer death in women in worldwide. (2) According to the National Institutes of Health (NIH), 22,530 new ovarian cancer cases and 13,980 ovarian cancer causing-deaths were estimated in 2019. (3) Additionally, the ovary is the fourth common cancer site of early onset before 15 and 15 to 34 years of age in Korea. (4) The incidence rate and age-standardized rate of ovarian cancer has increased in Korea (Figure 1, Figure 2). (4)

Because of the poor prognosis of ovarian cancer and its increasing incidence and prevalence rate, the significance of the epidemiology of ovarian cancer has attracted attention for primary, secondary, and tertiary prevention. Despite the importance of ovarian cancer studies, the research on ovarian cancer is limited, especially in Korea, because most studies on ovarian cancer have been published in Europe. Even in a meta-analysis article from an Asian country, the number of Asian studies was less than 10, and there were no Korean studies. (5, 6)



Figure 1. Age-standardized rate of ovarian cancer in Korea, 2002-2016

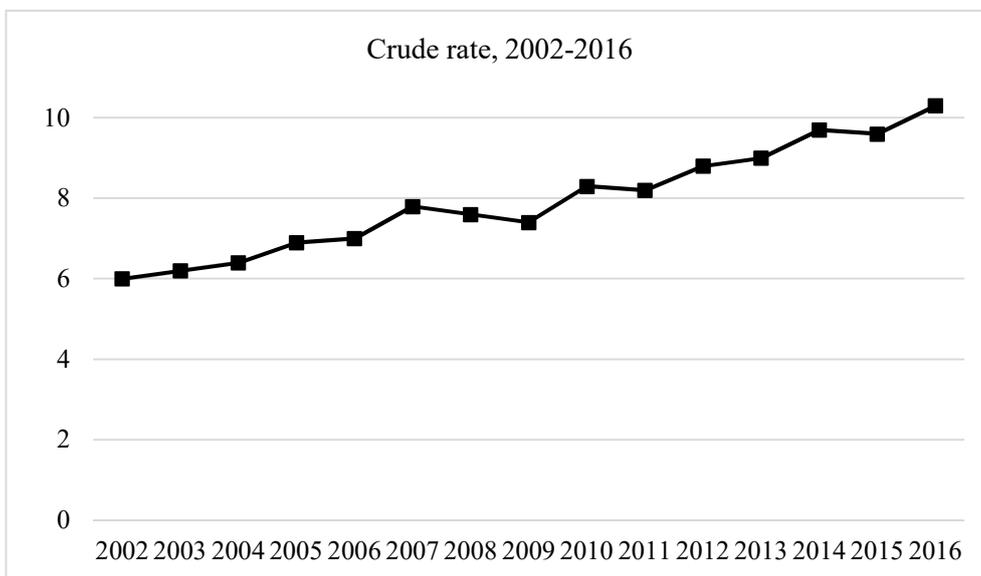


Figure 2. Crude rate of ovarian cancer in Korea, 2002-2016

2. Risk factors and protective factors

According to the International Agency for Research on Cancer (IARC) in 2019, tobacco smoking, estrogen menopausal therapy, and asbestos are the carcinogenic agents of ovarian cancer with sufficient evidence. (7) However, the studies on ovarian cancer suggest other protective and risk factors in addition to those three. One of the proposed hypotheses about ovarian cancer related factors is the number of ovulatory cycles called the incessant ovulation hypothesis. An increased number of ovulatory cycles has been suggested as a risk factor of ovarian cancer. (8) The other proposed hypothesis is that gonadotropins such as luteinizing hormone and follicle-stimulating hormone affect ovarian cancer: the gonadotropin hypothesis. (9)

A. Protective factors

Age at menarche is an observational factor related to pubertal hormone and related to heredity and environment. As a result of a meta-analysis of ovarian cancer, a decreasing risk of epithelial ovarian cancer was observed for every year older the women were at menses onset (age at menarche). (1, 5) Parity and breastfeeding also have been observed as protective factors. (1, 10) Oral contraceptives use, which is related to regulating the ovulation cycle, has been suggested as a protective factor for ovarian cancer. (1, 10)

B. Risk factors

Menopause is associated with reducing the ovulation cycle. According to a pooled analysis, late age at menopause is suggested to increase the risk of ovarian cancer. (1, 11)

Even though there are not enough studies that prove the relation between alcohol consumption and ovarian cancer risk, it has also been proposed as a risk factor for ovarian cancer risk. (1, 12)

3. Objectives

Our ultimate goal for this study was to suggest protective factors and risk factors for ovarian cancer in Korea. We hypothesized that there will be an association between ovarian cancer and age at menarche, menopausal status, cigarette smoking, oral contraceptives use, and postmenopausal hormone replacement therapy. To achieve this goal, we set up objectives to investigate the association between ovarian cancer and various factors such as reproductive, hormonal treatment, lifestyle, and family history in Korea. Moreover, we selected a method to reduce the number of limitations in this study.

II. Materials and methods

1. Study design and study population

The ovarian cancer case group was from the Korean Epithelial Ovarian Cancer Study (Ko-EVE), which was a prospective cohort study for epithelial ovarian cancer conducted since 2010 to explain risk factors for the progression and survival of epithelial ovarian cancer. The eligible criteria for the case group were as follows: 1) participants were from seven hospitals, Seoul National University hospital, Samsung Medical Center, Asan Medical Center, National Cancer Center, Gangnam Severance hospital, Kyung Hee University hospital at Gangdong, and Cheil General hospital; 2) primary ovarian cancer diagnosed incident cases at the time of enrollment; 3) participants who had histologically verified epithelial ovarian carcinoma and were stages I to III, and 3) women whose age was over 20 years at the time of enrollment. (13). Of the 1,410 total Ko-EVE women that had epidemiological information, 85, 120, 73, 116, 56, 44, and 97 were enrolled each year from 2010 to 2016, respectively.

The healthy control group was from the Health Examinees (HEXA) study. The eligibility criteria for the controls were as follows: 1) participants whose age was from 40 to 79 years at the time of enrollment; 2) those whose enrollment year was from 2004 to 2013, and 3) participants who have a community-representative health examinee system. (14). Of the 173,357 total HEXA participants, 114,063 and 59,294 were women and men, respectively. Additionally, 4,384 women had a past cancer history, and 109,679 women did not have a past cancer history. Among the women, 986, 14,591, and 14,143 were enrolled each year from 2004 to 2006, respectively. Moreover, 14,598, 15,072, 15,604, 15,979, 14,591, 5,121, and 3,378 were registered each year from 2007 to 2013, respectively.

We designed this study as a population based case-control study, which is restricted by age and enrollment year. The eligibility criteria of our study population were women whose enrollment year was from 2007 to 2016, and their age was 35 to 79 years. In the case group, we excluded participants from the Ko-EVE as follows: 1) those who did not provide informed consent; 2) those who did not have their age information, and 3) healthy participants or those who have an ovarian benign tumor. In the control group, we excluded participants from the HEXA as follows: 1) males and 2) those who had a past cancer history. As a result, a total of 81,510, which included 531 epithelial ovarian cancer cases and 80,979 healthy controls, were selected.

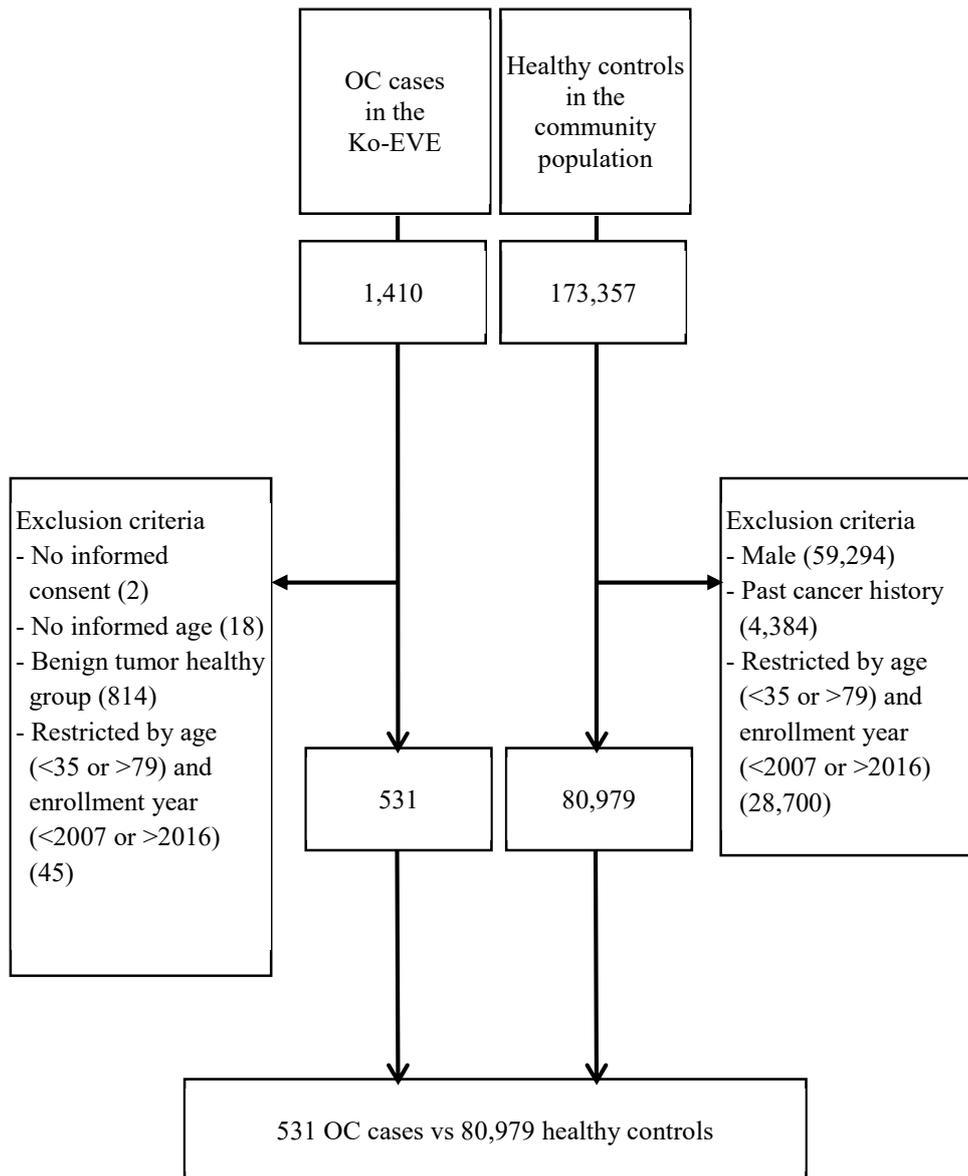


Figure 3. Flow chart of subject selection

2. Data collection

A. Explanatory variables and outcome variable

1) Age at menarche and menopausal factors

- Age at menarche

Information of age at menarche was collected by self-reported questionnaire. It was categorized by ≤ 13 years, 14-15 years, and ≥ 16 years.

- Menopausal status

Information of menopausal status was collected by self-reported questionnaire. It was classified as premenopausal status and postmenopausal status.

- Age at menopause

Information of age at menopause was collected by self-reported questionnaire. It was categorized by < 49 years, 49-51 years, ≥ 52 years.

2) Parity and breastfeeding factors

- Parity and number of parity

Information of parity and number of parity were collected by self-reported questionnaire. Parity was categorized by never and ever. Number of parity was classified as nulliparous, 1, and ≥ 2 .

- Breastfeeding and breastfeeding duration

Information of breastfeeding and breastfeeding duration were collected by self-reported questionnaire. Breastfeeding was categorized by nulliparous, never, and ever. Breastfeeding duration was classified as nulliparous, never, < 6 months, and ≥ 6 months.

3) Age of the childbirth and abortion factors

- Age of the first childbirth and age of the last childbirth

Information of age of the first childbirth and last childbirth were collected by self-reported questionnaire. Age of the first childbirth was categorized by < 24 years, 24-26 years, 27-29 years, and \geq 30 years. Age of the last childbirth was classified as < 29 years, 29-31 years, 32-35 years, and \geq 36 years. Both of two variables were analyzed among parous women.

- Spontaneous abortion and artificial abortion

Information of spontaneous and artificial abortion were collected by self-reported questionnaire. Both of two variables were categorized by never and ever.

4) Hormonal treatment and operation historical factors

- Oral contraceptives use and oral contraceptives use duration

Information of oral contraceptives use and its duration were collected by self-reported questionnaire. Oral contraceptives use was categorized by never and ever. Duration of its use was classified as never, < 10 months, and \geq 10 months.

- Postmenopausal hormone replacement therapy (HRT) and HRT duration

Information of HRT and its duration were collected by self-reported questionnaire. HRT was categorized by never and ever. Duration of its use was classified as never, \leq 12 months, and > 12 months.

- Tubal ligation, hysterectomy, and oophorectomy

Information of tubal ligation, hysterectomy, and oophorectomy were collected by self-reported questionnaire. Oophorectomy was defined in the questionnaire as surgical removal of one or two ovaries. All three of them were categorized by never and ever.

5) Cigarette smoking and alcohol drinking factors

- Cigarette smoking, smoking duration, smoking frequency, and smoking pack-year

Information of cigarette smoking related variables was collected by self-reported questionnaire. Cigarette smoking was categorized by never and ever. Smoking duration, smoking frequency, and smoking pack-year were classified respectively as never, < 30 years, and ≥ 30 years and never, < 10 cigarettes per day, and ≥ 10 cigarettes per day and never, < 10 pack-years, and ≥ 10 pack-years.

- Alcohol drinking, drinking duration, drinking frequency, and alcohol dose

Information of alcohol drinking related variables was collected by self-reported questionnaire. Alcohol drinking was categorized by never and ever. Drinking duration, drinking frequency, and alcohol dose were classified respectively as never, < 21 years, and ≥ 21 years and never, < 2 times per week, and ≥ 2 times per week and never, < 5 grams per week, 5-14 grams per week, and ≥ 15 grams per week.

6) Body mass index (BMI) and Regular exercise factors

- BMI

Information of BMI was calculated from height and weight which were collected by measurement at enrollment time: $BMI = \text{weight (kg)} / \text{height}^2 (\text{m}^2)$. It was categorized by < 18.5 kg/m², 18.5-22.9 kg/m², 23-24.9 kg/m², 25-29.9 kg/m², ≥ 30 kg/m².

- Regular exercise, exercise time, exercise frequency, and exercise duration

Information on regular exercise, such as working up a sweat and exercising regularly, was collected by the self-reported questionnaire. Regular exercise was categorized by never and ever. Exercise time, exercise frequency, and exercise duration were classified respectively as never, < 1 hour per time, 1-< 1.5 hours per

time, and ≥ 1.5 hours per time, and 0-2 times per week, 3-4 times per week, and ≥ 5 times per week and 0- < 2 hours per week and ≥ 2 hours per week.

7) Family history

- Family history of breast cancer, family history of ovarian cancer, and family history of breast cancer or ovarian cancer

Information of family history of breast cancer and ovarian cancer was collected by self-reported questionnaire. The information of family history was collected by questionnaire only for the family history of first degree relatives. They were categorized by no and yes.

8) Socioeconomic status

- Age

Information of family history of breast cancer and ovarian cancer were collected by self-reported questionnaire. It was categorized by 35-49 years, 50-64 years, and 65-79 years.

- Education

Information of education was collected by self-reported questionnaire. It was categorized by \leq middle school graduated, high school graduated, and college graduated.

- Income

Information of income was collected by self-reported questionnaire. It was categorized by < 2,000\$, 2,000-3,999\$, and $\geq 4,000$ \$. One dollar was approximately exchanged to 1,000 won which is the monetary unit of Korea.

9) Ovarian cancer

Ovarian cancer cases were defined as primary ovarian cancer diagnosed as invasive incident cases at the enrollment time which had histologically verified epithelial ovarian carcinoma and whose stages were I to III in our study.

B. Potential confounders

First, because age and enrollment year are basic and common factors that have various effects on disease development, we selected age and enrollment year as confounders and continuous variables. (Figure 4) Because the range of the enrollment years of the Ko-EVE and HEXA is a little different, we used enrollment year for the confounder as a classified form of two groups after restricting the enrollment year before 2007. (4) Second, we selected oral contraceptives use because estrogen related factors are a carcinogenic agent for ovarian cancer in humans according to the International Agency for Research on Cancer in 2019. We adjusted for oral contraceptives use as a categorical variable. (7) Third, a family history of breast cancer and ovarian cancer was selected because a family history is a significant factor for cancer risk. (15) Obesity is also one of the famous cancer related factors. (1) In addition, according to the result of analyzing the baseline characteristics, we choose education level, household income, and BMI as confounders.

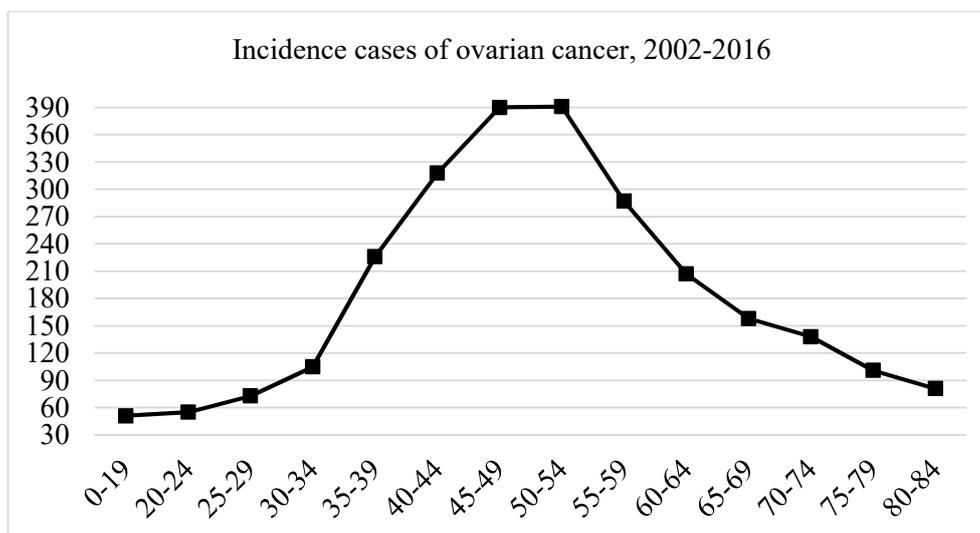


Figure 4. The number of incidence cases of ovarian cancer in Korea

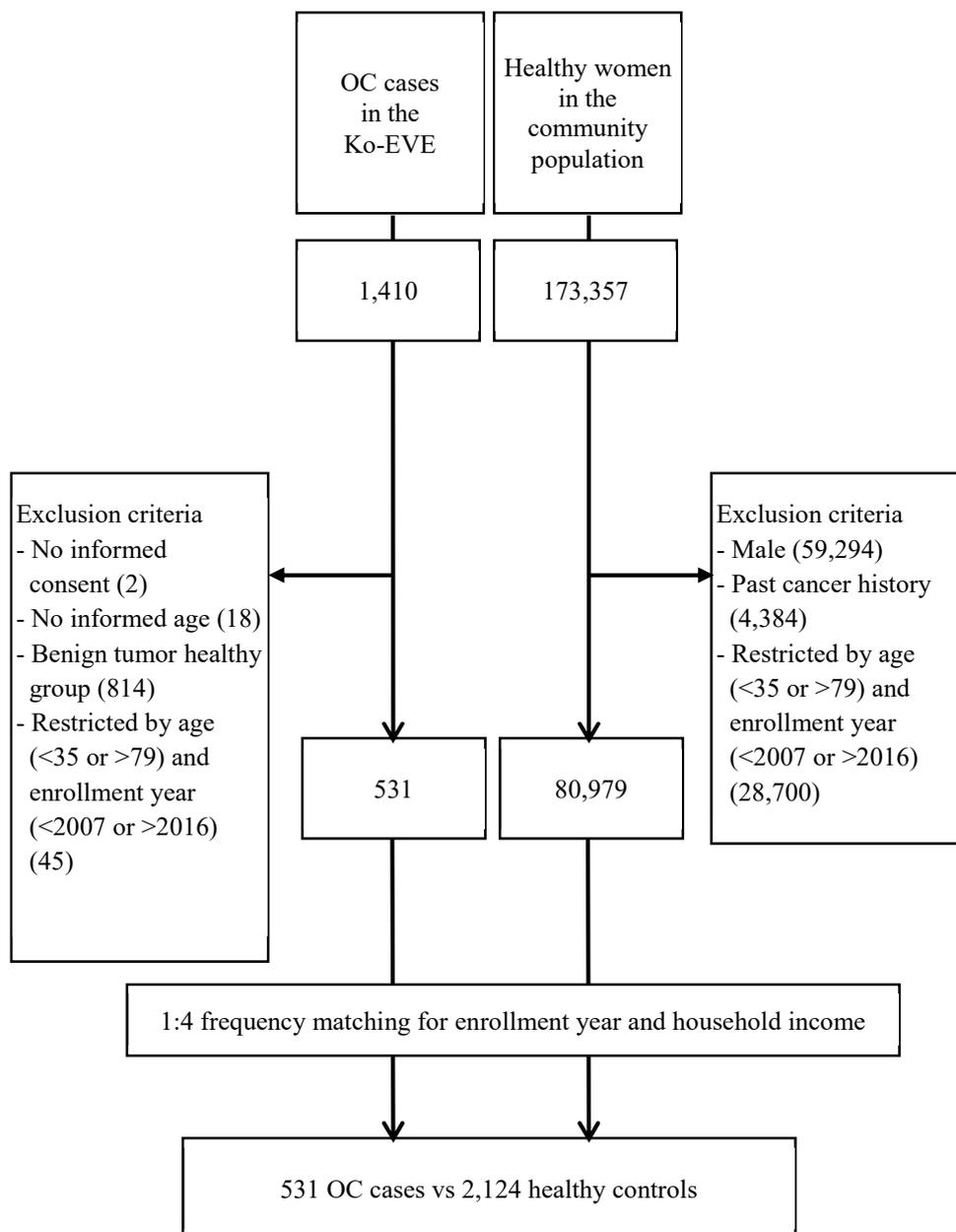


Figure 5. Flow chart of frequency matching

4. Statistical analysis

The baseline difference was compared between epithelial ovarian cancer cases and healthy controls using Chi-squared test for categorical variables and Student's t-test for continuous variables. The baseline characteristics that were compared were age at recruitment, enrollment year, height, weight, body mass index, age at menarche, age at menopause, breastfeeding duration, duration of oral contraceptives use, and duration of postmenopausal hormone replacement therapy as a continuous variable. Education level (\leq middle school graduated, high school graduated, and \geq college graduated), Household income ($< 2,000$ \$, $2,000-3,999$ \$, and $\geq 4,000$), marital status (married), cigarette smoking (cigarette smoker), alcohol drinking (alcohol drinker), regular exercise (ever exercised regularly), and history of hypertension (have past history of hypertension), diabetes mellitus (have past history of diabetes mellitus), and thyroid disease (have past history of thyroid disease) were compared as a categorical variable.

As the first step for minimizing the selection bias, we used 1:4 frequency matching for two variables: enrollment year as two groups (2007-2011/2012-2016) and household income ($< 1,000$ \$, $2,000-3,999$ \$, $3,000-4,999$ \$, and $\geq 5,000$).

To evaluate the association of various factors and ovarian cancer risk in the frequency matched study, the conditional logistic regression model was used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs).

Frequency matching, Chi-squared test, Student's t-test, Logistic regression, and Multivariate logistic regression were performed by using SAS 9.4.

III. Results

1. Characteristics of study

A. Characteristics of restricted data

The baseline characteristics of 531 ovarian cancer cases and 80,979 controls included in a total of 81,510 subjects are presented in Table 1. Between the case group and the control group, there was a statistically significant difference in their enrollment year group ($p < 0.01$). The mean of the enrollment year in the case group was 2012.4 while the mean of the same variable in the control group was 2009.3. Additionally, there was a significant difference between the case and the control for weight ($p = 0.03$) and body mass index (BMI) ($p < 0.01$). The mean weight in the case and control groups was 56.9 and 57.8 kg, respectively. In the case group, the mean BMI was 23.2 kg/m², and the mean BMI was 23.6 kg/m² in the control group. The duration of oral contraceptives (OC) use ($p < 0.01$), education level ($p < 0.01$), household income ($p < 0.01$), marital status ($p < 0.01$), alcohol drinking status ($p = 0.03$), and past history of hypertension ($p = 0.04$) also showed significant differences statistically between the two groups. The percentage of the below middle school graduates, high school graduates, and more than college graduates in the case group was respectively 26.7, 37.1, and 36.2%, and in the control group, it was respectively 37.1, 42.7, and 20.2%. The percentage of an income of under 2,000\$, 2,000-3,999\$, and 4,000\$ or more in the case group was respectively 20.9, 35.2, and 43.9%, and in the control group, it was respectively 34.8, 41.8, and 23.4%. Married woman in the case group consisted of 79.9% and in the control group 85.7%. Alcohol drinkers were 38.2% in the case group and 33.1% in the control group. Past history of hypertension was 21.2% in the cases and 17.7% in the controls. (Table 1)

Table 1. Selected characteristics of ovarian cancer cases and controls in the Korean Epithelial Ovarian Cancer Study (Ko-EVE), 2009-2016: Restricted data

	Ovarian cancer cases (N=531)	Controls (N=80,979)	p-value¹
	<u>Mean (SD)</u>	<u>Mean (SD)</u>	
Age (years)	53.4 (10.3)	52.7 (8.1)	0.12
Enrollment year	2012.4 (1.8)	2009.3 (1.7)	< 0.01
Height (cm)	156.7 (5.8)	156.4 (5.3)	0.30
Weight (kg)	56.9 (9.1)	57.8 (7.7)	0.03
Body mass index (kg/m ²)	23.2 (3.6)	23.6 (3.0)	< 0.01
Age at menarche (years)	15.1 (2.4)	15.2 (1.8)	0.45
Age at menopause (years) ²	49.1 (7.0)	49.3 (4.9)	0.56
	<u>Median (IQR)</u>	<u>Median (IQR)</u>	
Breastfeeding duration (months) ³	13.0 (2.0-25.0)	18.0 (6.0-30.0)	0.07
Duration of OC use (months) ⁴	5.0 (1.0-12.0)	8.0 (2.0-24.0)	< 0.01
Duration of HRT (months) ⁵	12.5 (3.0-48.0)	18.0 (5.0-48.0)	0.42
	<u>N (%)</u>	<u>N (%)</u>	
Education			< 0.01
≤ Middle school graduated	108 (26.7)	29,703 (37.1)	
High school graduated	150 (37.1)	34,218 (42.7)	
≥ College graduated	146 (36.2)	16,136 (20.2)	
Household income (\$)			< 0.01
< 2,000	111 (20.9)	26,112 (34.8)	
2,000 - 3,999	187 (35.2)	31,429 (41.8)	
≥ 4,000	233 (43.9)	17,551 (23.4)	
Married	333 (79.9)	69,151 (85.7)	< 0.01
Cigarette smoker ⁶	20 (5.0)	2,752 (3.4)	0.09
Alcohol drinker ⁷	156 (38.2)	26,730 (33.1)	0.03
Regular exercise ⁸	194 (47.1)	39,940 (49.5)	0.34
History of disease			
Hypertension	107 (21.2)	14,348 (17.7)	0.04
Diabetes mellitus	28 (5.5)	4,262 (5.3)	0.80
Thyroid disease	28 (5.5)	4,930 (6.1)	0.59

Abbreviations: OC, Oral contraceptives; HRT, Postmenopausal hormone replacement therapy

1. Student's t-test for continuous variables or chi-square test for categorical variables

2. Postmenopausal women

3. Parous women

4. Oral contraceptives ever users

5. Postmenopausal women having ever HRT use

6. Former or current smokers

7. Former or current drinkers

8. Regular exercise of sweat exercising

B. Characteristics of frequency matched data

The baseline characteristics of 531 ovarian cancer cases and frequency matched 2,124 controls included in a total of 2,655 subjects are presented in Table 2.

Between the case group and the control group, there was a statistically significant difference in their age and enrollment year group ($p < 0.01$). The mean age in the case group was 53.4 and that in the control group was 51.7. The mean of the enrollment year in the case group was 2012.4 while the mean of the same variable in the control group was 2011.1. The duration of OC use ($p < 0.01$), education level ($p < 0.01$), marital status ($p < 0.01$), and past history of hypertension ($p = 0.01$) also showed significant differences statistically between the two groups. The percentage of the below middle school graduates, high school graduates, and more than college graduates in the case group was respectively 26.7, 37.1, and 36.2%, and in the control group was respectively 25.1, 45.8, and 29.1%. Because household income was frequency matched, it has same distribution between case and control group. Married woman in the case group consisted of 79.9% and in the control group 92.0%. Alcohol drinker was 38.2% in the case group and 33.6% in the control group. Past history of hypertension was 21.2% in the cases and 15.5% in the controls. (Table 2)

Table 2. Selected characteristics of ovarian cancer cases and controls in the Korean Epithelial Ovarian Cancer Study (Ko-EVE), 2009-2016: Matched data

	Ovarian cancer cases (N=531)	Controls (N=2,124)	p-value¹
	<u>Mean (SD)</u>	<u>Mean (SD)</u>	
Age (years)	53.4 (10.3)	51.7 (7.7)	< 0.01
Enrollment year	2012.4 (1.8)	2011.1 (1.9)	< 0.01
Height (cm)	156.7 (5.8)	157.2 (5.4)	0.10
Weight (kg)	57.0 (9.1)	57.6 (8.0)	0.11
Body mass index (kg/m ²)	23.2 (3.6)	23.3 (3.0)	0.43
Age at menarche (years)	15.1 (2.4)	15.0 (1.8)	0.29
Age at menopause (years) ²	49.1 (7.0)	49.4 (4.8)	0.48
	<u>Median (IQR)</u>	<u>Median (IQR)</u>	
Breastfeeding duration (months) ³	13.0 (2.0-25.0)	13.0 (3.0-24.0)	0.11
Duration of OC use (months) ⁴	5.0 (1.0-12.0)	9.0 (2.0-12.0)	< 0.01
Duration of HRT (months) ⁵	12.5 (3.0-48.0)	18.0 (4.5-60.0)	0.65
	<u>N (%)</u>	<u>N (%)</u>	
Education			< 0.01
≤ Middle school graduated	108 (26.7)	530 (25.1)	
High school graduated	150 (37.1)	970 (45.8)	
≥ College graduated	146 (36.2)	616 (29.1)	
Household income (\$)			1.00
< 2,000	111 (20.9)	444 (20.9)	
2,000 - 3,999	187 (35.2)	748 (35.2)	
≥ 4,000	233 (43.9)	932 (43.9)	
Married	333 (79.9)	1,953 (92.0)	< 0.01
Cigarette smoker ⁶	20 (5.0)	67 (3.2)	0.07
Alcohol drinker ⁷	156 (38.2)	714 (33.6)	0.07
Regular exercise ⁸	194 (47.1)	1,088 (51.2)	0.12
History of disease			
Hypertension	107 (21.2)	329 (15.5)	< 0.01
Diabetes mellitus	28 (5.5)	104 (4.9)	0.57
Thyroid disease	28 (5.5)	111 (5.2)	0.79

Abbreviations: OC, Oral contraceptives; HRT, Postmenopausal hormone replacement therapy

1. Student's t-test for continuous variables or chi-square test for categorical variables

2. Postmenopausal women

3. Parous women

4. Oral contraceptives ever users

5. Postmenopausal women having ever HRT use

6. Former or current smokers

7. Former or current drinkers

8. Regular exercise of sweat exercising

2. Association between various factors and ovarian cancer

A. Menstrual factors

It indicates that age at menarche have a statistically significant association with ovarian cancer. Increased ovarian cancer risk was observed in the group of ≤ 13 years compared to the group of ≥ 16 years in both of the restricted (OR=1.51, 95% CI=1.11-2.05) and frequency matched design (OR=1.48, 95% CI=1.05-2.09). (Table 3)

Table 3. Ovarian cancer risk according to menstrual factors in the Korean Epithelial Ovarian Cancer Study (Ko-EVE), 2009-2016: Restricted and matched data

	Cases (N=531) N (%)	Restricted		Frequency matched	
		Controls (N=80,979) N (%)	OR (95% CI) ¹	Controls (N=2,124) N (%)	OR (95% CI) ²
Age at menarche (years)					
≤ 13	108 (22.7)	13,646 (17.1)	1.51 (1.11-2.05)	412 (19.5)	1.48 (1.05-2.09)
14-15	198 (41.7)	34,748 (43.7)	0.90 (0.69-1.18)	985 (46.7)	0.98 (0.74-1.32)
≥ 16	169 (35.6)	31,210 (39.2)	1.00	712 (33.8)	1.00
Menopausal status					
Premenopause	185 (35.9)	30,398 (37.7)	1.20 (0.87-1.64)	904 (42.6)	1.11 (0.78-1.58)
Postmenopause	331 (64.1)	50,227 (62.3)	1.00	1,218 (57.4)	1.00
Age at menopause (years)					
Premenopause	185 (38.8)	30,398 (39.6)	1.07 (0.74-1.56)	904 (44.2)	0.97 (0.65-1.46)
< 49	87 (18.3)	15,644 (20.4)	1.00	373 (18.2)	1.00
49-51	96 (20.2)	14,690 (19.1)	1.10 (0.78-1.54)	381 (18.6)	0.96 (0.66-1.40)
≥ 52	108 (22.7)	16,086 (20.9)	0.94 (0.67-1.34)	388 (19.0)	0.91 (0.62-1.34)

Abbreviations: CI, Confidence interval; OR, Odds ratio.

The bold values indicate statistical significance at 95% confidence levels.

The italic values indicate marginal statistical significance at 95% confidence levels.

1. The OR (95% CI) was estimated in logistic regression adjusted to age, enrollment year group, household income, oral contraceptive use, family history of ovarian cancer, family history of breast cancer, education level, and BMI.

2. The OR (95% CI) was estimated in conditional logistic regression stratified by enrollment year group (2007-2011/2012-2016) and household income and adjusted to age, oral contraceptive use, family history of ovarian cancer, family history of breast cancer, education level, and BMI.

B. Parity and breastfeeding factors

Parous woman had decreased ovarian cancer risk compared to the nulliparous women in both of the restricted (OR=0.31, 95% CI=0.22-0.44) and frequency matched design (OR=0.24, 95% CI=0.16-0.37). Also, compared to the nulliparous participants, women whose number of parity is one have lower ovarian cancer risk (OR=0.37, 95% CI=0.24-0.57; OR=0.33, 95% CI=0.20-0.55) and whose number of parity is two or more have much lower risk (OR=0.26, 95% CI=0.19-0.38; OR=0.23, 95% CI=0.15-0.35) in both of the restricted and frequency matched design. (Table 4)

Table 4. Ovarian cancer risk according to parity and breastfeeding factors in the Korean Epithelial Ovarian Cancer Study (Ko-EVE), 2009-2016: Restricted and matched data

	Cases (N=531) N (%)	Restricted		Frequency matched	
		Controls (N=80,979) N (%)	OR (95% CI) ¹	Controls (N=2,124) N (%)	OR (95% CI) ²
Parity					
Never	56 (10.5)	2,891 (3.6)	1.00	68 (3.2)	1.00
Ever	475 (89.5)	78,088 (96.4)	0.31 (0.22-0.44)	2,056 (96.8)	0.24 (0.16-0.37)
Number of parity					
Nullipara	56 (11.2)	2,891 (3.6)	1.00	68 (3.3)	1.00
1	65 (12.9)	8,313 (10.5)	0.37 (0.24-0.57)	244 (11.7)	0.33 (0.20-0.55)
2+	381 (75.9)	68,275 (85.9)	0.26 (0.19-0.38)	1,771 (85.0)	0.23 (0.15-0.35)
Breastfeeding					
Nullipara	56 (10.5)	2,891 (3.6)	3.08 (2.03-4.66)	68 (3.2)	3.58 (2.19-5.85)
Never	71 (13.4)	11,122 (13.7)	1.00	349 (16.4)	1.00
Ever	404 (76.1)	66,966 (82.7)	0.94 (0.70-1.26)	1,707 (80.4)	0.83 (0.60-1.14)
Breastfeeding duration (months)					
Nullipara	56 (10.6)	2,891 (3.6)	3.08 (2.04-4.66)	68 (3.2)	3.58 (2.19-5.85)
Never	71 (13.4)	11,122 (13.7)	1.00	349 (16.4)	1.00
< 6	66 (12.4)	10,205 (12.6)	1.00 (0.68-1.45)	339 (16.0)	0.84 (0.55-1.27)
≥ 6	338 (63.6)	56,761 (70.1)	0.92 (0.68-1.25)	1,368 (64.4)	0.83 (0.59-1.15)

Abbreviations: CI, Confidence interval; OR, Odds ratio.

The bold values indicate statistical significance at 95% confidence levels.

The italic values indicate marginal statistical significance at 95% confidence levels.

1. The OR (95% CI) was estimated in logistic regression adjusted to age, enrollment year group, household income, oral contraceptive use, family history of ovarian cancer, family history of breast cancer, education level, and BMI.

2. The OR (95% CI) was estimated in conditional logistic regression stratified by enrollment year group (2007-2011/2012-2016) and household income and adjusted to age, oral contraceptive use, family history of ovarian cancer, family history of breast cancer, education level, and BMI.

C. Age of the childbirth and abortions

Parous woman whose age of the first childbirth is 24-26 years had lower ovarian cancer risk compared to whose age of the first childbirth is less than 24 years in both of restricted (OR=0.61, 95% CI=0.44-0.85) and frequency matched design (OR=0.68, 95% CI=0.48-0.98). Increased ovarian cancer risk was observed in the group of parous women whose age of the last childbirth is 36 years or more compared to the women whose age of the last childbirth is less than 29 years in both of restricted (OR=1.45, 95% CI=0.97-2.14) and frequency matched design (OR=1.68, 95% CI=1.07-2.64). Decreased ovarian cancer risk was observed in the women who ever had artificial abortion compared who never had in both of restricted (OR=0.72, 95% CI=0.54-0.97) and frequency matched design (OR=0.66, 95% CI=0.48-0.91). (Table 5)

Table 5. Ovarian cancer risk according to age of the childbirth and abortions in the Korean Epithelial Ovarian Cancer Study (Ko-EVE), 2009-2016: Restricted and matched data

	Cases (N=531) N (%)	Restricted		Frequency matched	
		Controls (N=80,979) N (%)	OR (95% CI) ²	Controls (N=2,124) N (%)	OR (95% CI) ³
Age of the first childbirth (years) ¹					
< 24	95 (24.9)	18,424 (24.2)	1.00	401 (20.0)	1.00
24-26	115 (30.2)	28,924 (38.0)	0.61 (0.44-0.85)	722 (35.9)	0.68 (0.48-0.98)
27-29	106 (27.8)	20,187 (26.5)	0.74 (0.53-1.04)	604 (30.1)	0.85 (0.58-1.24)
≥ 30	65 (17.1)	8,634 (11.3)	0.85 (0.57-1.26)	282 (14.0)	0.99 (0.64-1.53)
Age of the last childbirth (years) ¹					
< 29	140 (35.3)	26,157 (38.6)	1.00	658 (37.2)	1.00
29-31	122 (30.7)	22,851 (33.7)	0.93 (0.70-1.24)	622 (35.2)	0.95 (0.70-1.31)
32-35	83 (20.9)	13,612 (20.1)	0.99 (0.72-1.37)	363 (20.6)	1.09 (0.76-1.56)
≥ 36	52 (13.1)	5,155 (7.6)	1.45 (0.97-2.14)	124 (7.0)	1.68 (1.07-2.64)
Spontaneous abortion					
Never	209 (41.8)	30,726 (38.2)	1.00	849 (40.0)	1.00
Ever	291 (58.2)	49,783 (61.8)	1.03 (0.83-1.28)	1,273 (60.0)	1.02 (0.80-1.29)
Artificial abortion					
Never	414 (83.6)	63,987 (79.4)	1.00	1,666 (78.5)	1.00
Ever	81 (16.4)	16,555 (20.6)	0.72 (0.54-0.97)	456 (21.5)	0.66 (0.48-0.91)

Abbreviations: CI, Confidence interval; OR, Odds ratio.

The bold values indicate statistical significance at 95% confidence levels.

The italic values indicate marginal statistical significance at 95% confidence levels.

1. Among parous women

2. The OR (95% CI) was estimated in logistic regression adjusted to age, enrollment year group, household income, oral contraceptive use, family history of ovarian cancer, family history of breast cancer, education level, and BMI.

3. The OR (95% CI) was estimated in conditional logistic regression stratified by enrollment year group (2007-2011/2012-2016) and household income and adjusted to age, oral contraceptive use, family history of ovarian cancer, family history of breast cancer, education level, and BMI.

D. History of hormonal use and surgical history of female genital organs

Decreased ovarian cancer risk was observed in the never used oral contraceptives women compared to the ever used oral contraceptives women in both the restricted (OR=0.59, 95% CI=0.41-0.87) and frequency matched design (OR=0.61, 95% CI=0.40-0.93). Compared to the never used oral contraceptives women, a lower ovarian cancer risk was also observed in the group of women whose oral contraceptive use duration was 10 months or more (OR=0.48, 95% CI=0.26-0.89; OR=0.50, 95% CI=0.26-0.96). Additionally, HRT ever treated postmenopausal women had a lower ovarian cancer risk compared to the never treated women in both the restricted (OR=0.49, 95% CI=0.33-0.74) and frequency matched design (OR=0.51, 95% CI=0.32-0.80). Postmenopausal women whose duration of HRT treatment was over 12 months had a lower risk compared to never treated postmenopausal women in both the restricted (OR=0.42, 95% CI=0.23-0.77) and frequency matched design (OR=0.44, 95% CI=0.23-0.84). In addition, tubal ligation in ever operated women and hysterectomy in ever operated women had decreased ovarian cancer risk, respectively, compared to never operated in both the restricted (OR=0.17, 95% CI=0.10-0.30; OR=0.32, 95% CI=0.18-0.56) and frequency matched design (OR=0.17, 95% CI=0.10-0.31; OR=0.34, 95% CI=0.19-0.62). (Table 6)

Table 6. Ovarian cancer risk according to history of hormonal use and surgical history of female genital organs in the Korean Epithelial Ovarian Cancer Study (Ko-EVE), 2009-2016: Restricted and matched data

	Cases (N=531) N (%)	Restricted	Frequency matched		
		Controls (N=80,979) N (%)	OR (95% CI) ²	Controls (N=2,124) N (%)	OR (95% CI) ³
OC use					
Never	450 (90.2)	67,261 (83.6)	1.00	1,862 (87.8)	1.00
Ever	49 (9.8)	13,183 (16.4)	0.59 (0.41-0.87)⁴	258 (12.2)	0.61 (0.40-0.93)⁵
OC use duration (months)					
Never	450 (92.2)	67,261 (85.2)	1.00	1,862 (88.5)	1.00
< 10	21 (4.3)	5,941 (7.5)	0.60 (0.35-1.03) ⁴	122 (5.8)	0.59 (0.33-1.06) ⁵
≥ 10	17 (3.5)	5,745 (7.3)	0.48 (0.26-0.89)⁴	121 (5.7)	0.50 (0.26-0.96)⁵
HRT ¹					
Never	228 (86.4)	35,572 (74.7)	1.00	894 (77.2)	1.00
Ever	36 (13.6)	12,081 (25.3)	0.49 (0.33-0.74)	264 (22.8)	0.51 (0.32-0.80)
HRT duration (months) ¹					
Never	228 (86.7)	35,572 (75.7)	1.00	894 (77.8)	1.00
≤ 12	17 (6.5)	5,550 (11.8)	0.56 (0.33-0.98)	120 (10.4)	0.56 (0.30-1.04)
> 12	18 (6.8)	5,872 (42.5)	0.42 (0.23-0.77)	136 (11.8)	0.44 (0.23-0.84)
Tubal ligation					
Never	400 (96.4)	61,456 (76.4)	1.00	1,681 (79.3)	1.00
Ever	15 (3.6)	18,987 (23.6)	0.17 (0.10-0.30)	439 (20.7)	0.17 (0.10-0.31)
Hysterectomy					
Never	463 (95.9)	72,213 (89.6)	1.00	1,912 (90.2)	1.00
Ever	20 (4.1)	8,412 (10.4)	0.32 (0.18-0.56)	209 (9.8)	0.34 (0.19-0.62)
Oophorectomy					
Never	484 (95.7)	75,094 (93.3)	1.00	1,992 (93.9)	1.00
Ever	22 (4.3)	5,367 (6.7)	0.71 (0.44-1.15)	129 (6.1)	0.72 (0.42-1.23)

Abbreviations: OC, Oral contraceptives; HRT, Postmenopausal hormone replacement therapy; CI, Confidence interval; OR, Odds ratio.

The bold values indicate statistical significance at 95% confidence levels. The italic values indicate marginal statistical significance at 95% confidence levels.

1. Among postmenopausal women

2. The OR (95% CI) was estimated in logistic regression adjusted to age, enrollment year group, household income, oral contraceptive use, family history of ovarian cancer, family history of breast cancer, education level, and BMI. 3. The OR (95% CI) was estimated in conditional logistic regression stratified by enrollment year group (2007-2011/2012-2016) and household income and adjusted to age, oral contraceptive use, family history of ovarian cancer, family history of breast cancer, education level, and BMI. 4. The OR (95% CI) was estimated in logistic regression adjusted to age, enrollment year group, household income, family history of ovarian cancer, family history of breast cancer, education level, and BMI. 5. The OR (95% CI) was estimated in conditional logistic regression stratified by enrollment year group (2007-2011/2012-2016) and household income and adjusted to age, family history of ovarian cancer, family history of breast cancer, education level, and BMI.

E. Cigarette smoking and alcohol drinking factors

It indicates that cigarette smoking experience and alcohol drinking experience have a statistically significant association with ovarian cancer. Increased ovarian cancer risk was observed in the group of past cigarette smoker compared to the never cigarette smoker in both of the restricted (OR=3.69, 95% CI=2.04-6.67) and frequency matched design (OR=3.69, 95% CI=1.75-7.78). In addition, higher ovarian cancer risk was also shown in the group of women whose smoking pack-year is 10 months or more in both of the restricted (OR=2.49, 95% CI=1.20-5.15) and frequency matched design (OR=3.14, 95% CI=1.32-7.44). Compared to the never alcohol drunk women, higher ovarian cancer risk was shown in the past drunken group in both of the restricted (OR=10.41, 95% CI=7.46-14.53) and frequency matched design (OR=11.20, 95% CI=6.75-18.59). (Table 7)

Table 7. Ovarian cancer risk according to cigarette smoking and alcohol drinking factors in the Korean Epithelial Ovarian Cancer Study (Ko-EVE), 2009-2016:

Restricted and matched data

	Cases (N=531) N (%)	Restricted		Frequency matched	
		Controls (N=80,979) N (%)	OR (95% CI) ¹	Controls (N=2,124) N (%)	OR (95% CI) ²
Cigarette smoking					
Never	382 (95.0)	77,630 (96.6)	1.00	2,052 (96.8)	1.00
Past smoking	14 (3.5)	730 (0.9)	3.69 (2.04-6.67)	20 (1.0)	3.69 (1.75-7.78)
Current smoking	6 (1.5)	2,022 (2.5)	0.67 (0.29-1.54)	47 (2.2)	0.88 (0.37-2.11)
Smoking duration (years)					
Never	382 (95.0)	77,630 (96.6)	1.00	2,052 (96.8)	1.00
< 30	17 (4.2)	2,426 (3.0)	1.62 (0.97-2.73)	65 (3.1)	1.63 (0.92-2.91)
≥ 30	3 (0.8)	326 (0.4)	1.21 (0.34-4.30)	2 (0.1)	5.11 (0.70-37.11)
Smoking frequency (cigarettes/day)					
Never	382 (95.7)	77,630 (96.6)	1.00	2,052 (96.8)	1.00
< 10	8 (2.0)	1,224 (1.5)	1.44 (0.70-2.97)	31 (1.5)	1.58 (0.69-3.59)
≥ 10	9 (2.3)	1,476 (1.9)	1.40 (0.68-2.87)	36 (1.7)	1.51 (0.68-3.34)
Smoking pack-year (pack-years)					
Never	382 (95.7)	77,630 (96.7)	1.00	2,052 (96.8)	1.00
< 10	8 (2.0)	1,833 (2.3)	1.01 (0.49-2.08)	49 (2.3)	1.00 (0.45-2.19)
≥ 10	9 (2.3)	813 (1.0)	2.49 (1.20-5.15)	18 (0.9)	3.14 (1.32-7.44)
Alcohol drinking					
Never	252 (61.8)	53,944 (66.9)	1.00	1,409 (66.4)	1.00
Past drinking	56 (13.7)	1,451 (1.8)	10.41 (7.46-14.53)	28 (1.3)	11.20 (6.75-18.59)
Current drinking	100 (24.5)	25,279 (31.3)	0.84 (0.65-1.09)	686 (32.3)	0.87 (0.65-1.14)
Drinking duration (years)					
Never	252 (66.8)	53,944 (67.8)	1.00	1,409 (66.6)	1.00
< 21	83 (22.0)	17,775 (22.3)	1.14 (0.87-1.50)	485 (22.9)	1.08 (0.80-1.46)
≥ 21	42 (11.2)	7,891 (9.9)	1.05 (0.74-1.49)	221 (10.5)	1.12 (0.76-1.65)
Drinking frequency (times/week)					
Never	252 (66.3)	53,944 (66.9)	1.00	1,409 (66.4)	1.00
< 2	96 (25.3)	20,449 (25.3)	1.08 (0.84-1.39)	544 (25.6)	1.11 (0.83-1.47)
≥ 2	32 (8.4)	6,281 (7.8)	1.22 (0.83-1.80)	170 (8.0)	1.14 (0.73-1.77)
Alcohol dose (g/week)					
Never	252 (66.3)	53,944 (66.9)	1.00	1,409 (66.4)	1.00
< 5	79 (20.8)	16,734 (20.7)	1.08 (0.82-1.42)	432 (20.3)	1.12 (0.82-1.51)
5-14	18 (4.7)	3,786 (4.7)	1.13 (0.69-1.87)	113 (5.3)	1.13 (0.66-1.95)
≥ 15	31 (8.2)	6,210 (7.7)	1.19 (0.81-1.76)	169 (8.0)	1.10 (0.71-1.72)

Abbreviations: CI, Confidence interval; OR, Odds ratio.

The bold values indicate statistical significance at 95% confidence levels.

The italic values indicate marginal statistical significance at 95% confidence levels.

1. The OR (95% CI) was estimated in logistic regression adjusted to age, enrollment year group, household income, oral contraceptive use, family history of ovarian cancer, family history of breast cancer, education level, and BMI.
2. The OR (95% CI) was estimated in conditional logistic regression stratified by enrollment year group (2007-2011/2012-2016) and household income and adjusted to age, oral contraceptive use, family history of ovarian cancer, family history of breast cancer, education level, and BMI.

F. BMI and regular exercising factors

It indicates that BMI, regular exercise time, exercise frequency, and exercise duration have a statistically significant association with ovarian cancer. Increased ovarian cancer risk was observed in the group of women whose BMI was less than 18.5 kg/m² compared to the group whose BMI was 18.5 to 22.9 kg/m² in both the restricted (OR=2.01, 95% CI=1.26-3.22) and frequency matched design (OR=1.80, 95% CI=1.04-3.13). Decreased ovarian cancer risk was shown in women whose exercise time was 1 to 1.5 hours/time and 1.5 hours/time or longer compared to women whose exercise time was less than one hour/time in both the restricted (OR=0.77, 95% CI=0.60-1.00; OR=0.70, 95% CI=0.51-0.97) and frequency matched design (OR=0.74, 95% CI=0.55-0.98; OR=0.60, 95% CI=0.41-0.86). Compared to women whose exercise frequency was less than 2 times per week, a lower ovarian cancer risk was also observed in the group of women whose exercise frequency was 5 times/week or more in both the restricted (OR=0.44, 95% CI=0.31-0.62) and frequency matched design (OR=0.41, 95% CI=0.28-0.60). In addition, women who exercise regularly 2 hours per week or more had a decreased ovarian cancer risk compared to those who exercised regularly less than 2 hours/week in both the restricted (OR=0.51, 95% CI=0.40-0.65) and frequency matched design (OR=0.47, 95% CI=0.35-0.61). (Table 8)

Table 8. Ovarian cancer risk according to body mass index and regular exercising factors in the Korean Epithelial Ovarian Cancer Study (Ko-EVE), 2009-2016:

Restricted and matched data

	Cases (N=531) N (%)	Restricted		Frequency matched	
		Controls (N=80,979) N (%)	OR (95% CI) ²	Controls (N=2,124) N (%)	OR (95% CI) ³
BMI (kg/m²)					
< 18.5	32 (6.1)	1,718 (2.1)	2.01 (1.26-3.22)	63 (3.0)	1.80 (1.04-3.13)[†]
18.5-22.9	246 (46.4)	34,673 (42.9)	1.00	1,009 (47.6)	1.00
23-24.9	111 (20.9)	21,331 (26.4)	0.87 (0.66-1.13)	504 (23.7)	0.94 (0.70-1.28) [†]
25-29.9	125 (23.6)	20,804 (25.7)	1.11 (0.86-1.44)	485 (22.9)	1.20 (0.90-1.60) [†]
≥ 30	16 (3.0)	2,366 (2.9)	1.02 (0.54-1.92)	59 (2.8)	0.98 (0.48-2.02) [†]
Regular exercise¹					
No	218 (52.9)	40,821 (50.6)	1.00	1,036 (48.8)	1.00
Yes	194 (47.1)	39,940 (49.4)	0.88 (0.72-1.08)	1,088 (51.2)	0.86 (0.68-1.09)
Exercise time (hours/time)					
0 - < 1	280 (68.6)	49,617 (63.3)	1.00	1,237 (59.1)	1.00
1 - < 1.5	80 (19.6)	16,346 (20.9)	0.77 (0.60-1.00)	511 (24.4)	0.74 (0.55-0.98)
≥ 1.5	48 (11.8)	12,423 (15.8)	0.70 (0.51-0.97)	344 (16.5)	0.60 (0.41-0.86)
Exercise frequency (times/week)					
0 - 2	294 (72.6)	49,622 (63.0)	1.00	1,265 (60.3)	1.00
3-4	71 (17.5)	14,844 (18.9)	0.79 (0.60-1.03)	413 (19.7)	0.78 (0.58-1.06)
5+	40 (9.9)	14,296 (18.1)	0.44 (0.31-0.62)	420 (20.0)	0.41 (0.28-0.60)
Exercise duration (hours/week)					
0 - < 2	316 (78.0)	51,290 (65.5)	1.00	1,300 (62.1)	1.00
≥ 2	89 (22.0)	27,062 (34.5)	0.51 (0.40-0.65)	792 (37.9)	0.47 (0.35-0.61)

Abbreviations: BMI, Body mass index; CI, Confidence interval; OR, Odds ratio.

The bold values indicate statistical significance at 95% confidence levels.

The italic values indicate marginal statistical significance at 95% confidence levels.

1. Work up a sweat exercising

2. The OR (95% CI) was estimated in logistic regression adjusted to age, enrollment year group, household income, oral contraceptive use, family history of ovarian cancer, family history of breast cancer, education level, and BMI. 3. The OR (95% CI) was estimated in conditional logistic regression stratified by enrollment year group (2007-2011/2012-2016) and household income and adjusted to age, oral contraceptive use, family history of ovarian cancer, family history of breast cancer, education level, and BMI. 4. The OR (95% CI) was estimated in logistic regression adjusted to age, enrollment year group, oral contraceptive use, household income, family history of ovarian cancer, family history of breast cancer, and education level.

G. Family history

It indicates that family history of breast cancer, family history of ovarian cancer, and family history of breast cancer or ovarian cancer have a statistically significant association with ovarian cancer. The group who have family history of breast cancer had increased ovarian cancer risk compared to who do not have in both of the restricted (OR=5.00, 95% CI=3.53-7.08) and frequency matched design (OR=3.924, 95% CI=2.47-6.21). Women who have family history of ovarian cancer also were shown to have higher risk in both of the restricted (OR=23.77, 95% CI=13.26-42.61) and frequency matched design (OR=33.65, 95% CI=9.67-117.13). In addition, higher risk was observed in the group who have family history of breast cancer or ovarian cancer compared to who do not have in both of the restricted (OR=7.27, 95% CI=5.40-9.78) and frequency matched design (OR=6.50, 95% CI=4.38-9.65). (Table 9)

Table 9. Ovarian cancer risk according to family history in the Korean Epithelial Ovarian Cancer Study (Ko-EVE), 2009-2016: Restricted and matched data

	Cases (N=531) N (%)	Restricted		Frequency matched	
		Controls (N=80,979) N (%)	OR (95% CI) ¹	Controls (N=2,124) N (%)	OR (95% CI) ²
Family history of breast cancer					
No	353 (89.1)	79,427 (98.1)	1.00	2,070 (97.5)	1.00
Yes	43 (10.9)	1,552 (1.9)	5.00 (3.53-7.08)³	54 (2.5)	3.92 (2.47-6.21)⁶
Family history of ovarian cancer					
No	373 (94.2)	80,628 (99.8)	1.00	2,121 (99.9)	1.00
Yes	23 (5.8)	140 (0.2)	23.77 (13.26-42.61)⁴	3 (0.1)	33.65 (9.67-117.13)⁷
Family history of breast cancer or ovarian cancer					
No	339 (84.8)	79,088 (97.9)	1.00	2,067 (97.3)	1.00
Yes	61 (15.2)	1,680 (2.1)	7.27 (5.40-9.78)⁵	57 (2.7)	6.50 (4.38-9.65)⁸

Abbreviations: CI, Confidence interval; OR, Odds ratio.

The bold values indicate statistical significance at 95% confidence levels.

The italic values indicate marginal statistical significance at 95% confidence levels.

1. The OR (95% CI) was estimated in logistic regression adjusted to age, enrollment year group, household income, oral contraceptive use, family history of ovarian cancer, family history of breast cancer, education level, and BMI. 2. The OR (95% CI) was estimated in conditional logistic regression stratified by enrollment year group (2007-2011/2012-2016) and household income and adjusted to age, oral contraceptive use, family history of ovarian cancer, family history of breast cancer, education level, and BMI. 3. The OR (95% CI) was estimated in logistic regression adjusted to age, enrollment year group, household income, oral contraceptive use, family history of ovarian cancer, education level, and BMI. 4. The OR (95% CI) was estimated in logistic regression adjusted to age, enrollment year group, household income, oral contraceptive use, family history of breast cancer, education level, and BMI. 5. The OR (95% CI) was estimated in logistic regression adjusted to age, enrollment year group, household income, oral contraceptive use, education level, and BMI. 6. The OR (95% CI) was estimated in conditional logistic regression stratified by enrollment year group (2007-2011/2012-2016) and household income and adjusted to age, oral contraceptive use, family history of ovarian cancer, education level, and BMI. 7. The OR (95% CI) was estimated in conditional logistic regression stratified by enrollment year group (2007-2011/2012-2016) and household income and adjusted to age, oral contraceptive use, family history of breast cancer, education level, and BMI. 8. The OR (95% CI) was estimated in conditional logistic regression stratified by enrollment year group (2007-2011/2012-2016) and household income and adjusted to age, oral contraceptive use, education level, and BMI.

H. Socioeconomic status

It indicates that age, education, and household income have a statistically significant association with ovarian cancer. Participants whose age is 50 years to 64 years had decreased ovarian cancer risk compared to whose age is 35 years to 49 years in the frequency matched design (OR=0.76, 95% CI=0.58-0.99). On the other hand, Participants whose age is 65 years to 79 years had increased ovarian cancer risk compared to whose age is 35 years to 49 years in both of the restricted (OR=2.45, 95% CI=1.73-3.48) and frequency matched design (OR=2.17, 95% CI=1.43-3.30). Compared to the group who graduated middle school or less, the group who graduated more than a college were shown to have higher risk in frequency matched and the group who graduated high school in both of the restricted (OR=1.52, 95% CI=1.11-2.10) and frequency matched design (OR=1.48, 95% CI=1.03-2.13) were shown to have lower risk. In addition, higher ovarian cancer risk was observed in the group whose household income is 4,000 dollars or more in the restricted design (OR=2.39, 95% CI=1.74-3.29) compared to whose income is less than 2,000 dollars. (Table 10)

Table 10. Ovarian cancer risk according to socioeconomic status in the Korean Epithelial Ovarian Cancer Study (Ko-EVE), 2009-2016: Restricted and matched data

	Cases (N=531) N (%)	Restricted		Frequency matched	
		Controls (N=80,979) N (%)	OR (95% CI) ¹	Controls (N=2,124) N (%)	OR (95% CI) ²
Age (years)					
35-49	216 (40.7)	29,833 (36.8)	1.00	881 (41.5)	1.00
50-64	227 (42.7)	43,658 (53.9)	0.83 (0.65-1.05) ³	1,098 (51.7)	0.76 (0.58-0.99)⁶
65-79	88 (16.6)	7,488 (9.3)	2.45 (1.73-3.48)³	145 (6.8)	2.17 (1.43-3.30)⁶
Education (graduates)					
≤ Middle school	108 (26.7)	29,703 (37.1)	1.00	530 (25.1)	1.00
High school	150 (37.1)	34,218 (42.7)	0.85 (0.64-1.14) ⁴	970 (45.8)	0.91 (0.66-1.26) ⁷
≥ College	146 (36.2)	16,136 (20.2)	1.52 (1.11-2.10)⁴	616 (29.1)	1.48 (1.03-2.13)⁷
Household income (\$)					
< 2,000	111 (20.9)	26,112 (34.8)	1.00	328 (22.7)	NA*
2,000 – 3,999	187 (35.2)	31,429 (41.8)	1.25 (0.94-1.66) ⁵	524 (36.3)	NA
≥ 4,000	233 (43.9)	17,551 (23.4)	2.67 (1.98-3.60)⁵	592 (41.0)	NA

Abbreviations: CI, Confidence interval; OR, Odds ratio.

The bold values indicate statistical significance at 95% confidence levels.

The italic values indicate marginal statistical significance at 95% confidence levels

* Household income was a frequency matched variable.

1. The OR (95% CI) was estimated in logistic regression adjusted to age, enrollment year group, household income, oral contraceptive use, family history of ovarian cancer, family history of breast cancer, education level, and BMI. 2. The OR (95% CI) was estimated in conditional logistic regression stratified by enrollment year group (2007-2011/2012-2016) and household income and adjusted to age, oral contraceptive use, family history of ovarian cancer, family history of breast cancer, education level, and BMI. 3. The OR (95% CI) was estimated in logistic regression adjusted to enrollment year group, household income, oral contraceptive use, family history of ovarian cancer, family history of breast cancer, education level, and BMI. 4. The OR (95% CI) was estimated in logistic regression adjusted to age, enrollment year group, household income, oral contraceptive use, family history of ovarian cancer, family history of breast cancer, and BMI. 5. The OR (95% CI) was estimated in logistic regression adjusted to age, enrollment year group, oral contraceptive use, family history of ovarian cancer, family history of breast cancer, education level, and BMI. 6. The OR (95% CI) was estimated in conditional logistic regression stratified by enrollment year group (2007-2011/2012-2016) and household income and adjusted to oral contraceptive use, family history of ovarian cancer, family history of breast cancer, education level, and BMI. 7. The OR (95% CI) was estimated in conditional logistic regression stratified by enrollment year group (2007-2011/2012-2016) and household income and adjusted to age, oral contraceptive use, family history of ovarian cancer, family history of breast cancer, and BMI.

IV. Discussions

1. Summary of results

As a result of our study, early age at menarche (OR=1.48, 95% CI=1.05-2.09), late age of the last childbirth (OR=1.68, 95% CI=1.07-2.64), past cigarette smoking (OR=3.69, 95% CI=1.75-7.78), smoking pack-year \geq 10 pack-years (OR=3.14, 95% CI=1.32-7.44), past drinking (OR=11.20, 95% CI=6.75-18.59), BMI $<$ 18.5 Kg/m² (OR=1.80, 95% CI=1.04-3.13), family history of breast cancer (OR=3.92, 95% CI=2.47-6.21), and family history of ovarian cancer (OR=33.65, 95% CI=9.67-117.13) were shown as definite risk factors of epithelial ovarian cancer. (Table 11)

On the other hand, parity (OR=0.24, 95% CI=0.16-0.37), number of parity \geq 2 (OR=0.23, 95% CI=0.15-0.35), artificial abortion (OR=0.66, 95% CI=0.48-0.91), HRT (OR=0.51, 95% CI=0.32-0.80), tubal ligation (OR=0.17, 95% CI=0.10-0.31), OC use (OR=0.59, 95% CI=0.41-0.87), oral contraceptives (OC) use duration \geq 10 months (OR=0.59, 95% CI=0.41-0.87), hysterectomy (OR=0.34, 95% CI=0.19-0.62), regular exercise \geq 1.5 hour/time (OR=0.60, 95% CI=0.41-0.86), regular exercise \geq 5 times/week (OR=0.41, 95% CI=0.28-0.60), regular exercise \geq 2 hours/week (OR=0.47, 95% CI=0.35-0.61) were shown as protective factors definitely for epithelial ovarian cancer. In the case of postmenopausal hormone replacement therapy (HRT), it was shown as a protective factor (OR=0.51, 95% CI=0.32-0.80). However, it cannot be said it is a definite protective factor because the information on HRT was not clear. (Table 12)

Table 11. Summary of risk factors of ovarian cancer in Ko-EVE

Risk factors	Restricted	Frequency matched
	OR (95% CI)	OR (95% CI)
Early age at menarche	1.51 (1.11-2.05)	1.48 (1.05-2.09)
Late age of the last childbirth	1.49 (0.97-2.14)	1.68 (1.07-2.64)
Cigarette smoking	3.69 (2.04-6.67)	3.69 (1.75-7.78)
Smoking pack-year \geq 10 pack-years	2.49 (1.20-5.15)	3.14 (1.32-7.44)
Alcohol drinking	10.41 (7.46-14.53)	11.20 (6.75-18.59)
BMI $<$ 18.5 kg/m ²	2.01 (1.26-3.22)	1.80 (1.04-3.13)
Family history of breast cancer	5.00 (3.53-7.08)	3.92 (2.47-6.21)
Family history of ovarian cancer	23.77 (13.26-42.61)	33.65 (9.67-117.13)
Age \geq 65 years	2.45 (1.73-3.48)	2.17 (1.43-3.30)
Education \geq College graduates	1.52 (1.11-2.10)	1.48 (1.03-2.13)

Table 12. Summary of protective factors of ovarian cancer in Ko-EVE

Protective factors	Restricted	Frequency matched
	OR (95% CI)	OR (95% CI)
Parity	0.31 (0.22-0.44)	0.24 (0.16-0.37)
Number of parity \geq 2	0.26 (0.19-0.38)	0.23 (0.15-0.35)
Artificial abortion	0.72 (0.54-0.97)	0.66 (0.48-0.91)
OC use	0.59 (0.41-0.87)	0.61 (0.40-0.93)
OC use duration \geq 10 months	0.48 (0.26-0.89)	0.50 (0.26-0.96)
HRT	0.49 (0.33-0.74)	0.51 (0.32-0.80)
Tubal ligation	0.17 (0.10-0.30)	0.17 (0.10-0.31)
Hysterectomy	0.32 (0.18-0.56)	0.34 (0.19-0.62)
Regular exercise \geq 1.5 hours/time	0.70 (0.51-0.97)	0.60 (0.41-0.86)
Regular exercise \geq 5 times/week	0.44 (0.31-0.62)	0.41 (0.28-0.60)
Regular exercise \geq 2 hours/week	0.51 (0.40-0.65)	0.47 (0.35-0.61)

2. Limitations and strengths

The limitations of this study is that, first, there was a limitation on analyzing the association between hormonal treatments such as oral contraceptives and postmenopausal hormone replacement therapy. There can be information bias because the classification according to including the hormone of the hormonal treatments is not clear in Korea. In addition, there have been few women who have ever been treated with postmenopausal hormone replacement therapy in Korea. Female related hormones are importance factors in ovarian cancer. Thus, there could be limitations due to them.

Although there are some limitations, our study also has strengths. First, there are only a few studies analyzing the association between the various factors and ovarian cancer risk. Especially, an ovarian cancer risk profiling observational study has been never reported in Korea. Our hospital derived case data are accurate for the ovarian cancer subjects. In Asia including Korea, ovarian cancer risk has been increasing. Moreover, it has a very poor prognosis because it is usually detected only in the advanced stages. However, we can suggest a way to prevent and manage ovarian cancer in the population. Second, even though our control data originated from a different source as our case data, it has a large number of participants. Thus, it could be used in various ways such as matching without any limitation in the number of controls.

To improve the suitability of the model in our study, a more robust model is required. Our goal for the following study is to establish an optimized model for ovarian cancer like the Gail model for breast cancer. Moreover, we performed an

analysis of the relation between epithelial ovarian cancer and its risk factors considering the preliminary histological group: high-grade serous, low-grade serous, mucinous, endometrioid, and clear cell. The five types have different aspects in the correlation between risk factors and the disease. (1) We will try to verify the association in the strata of histological groups.

V. Conclusions

We suggest that parity, artificial abortion, OC use, tubal ligation, hysterectomy, and regular exercise may have a protective effect for ovarian cancer. Moreover, especially for parity, the duration of OC use and regular exercise, increase in the number of parity, longer duration of OC use, and more and longer hours of regular exercise have more preventive effects for ovarian cancer. We also propose that early age at menarche, late age of last childbirth, cigarette smoking, alcohol drinking, BMI <18.5 kg/m², and family history of breast cancer and ovarian cancer are risk factors for ovarian cancer. Especially for cigarette smoking, a smoking pack-year of 10 pack-years or more has a higher risk for ovarian cancer. In the case of postmenopausal replacement therapy, we have to investigate further to include hormones.

Supplementary Table 1. The distribution and the ORs (95% CIs) of menstrual factors between cases classified by histological subtype and controls in the Korean Epithelial Ovarian Cancer Study (Ko-EVE), 2009-2016: Restricted data

	Histological subtypes of ovarian cancer cases				
	Controls (N=80,979)	HGS (N=209)	Mucinous (N=30)	Endometrioid (N=28)	Clear cell (N=32)
	N (%)	N (%)	N (%)	N (%)	N (%)
Age at menarche (years)					
< 13	13,646 (17.1)	32 (16.6)	7 (28.0)	12 (42.8)	14 (43.8)
14-15	34,748 (43.7)	76 (39.4)	10 (40.0)	5 (17.9)	12 (37.5)
≥ 16	31,210 (39.2)	85 (44.0)	8 (32.0)	11 (39.3)	6 (18.7)
Menopausal status					
Premenopause	30,398 (37.7)	52 (25.0)	11 (36.7)	13 (46.4)	17 (53.1)
Postmenopause	50,227 (62.3)	156 (75.0)	19 (63.3)	15 (53.6)	15 (46.9)
Age at menopause (years)					
Premenopause	30,398 (39.6)	52 (26.4)	11 (40.8)	13 (48.2)	17 (53.1)
< 49	15,644 (20.4)	39 (19.8)	8 (29.6)	6 (22.2)	6 (16.8)
49-51	14,690 (19.1)	53 (26.9)	3 (11.1)	5 (18.5)	5 (15.6)
≥ 52	16,086 (20.9)	53 (26.9)	5 (18.5)	3 (11.1)	4 (12.5)

	HGS (N=209) OR (95% CI)	Mucinous (N=30) OR (95% CI)	Endometrioid (N=28) OR (95% CI)	Clear cell (N=32) OR (95% CI)
Age at menarche (years)				
< 13 ¹	0.85 (0.54-1.35)	3.40 (1.11-10.38)	1.43 (0.54-3.78)	3.15 (1.03-9.66)
14-15	0.74 (0.52-1.04)	1.53 (0.56-4.20)	0.33 (0.11-0.98)	1.10 (0.37-3.28)
≥ 16	1.00	1.00	1.00	1.00
< 13 ²	0.92 (0.54-1.55)	3.15 (0.94-10.52)	1.12 (0.41-3.06)	3.86 (1.12-13.30)
14-15	0.76 (0.51-1.14)	1.16 (0.38-3.57)	0.28 (0.09-0.88)	1.16 (0.34-3.97)
≥ 16	1.00	1.00	1.00	1.00
Menopausal status				
Premenopause ¹	0.97 (0.61-1.55)	5.82 (1.65-20.50)	1.26 (0.38-4.18)	1.27 (0.37-4.33)
Postmenopause	1.00	1.00	1.00	1.00
Premenopause ²	0.78 (0.45-1.36)	5.02 (1.23-20.47)	1.04 (0.30-3.67)	1.01 (0.27-3.82)
Postmenopause	1.00	1.00	1.00	1.00
Age at menopause (years)				
Premenopause ¹	0.85 (0.49-1.46)	5.17 (1.31-20.41)	1.15 (0.32-4.19)	1.07 (0.28-4.14)
< 49	1.00	1.00	1.00	1.00
49-51	1.36 (0.87-2.14)	0.41 (0.10-1.59)	0.80 (0.23-2.80)	0.88 (0.22-3.51)
≥ 52	1.18 (0.75-1.85)	0.41 (0.12-1.34)	0.41 (0.09-1.79)	0.93 (0.22-3.88)
Premenopause ²	0.85 (0.45-1.57)	3.16 (0.71-14.07)	0.80 (0.21-3.00)	0.79 (0.19-3.30)
< 49	1.00	1.00	1.00	1.00
49-51	1.22 (0.74-2.02)	0.31 (0.06-1.56)	0.75 (0.21-2.64)	0.80 (0.18-3.49)
≥ 52	0.80 (0.47-1.36)	0.40 (0.11-1.40)	0.43 (0.10-1.86)	0.83 (0.18-3.90)

Abbreviations: HGS, High grade serous; CI, Confidence interval; OR, Odds ratio.
 Low grade serous was not included in the analysis because its number was 7 which was too small to get the values.
 The bold values indicate statistical significance at 95% confidence levels.
 The italic values indicate marginal statistical significance at 95% confidence levels.
 1. The OR (95% CI) was estimated in logistic regression adjusted by age and enrollment year.
 2. The OR (95% CI) was estimated in logistic regression adjusted by age, enrollment year, breast cancer or ovarian cancer family history, and oral contraceptive use.
 † Estimated by performing Cochran-Mantel-Haenszel.

Supplementary Table 2. The distribution and the ORs (95% CIs) of parity and breastfeeding factors between cases classified by histological subtype and controls in the Korean Epithelial Ovarian Cancer Study (KOEVE), 2009-2016: Restricted data

	Controls (N=80,979) N (%)	Histological subtypes of ovarian cancer cases			
		HGS (N=209) N (%)	Mucinous (N=30) N (%)	Endometrioid (N=28) N (%)	Clear cell (N=32) N (%)
Parity					
Never	2,891 (3.6)	14 (6.7)	5 (16.7)	7 (25.0)	8 (25.0)
Ever	78,088 (96.4)	195(93.3)	25 (83.3)	21 (75.0)	24 (75.0)
Number of parity					
Nullipara	2,891 (3.6)	14 (6.8)	5 (16.7)	7 (25.0)	8 (25.0)
1	8,313 (10.5)	26 (12.6)	7 (23.3)	4 (14.3)	5 (15.6)
2+	68,275 (85.9)	166 (80.6)	18 (60.0)	17 (60.7)	19 (59.4)
Breastfeeding					
Nullipara	2,891 (3.6)	14 (6.7)	5 (16.7)	7 (25.0)	8 (25.0)
Never	11,122 (13.7)	28 (13.4)	7 (23.3)	4 (14.3)	6 (18.8)
Ever	66,966 (82.7)	167 (79.9)	18 (60.0)	17 (60.7)	18 (56.3)
Breastfeeding duration (months)					
Nullipara	2,891 (3.6)	14 (6.7)	5 (16.7)	7 (25.0)	8 (25.0)
Never	11,122 (13.7)	28 (13.4)	7 (23.3)	4 (14.3)	6 (18.8)
< 6	10,205 (12.6)	34 (16.3)	2 (6.7)	5 (17.8)	2 (6.2)
≥ 6	56,761 (70.1)	133 (63.6)	16 (53.3)	12 (42.9)	16 (50.0)

	HGS (N=209) OR (95% CI)	Mucinous (N=30) OR (95% CI)	Endometrioid (N=28) OR (95% CI)	Clear cell (N=32) OR (95% CI)
Parity				
Never ¹	1.00	1.00	1.00	1.00
Ever	0.44 (0.25-0.79)	0.19 (0.06-0.55)	0.14 (0.05-0.35)	0.21 (0.08-0.55)
Never ²	1.00	1.00	1.00	1.00
Ever	0.41 (0.21-0.80)	0.21 (0.06-0.72)	0.14 (0.05-0.37)	0.22 (0.07-0.66)
Number of parity				
Nullipara ¹	1.00	1.00	1.00	1.00
1	0.53 (0.27-1.06)	0.47 (0.13-1.64)	0.23 (0.07-0.83)	0.36 (0.10-1.24)
2+	0.43 (0.24-0.77)	0.14 (0.05-0.44)	0.12 (0.05-0.33)	0.18 (0.07-0.51)
Nullipara ²	1.00	1.00	1.00	1.00
1	0.61 (0.28-1.33)	0.59 (0.14-2.50)	0.24 (0.06-0.92)	0.44 (0.11-1.68)
2+	0.40 (0.20-0.78)	0.17 (0.04-0.61)	0.14 (0.05-0.38)	0.20 (0.06-0.64)
Breastfeeding				
Nullipara ¹	2.43 (1.23-4.81)	2.37 (0.68-8.20)	6.86 (1.85-25.45)	3.17 (0.96-10.44)
Never	1.00	1.00	1.00	1.00
Ever	1.10 (0.71-1.70)	0.33 (0.13-0.83)	0.91 (0.28-2.92)	0.56 (0.21-1.48)
Nullipara ²	2.24 (1.03-4.87)	2.49 (0.56-10.96)	5.64 (1.50-21.22)	2.52 (0.70-9.08)
Never	1.00	1.00	1.00	1.00
Ever	0.91 (0.55-1.50)	0.43 (0.14-1.29)	0.72 (0.22-2.31)	0.43 (0.16-1.22)
Breastfeeding duration (months)				
Nullipara ¹	2.46 (1.24-4.87)	2.37 (0.68-8.19)	6.94 (1.87-25.71)	3.14 (0.95-10.35)
Never	1.00	1.00	1.00	1.00
< 6	1.56 (0.90-2.69)	0.31 (0.06-1.57)	1.53 (0.38-6.17)	0.39 (0.08-1.97)
≥ 6	1.00 (0.63-1.57)	0.34 (0.13-0.87)	0.75 (0.22-2.54)	0.61 (0.22-1.65)
Nullipara ²	2.26 (1.04-4.91)	2.48 (0.56-10.93)	5.62 (1.49-21.16)	2.51 (0.70-9.08)
Never	1.00	1.00	1.00	1.00
< 6	1.50 (0.81-2.78)	0.35 (0.06-2.20)	1.50 (0.38-5.90)	0.41 (0.08-2.09)
≥ 6	0.79 (0.47-1.32)	0.45 (0.15-1.38)	0.54 (0.16-1.84)	0.44 (0.15-1.29)

Abbreviations: HGS, High grade serous; CI, Confidence interval; OR, Odds ratio.
 Low grade serous was not included in the analysis because its number was 7 which was too small to get the values.
 The bold values indicate statistical significance at 95% confidence levels.

The italic values indicate marginal statistical significance at 95% confidence levels.

1. The OR (95% CI) was estimated in logistic regression adjusted by age and enrollment year.

2. The OR (95% CI) was estimated in logistic regression adjusted by age, enrollment year, breast cancer or ovarian cancer family history, and oral contraceptive use.

† Estimated by performing Cochran-Mantel-Haenszel.

Supplementary Table 3. The distribution and the ORs (95% CIs) of age of the childbirth and abortions between cases classified by histological subtype and controls in the Korean Epithelial Ovarian Cancer Study (Ko-EVE), 2009-2016: Restricted data

	Controls (N=80,979) N (%)	Histological subtypes of ovarian cancer cases			
		HGS (N=209) N (%)	Mucinous (N=30) N (%)	Endometrioid (N=28) N (%)	Clear cell (N=32) N (%)
		N (%)	N (%)	N (%)	N (%)
Age of the first childbirth (years) ¹					
< 24	18,424 (24.2)	49 (27.2)	4 (18.2)	1 (5.0)	2 (8.7)
24-26	28,924 (38.0)	59 (32.8)	8 (36.4)	6 (30.0)	9 (39.1)
27-29	20,187 (26.5)	41 (22.8)	5 (22.7)	9 (45.0)	5 (21.8)
≥ 30	8,634 (11.3)	31 (17.2)	5 (22.7)	4 (20.0)	7 (30.4)
Age of the last childbirth (years) ¹					
< 29	26,157 (38.6)	71 (39.4)	10 (43.5)	6 (28.6)	6 (25.0)
29-31	22,851 (33.7)	47 (26.1)	8 (34.8)	8 (38.1)	6 (25.0)
32-35	13,612 (20.1)	37 (20.6)	3 (13.0)	7 (33.3)	8 (33.3)
≥ 36	5,155 (7.6)	25 (13.9)	2 (8.7)	0	4 (16.7)
Spontaneous abortion					
Never	30,726 (38.2)	71 (34.3)	15 (50.0)	16 (57.1)	18 (56.2)
Ever	49,783 (61.8)	136 (65.7)	15 (50.0)	12 (42.9)	14 (43.8)
Artificial abortion					
Never	63,987 (79.4)	176 (85.0)	24 (82.8)	25 (89.3)	30 (93.8)
Ever	16,555 (20.6)	31 (15.0)	5 (17.2)	3 (10.7)	2 (6.2)
		HGS (N=209) OR (95% CI)	Mucinous (N=30) OR (95% CI)	Endometrioid (N=28) OR (95% CI)	Clear cell (N=32) OR (95% CI)
Age of the first childbirth (years) ¹					
< 24 ²	1.00	1.00	1.00	1.00	1.00
24-26	0.81 (0.53-1.22)	1.64 (0.48-5.68)	4.76 (0.54-42.38)	3.33 (0.60-18.55)	
27-29	0.77 (0.49-1.22)	1.28 (0.32-5.14)	8.22 (0.95-71.06)	2.58 (0.41-16.04)	
≥ 30	1.36 (0.82-2.25)	3.76 (0.94-15.01)	6.29 (0.61-64.38)	3.59 (0.55-23.27)	
< 24 ³	1.00	1.00	1.00	1.00	1.00
24-26	0.71 (0.44-1.15)	1.05 (0.25-4.34)	5.01 (0.53-47.25)	3.28 (0.39-27.35)	
27-29	0.75 (0.45-1.27)	1.36 (0.30-6.12)	8.34 (0.91-76.80)	2.81 (0.31-25.68)	
≥ 30	1.05 (0.57-1.93)	4.47 (1.02-19.56)	5.69 (0.52-62.31)	4.08 (0.43-38.93)	
Age of the last childbirth (years) ¹					
< 29 ²	1.00	1.00	1.00	1.00	1.00
29-31	0.84 (0.57-1.25)	1.21 (0.46-3.15)	1.65 (0.55-4.91)	1.35 (0.41-4.40)	
32-35	1.13 (0.73-1.74)	0.61 (0.15-2.44)	1.76 (0.54-5.72)	2.29 (0.71-7.41)	
≥ 36	1.91 (1.15-3.19)	1.39 (0.30-6.51)	2.39 (0.46-12.43) [†]	2.23 (0.52-9.51)	
< 29 ³	1.00	1.00	1.00	1.00	1.00
29-31	0.79 (0.50-1.25)	1.40 (0.47-4.15)	1.24 (0.39-3.97)	1.43 (0.41-4.96)	
32-35	1.09 (0.66-1.79)	0.86 (0.19-3.81)	1.80 (0.55-5.89)	1.53 (0.39-5.96)	
≥ 36	1.43 (0.76-2.67)	1.15 (0.17-7.68)	1.14 (0.16-8.08) [†]	2.03 (0.43-9.69)	
Spontaneous abortion					
Never ²	1.00	1.00	1.00	1.00	1.00
Ever	1.30 (0.95-1.78)	0.67 (0.32-1.41)	0.78 (0.35-1.75)	0.48 (0.21-1.08)	
Never ³	1.00	1.00	1.00	1.00	1.00
Ever	1.35 (0.94-1.95)	0.48 (0.20-1.13)	0.73 (0.32-1.69)	0.38 (0.16-0.95)	
Artificial abortion					
Never ²	1.00	1.00	1.00	1.00	1.00
Ever	0.78 (0.51-1.18)	0.96 (0.35-2.63)	0.61 (0.18-2.05)	0.36 (0.09-1.54)	
Never ³	1.00	1.00	1.00	1.00	1.00
Ever	0.81 (0.50-1.32)	0.67 (0.19-2.30)	0.51 (0.14-1.96)	0.05 (0.01-1.16)	

Abbreviations: HGS, High grade serous; CI, Confidence interval; OR, Odds ratio.

The bold values indicate statistical significance at 95% confidence levels.

The italic values indicate marginal statistical significance at 95% confidence levels.

Low grade serous was not included in the analysis because its number was 7 which was too small to get the values.

1. Among parous women 2. The OR (95% CI) was estimated in logistic regression adjusted by age and enrollment.

3. The OR (95% CI) was estimated in logistic regression adjusted by age, enrollment year, breast cancer or ovarian cancer family history, and oral contraceptive use.

[†] Estimated by performing Cochran-Mantel-Haenszel.

Supplementary Table 4. The distribution and the ORs (95% CIs) of history of hormonal use and surgical history of female genital organs between cases classified by histological subtype and controls in the Korean Epithelial Ovarian Cancer Study (Ko-EVE), 2009-2016: Restricted data

	Controls (N=80,979) N (%)	Histological subtypes of ovarian cancer cases			
		HGS (N=209) N (%)	Mucinous (N=30) N (%)	Endometrioid (N=28) N (%)	Clear cell (N=32) N (%)
		N (%)	N (%)	N (%)	N (%)
Oral contraceptive use					
Never	67,261 (83.6)	185 (89.8)	27 (90.0)	24 (85.7)	28 (90.3)
Ever	13,183 (16.4)	21 (10.2)	3 (10.0)	4 (14.3)	3 (9.7)
Oral contraceptive use duration (months)					
Never	67,261 (85.2)	185 (93.0)	27 (90.0)	24 (85.6)	28 (90.3)
< 10	5,941 (7.5)	9 (4.5)	0	2 (7.2)	2 (6.5)
≥ 10	5,745 (7.3)	5 (2.5)	3 (10.0)	2 (7.2)	1 (3.2)
HRT¹					
Never	35,572 (74.7)	116 (85.3)	16 (88.9)	12 (85.7)	11 (84.6)
Ever	12,081 (25.3)	20 (14.7)	2 (11.1)	2 (14.3)	2 (15.4)
HRT duration (months)¹					
Never	35,572 (75.7)	116 (85.9)	16 (88.8)	12 (85.8)	11 (84.6)
≤ 12	5,550 (11.8)	8 (5.9)	1 (5.6)	1 (7.1)	1 (7.7)
> 12	5,872 (12.5)	11 (8.2)	1 (5.6)	1 (7.1)	1 (7.7)
Tubal ligation					
Never	61,456 (76.4)	163 (95.9)	23 (95.8)	21 (95.4)	28 (100.0)
Ever	18,987 (23.6)	7 (4.1)	1 (4.2)	1 (4.6)	0
Hysterectomy					
Never	72,213 (89.6)	197 (97.5)	25 (92.6)	24 (88.9)	31 (100.0)
Ever	8,412 (10.4)	5 (2.5)	2 (7.4)	3 (11.1)	0
Oophorectomy					
Never	75,094 (93.3)	204 (98.1)	29 (96.7)	27 (96.4)	27 (84.4)
Ever	5,367 (6.7)	4 (1.9)	1 (3.3)	1 (3.6)	5 (15.6)

Continued

Supplementary Table 4 *Continued*

	HGS (N=209)	Mucinous (N=30)	Endometrioid (N=28)	Clear cell (N=32)
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Oral contraceptive use				
Never ²	1.00	1.00	1.00	1.00
Ever	0.87 (0.54-1.41)	0.88 (0.26-2.96)	1.07 (0.32-3.55)	1.38 (0.41-4.70)
Never [†]	1.00	1.00	1.00	1.00
Ever	0.49 (0.25-0.95)	0.41 (0.08-2.17)	0.36 (0.07-1.85)	1.01 (0.23-4.38)
Oral contraceptive use duration (months)				
Never ²	1.00	1.00	1.00	1.00
< 10	0.72 (0.35-1.45)	-	1.04 (0.21-5.24)	1.66 (0.38-7.16)
≥ 10	0.44 (0.17-1.10)	1.86 (0.55-6.31)	1.13 (0.21-6.06)	1.05 (0.14-7.91)
Never [†]	1.00	1.00	1.00	1.00
< 10	0.40 (0.15-1.05)	-	0.31 (0.04-2.68)	0.98 (0.13-7.29)
≥ 10	0.39 (0.14-1.14)	1.28 (0.27-5.97)	0.44 (0.05-3.84)	1.07 (0.14-8.32)
HRT ¹				
Never ²	1.00	1.00	1.00	1.00
Ever	0.57 (0.35-0.93)	0.38 (0.09-1.65)	0.62 (0.14-2.81)	0.88 (0.18-4.34)
Never ³	1.00	1.00	1.00	1.00
Ever	0.59 (0.34-1.03)	0.52 (0.11-2.35)	0.60 (0.13-2.72)	1.10 (0.21-5.74)
HRT duration (months) ¹				
Never ²	1.00	1.00	1.00	1.00
≤ 12	0.51 (0.25-1.06)	0.41 (0.05-3.15)	0.66 (0.09-5.18)	1.04 (0.13-8.57)
> 12	0.61 (0.32-1.16)	0.36 (0.05-2.71)	0.60 (0.08-4.68)	0.79 (0.10-6.60)
Never ³	1.00	1.00	1.00	1.00
≤ 12	0.52 (0.23-1.16)	0.57 (0.07-4.49)	0.61 (0.08-4.80)	1.35 (0.16-11.74)
> 12	0.63 (0.30-1.33)	0.49 (0.06-3.78)	0.60 (0.08-4.72)	0.95 (0.11-8.41)
Tubal ligation				
Never ²	1.00	1.00	1.00	1.00
Ever	0.11 (0.05-0.26)	0.13 (0.02-1.01)	0.23 (0.03-1.80)	-
Never ³	1.00	1.00	1.00	1.00
Ever	0.13 (0.05-0.32)	0.17 (0.02-1.33)	0.27 (0.04-2.14)	-
Hysterectomy				
Never ²	1.00	1.00	1.00	1.00
Ever	0.23 (0.10-0.57)	0.33 (0.06-1.92)	1.35 (0.39-4.62)	-
Never ³	1.00	1.00	1.00	1.00
Ever	0.24 (0.09-0.65)	0.32 (0.04-2.43)	1.49 (0.43-5.17)	-
Oophorectomy				
Never ²	1.00	1.00	1.00	1.00
Ever	0.27 (0.10-0.74)	0.47 (0.06-3.47)	0.64 (0.09-4.79)	3.29 (1.16-9.28)
Never ³	1.00	1.00	1.00	1.00
Ever	0.31 (0.11-0.89)	0.63 (0.08-4.75)	0.70 (0.09-5.26)	2.57 (0.80-8.28)

Abbreviations: HGS, High grade serous; HRT, Postmenopausal hormone replacement therapy; CI, Confidence interval; OR, Odds ratio.

The bold values indicate statistical significance at 95% confidence levels.

The italic values indicate marginal statistical significance at 95% confidence levels.

Low grade serous was not included in the analysis because its number was 7 which was too small to get the values.

1. Among postmenopausal women

2. The OR (95% CI) was estimated in logistic regression adjusted by age and enrollment year.

3. The OR (95% CI) was estimated in logistic regression adjusted by age, enrollment year, breast cancer or ovarian cancer family history, and oral contraceptive use.

† The OR (95% CI) was estimated in logistic regression adjusted by age, enrollment year, and breast cancer or ovarian cancer family history.

‡ Estimated by performing Cochran-Mantel-Haenszel.

Supplementary Table 5. The distribution and the ORs (95% CIs) of cigarette smoking and alcohol drinking factors between cases classified by histological subtype and controls in the Korean Epithelial Ovarian Cancer Study (Ko-EVE), 2009-2016: Restricted data

	Controls (N=80,979) N (%)	Histological subtypes of ovarian cancer cases			
		HGS (N=209) N (%)	Mucinous (N=30) N (%)	Endometrioid (N=28) N (%)	Clear cell (N=32) N (%)
Cigarette smoking					
Never	77,630 (96.6)	145 (94.2)	21 (91.2)	25 (100.0)	24 (96.0)
Past smoking	730 (0.9)	7 (4.5)	1 (4.4)	0	1 (4.0)
Current smoking	2,022 (2.5)	2 (1.3)	1 (4.4)	0	0
Smoking duration (years)					
Never	77,630 (96.6)	145 (94.2)	21 (91.2)	25 (100.0)	24 (96.0)
< 30	2,426 (3.0)	8 (5.2)	1 (4.4)	0	1 (4.0)
≥ 30	326 (0.4)	1 (0.6)	1 (4.4)	0	0
Smoking frequency (cigarette per day)¹					
Never	77,630 (96.6)	145 (94.8)	21 (95.4)	25 (100.0)	24 (96.0)
< 10	1,224 (1.5)	2 (1.3)	0	0	0
≥ 10	1,476 (1.8)	6 (3.9)	1 (4.6)	0	1 (4.0)
Smoking pack-year (pack-years)					
Never	77,630 (96.7)	145 (94.8)	21 (95.4)	25 (100.0)	24 (96.0)
< 10	1,833 (2.3)	2 (1.3)	0	0	0
≥ 10	813 (1.0)	6 (3.9)	1 (4.6)	0	1 (4.0)
Alcohol drinking					
Never	53,944 (66.9)	100 (64.9)	12 (50.0)	18 (72.0)	15 (55.6)
Past drinking	1,451 (1.8)	23 (15.0)	4 (16.7)	4 (16.0)	3 (11.1)
Current drinking	25,279 (31.3)	31 (20.1)	8 (33.3)	3 (12.0)	9 (33.3)
Drinking duration (year)					
Never	53,944 (67.8)	100 (69.9)	12 (52.2)	18 (78.3)	15 (60.0)
< 21	17,775 (22.3)	26 (18.2)	7 (30.4)	1 (4.3)	7 (28.0)
≥ 21	7,891 (9.9)	17 (11.9)	4 (17.4)	4 (17.4)	3 (12.0)
Drinking frequency (times/week)					
Never	53,944 (66.9)	100 (69.9)	12 (50.0)	18 (81.8)	15 (60.0)
< 2	20,449 (25.3)	30 (21.0)	11 (45.8)	3 (13.6)	8 (32.0)
≥ 2	6,281 (7.8)	13 (9.1)	1 (4.2)	1 (4.6)	2 (8.0)
Alcohol dose (g/week)					
Never	53,944 (66.9)	100 (69.9)	12 (50.0)	18 (81.8)	15 (60.0)
< 5	16,734 (20.7)	28 (19.6)	8 (33.3)	2 (9.2)	5 (20.0)
5-14	3,786 (4.7)	3 (2.1)	3 (12.5)	1 (4.5)	3 (12.0)
≥ 15	6,210 (7.7)	12 (8.4)	1 (4.2)	1 (4.5)	2 (8.0)

Continued

Supplementary Table 5 Continued

	HGS (N=209) OR (95% CI)	Mucinous (N=30) OR (95% CI)	Endometrioid (N=28) OR (95% CI)	Clear cell (N=32) OR (95% CI)
Cigarette smoking				
Never ¹	1.00	1.00	1.00	1.00
Past smoking	4.52 (1.89-10.81)	5.60 (0.73-43.00)	20.12 (6.56-61.78)[†]	0.19 (0.01-253.43)
Current smoking	0.80 (0.19-3.27)	0.69 (0.03-14.28)	10.44 (3.82-28.51)[†]	9.30 (3.24-26.65)[†]
Never ²	1.00	1.00	1.00	1.00
Past smoking	4.97 (2.01-12.26)	6.37 (0.82-49.25)	18.91 (5.70-62.72)[†]	0.20 (0.01-185.74)
Current smoking	0.72 (0.17-3.02)	0.75 (0.04-13.39)	8.09 (2.86-33.90)[†]	9.60 (3.15-29.19)[†]
Smoking duration (years)				
Never ¹	1.00	1.00	1.00	1.00
< 30	2.02 (1.02-4.74)	0.58 (0.03-10.93)	7.20 (2.56-20.27)[†]	6.90 (2.54-18.71)[†]
≥ 30	1.51 (0.19-12.29)	13.62 (1.67-111.30)	35.02 (7.39-165.96)[†]	75.22 (2.10-2698.42)[†]
Never ²	1.00	1.00	1.00	1.00
< 30	2.25 (1.03-4.88)	0.64 (0.04-10.60)	5.56 (1.81-17.11)[†]	6.86 (2.40-19.56)[†]
≥ 30	0.89 (0.07-10.78)	15.88 (1.93-130.68)	18.81 (3.22-109.96)[†]	67.44 (1.88-2419.85)[†]
Smoking frequency (cigarettes/day)				
Never ¹	1.00	1.00	1.00	1.00
< 10	1.09 (0.26-4.53)	18.12 (5.41-60.71)[†]	16.16 (5.84-44.71)[†]	13.25 (4.54-38.71)[†]
≥ 10	2.52 (1.03-6.20)	0.95 (0.05-18.71)	11.06 (3.89-3.43)[†]	0.21 (0.01-28.46)
Never ²	1.00	1.00	1.00	1.00
< 10	0.79 (0.19-3.30)	13.53 (2.38-76.80)[†]	6.84 (2.20-21.25)[†]	8.76 (3.03-25.34)[†]
≥ 10	4.43 (1.79-10.99)	1.08 (0.04-28.89)	16.41 (4.50-59.83)[†]	0.22 (0.01-134.68)
Smoking pack-year (pack-years)				
Never ¹	1.00	1.00	1.00	1.00
< 10	0.75 (0.18-3.09)	14.87 (4.50-49.10)[†]	10.00 (3.68-27.21)[†]	8.40 (2.94-23.97)[†]
≥ 10	4.31 (1.70-10.92)	1.52 (0.07-31.37)	20.82 (6.80-63.75)[†]	0.34 (0.01-72.42)
Never ²	1.00	1.00	1.00	1.00
< 10	1.19 (0.28-4.95)	17.13 (3.52-83.36)[†]	15.84 (5.11-49.09)[†]	12.93 (4.18-40.05)[†]
≥ 10	2.24 (0.87-5.79)	0.79 (0.03-18.32)	8.01 (2.71-23.72)[†]	0.16 (0.01-50.52)
Alcohol drinking				
Never ¹	1.00	1.00	1.00	1.00
Past drinking	13.88 (7.53-25.56)	25.24 (7.54-84.44)	5.81 (1.40-24.16)	10.28 (2.15-49.12)
Current drinking	0.83 (0.53-1.29)	1.60 (0.59-4.38)	0.32 (0.09-1.17)	1.29 (0.49-3.39)
Never ²	1.00	1.00	1.00	1.00
Past drinking	14.33 (7.69-26.70)	31.65 (9.15-109.48)	6.15 (1.52-24.88)	9.57 (2.00-45.93)
Current drinking	0.81 (0.52-1.28)	1.70 (0.60-4.81)	0.33 (0.09-1.19)	1.24 (0.47-3.27)
Drinking duration (years)				
Never ¹	1.00	1.00	1.00	1.00
< 21	0.89 (0.54-1.46)	2.46 (0.88-6.89)	0.12 (0.01-1.01)	1.09 (0.37-3.17)
≥ 21	1.35 (0.76-2.41)	2.77 (0.83-9.28)	1.53 (0.49-4.74)	1.62 (0.42-6.17)
Never ²	1.00	1.00	1.00	1.00
< 21	0.81 (0.48-1.36)	2.20 (0.75-6.50)	0.11 (0.01-0.98)	0.93 (0.30-2.90)
≥ 21	1.39 (0.77-2.49)	2.99 (0.86-10.35)	1.55 (0.50-4.81)	1.63 (0.41-6.47)
Drinking frequency (times/week)				
Never ¹	1.00	1.00	1.00	1.00
< 2	1.03 (0.65-1.64)	2.95 (1.19-7.29)	0.41 (0.11-1.52)	1.57 (0.55-4.44)
≥ 2	1.15 (0.59-2.22)	1.08 (0.14-8.63)	0.38 (0.05-2.94)	0.67 (0.11-4.24)
Never ²	1.00	1.00	1.00	1.00
< 2	1.05 (0.66-1.66)	3.17 (1.24-8.09)	0.43 (0.12-1.56)	1.52 (0.54-4.34)
≥ 2	1.09 (0.56-2.13)	1.22 (0.15-9.92)	0.38 (0.05-2.96)	0.69 (0.11-4.25)
Alcohol dose (g/week)				
Never ¹	1.00	1.00	1.00	1.00
< 5	1.24 (0.78-1.98)	2.91 (1.11-7.64)	0.33 (0.07-1.59)	1.75 (0.58-5.24)
5-14	0.36 (0.09-1.38)	3.02 (0.65-13.97)	0.72 (0.09-5.56)	1.02 (0.13-8.11)
≥ 15	1.11 (0.57-2.18)	1.10 (0.14-8.78)	0.38 (0.05-2.97)	0.67 (0.11-4.25)
Never ²	1.00	1.00	1.00	1.00
< 5	1.27 (0.79-2.03)	3.08 (1.13-8.40)	0.35 (0.07-1.65)	1.69 (0.56-5.10)
5-14	0.38 (0.10-1.41)	3.44 (0.75-15.85)	0.71 (0.09-5.46)	1.01 (0.13-8.07)
≥ 15	1.04 (0.52-2.07)	1.24 (0.15-10.09)	0.38 (0.05-2.98)	0.69 (0.11-4.27)

Abbreviations: HGS, High grade serous; CI, Confidence interval; OR, Odds ratio.

The bold values indicate statistical significance at 95% confidence levels.

The italic values indicate marginal statistical significance at 95% confidence levels.

Low grade serous was not included in the analysis because its number was 7 which was too small to get the values.

1. The OR (95% CI) was estimated in logistic regression adjusted by age and enrollment year.

2. The OR (95% CI) was estimated in logistic regression adjusted by age, enrollment year, breast cancer or ovarian cancer family history, and oral contraceptive use. † Estimated by performing Cochran-Mantel-Haenszel.

Supplementary Table 6. The distribution and the ORs (95% CIs) of BMI and regular exercise factors between cases classified by histological subtype and controls in the Korean Epithelial Ovarian Cancer Study (KOEVE), 2009-2016: Restricted data

	Histological subtypes of ovarian cancer cases				
	Controls (N=80,979)	HGS (N=209)	Mucinous (N=30)	Endometrioid (N=28)	Clear cell (N=32)
	N (%)	N (%)	N (%)	N (%)	N (%)
BMI (kg/m²)					
< 18.5	1,718 (2.1)	9 (4.3)	1 (3.3)	1 (3.6)	1 (3.1)
18.5-22.9	34,673 (48.9)	97 (46.4)	12 (40.0)	15 (53.6)	20 (62.6)
23-24.9	21,661 (26.4)	48 (23.0)	7 (23.3)	5 (17.8)	5 (15.6)
25-29.9	20,804 (25.7)	49 (23.4)	10 (33.4)	6 (21.4)	5 (15.6)
≥ 30	2,366 (2.9)	6 (2.9)	0	1 (3.6)	1 (3.1)
Regular exercise¹					
No	40,821 (50.6)	72 (46.4)	14 (58.3)	19 (76.0)	6 (22.2)
Yes	39,940 (49.4)	83 (53.6)	10 (41.7)	6 (24.20)	21 (77.8)
Exercise time (hours/time)					
0 - < 1	49,617 (63.3)	98 (63.6)	18 (75.0)	23 (92.0)	13 (48.2)
1 - < 1.5	16,346 (20.9)	36 (23.4)	4 (16.7)	1 (4.0)	9 (33.3)
≥ 1.5	12,423 (15.8)	20 (13.0)	2 (8.3)	1 (4.0)	5 (18.5)
Exercise frequency (times/week)					
0 - 2	49,622 (63.0)	114 (74.5)	20 (83.3)	23 (95.8)	16 (59.3)
3-4	14,844 (18.9)	27 (17.7)	3 (12.5)	0	9 (33.3)
5+	14,296 (18.1)	12 (7.8)	1 (4.2)	1 (4.2)	2 (7.4)
Exercise duration (hours/week)					
0 - < 2	51,290 (65.5)	119 (77.8)	21 (87.5)	24 (100.0)	19 (70.4)
≥ 2	27,062 (34.5)	34 (22.2)	3 (12.5)	0	8 (29.6)

	HGS (N=209)	Mucinous (N=30)	Endometrioid (N=28)	Clear cell (N=32)
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
BMI (kg/m²)				
< 18.5 ²	1.80 (0.89-3.66)	1.78 (0.23-14.06)	0.96 (0.12-7.91)	0.19 (0.01-5.03)
18.5-22.9	1.00	1.00	1.00	1.00
23-24.9	0.86 (0.59-1.25)	1.28 (0.48-3.40)	0.84 (0.30-2.40)	0.39 (0.12-1.30)
25-29.9	0.82 (0.56-1.20)	1.64 (0.67-3.98)	0.91 (0.33-2.50)	0.59 (0.21-1.66)
≥ 30	0.79 (0.32-1.97)	4.02(0.77-20.93) [†]	1.38 (0.18-10.67)	1.01 (0.13-7.68)
< 18.5 ³	2.11 (0.95-4.68)	2.74 (0.33-22.64)	1.15 (0.14-9.82)	0.14 (0.01-9.07)
18.5-22.9	1.00	1.00	1.00	1.00
23-24.9	0.83 (0.53-1.30)	1.14 (0.36-3.64)	0.87 (0.29-2.62)	0.43 (0.12-1.54)
25-29.9	0.89 (0.57-1.37)	2.02 (0.74-5.53)	1.11 (0.40-3.10)	0.66 (0.22-2.00)
≥ 30	0.68 (0.23-2.05)	1.46 (0.29-7.33) [†]	1.62 (0.21-12.78)	0.58 (0.04-7.59)
Regular exercise¹				
No ²	1.00	1.00	1.00	1.00
Yes	1.11 (0.78-1.58)	0.73 (0.31-1.73)	0.45 (0.17-1.16)	6.00 (1.81-19.89)
No ³	1.00	1.00	1.00	1.00
Yes	1.13 (0.79-1.61)	0.68 (0.28-1.65)	0.43 (0.17-1.12)	6.19 (1.87-20.53)
Exercise time (hours/time)				
0 - < 1 ²	1.00	1.00	1.00	1.00
1 - < 1.5	0.80 (0.52-1.24)	0.45 (0.14-1.46)	0.15 (0.02-1.09)	2.88 (1.09-7.61)
≥ 1.5	0.81 (0.48-1.37)	0.50 (0.11-2.16)	0.23 (0.03-1.71)	2.43 (0.77-7.72)
0 - < 1 ³	1.00	1.00	1.00	1.00
1 - < 1.5	0.85 (0.55-1.31)	0.50 (0.15-1.66)	0.15 (0.02-1.09)	3.18 (1.16-8.68)
≥ 1.5	0.81 (0.48-1.38)	0.48 (0.11-2.17)	0.23 (0.03-1.69)	2.63 (0.80-8.62)
Exercise frequency (times/week)				
0 - 2 ²	1.00	1.00	1.00	1.00
3-4	0.75 (0.47-1.21)	0.61 (0.18-2.08)	-	2.03 (0.78-5.28)
5+	0.36 (0.19-0.67)	0.16 (0.02-1.24)	0.18 (0.02-1.35)	0.70 (0.15-3.22)
0 - 2 ³	1.00	1.00	1.00	1.00
3-4	0.76 (0.47-1.22)	0.54 (0.15-1.93)	-	2.11 (0.81-5.50)
5+	0.37 (0.20-0.69)	0.10 (0.10-0.99)	0.18 (0.02-1.35)	0.71 (0.16-3.28)
Exercise duration (hours/week)				
0 - < 2 ²	1.00	1.00	1.00	1.00
≥ 2	0.48 (0.31-0.73)	0.27 (0.08-0.91)	-	1.01 (0.41-2.49)
0 - < 2 ³	1.00	1.00	1.00	1.00
≥ 2	0.50 (0.33-0.76)	0.21 (0.05-0.80)	-	1.05 (0.42-2.64)

Abbreviations: HGS, High grade serous; BMI, Body mass index; CI, Confidence interval; OR, Odds ratio.
The bold values indicate statistical significance at 95% confidence levels. The italic values indicate marginal statistical significance at 95% confidence levels. Low grade serous was not included in the analysis because its number was 7 which was too small to get the values. 1. Work up a sweat exercising.
2. The OR (95% CI) was estimated in logistic regression adjusted by age and enrollment year.
3. The OR (95% CI) was estimated in logistic regression adjusted by age, enrollment year, breast cancer or ovarian cancer family history, and oral contraceptive use. † Estimated by performing Cochran-Mantel-Haenszel.

Supplementary Table 7. The distribution and the ORs (95% CIs) of family history between cases classified by histological subtype and controls in the Korean Epithelial Ovarian Cancer Study (Ko-EVE), 2009-2016: Restricted data

	Controls (N=80,979) N (%)	Histological subtypes of ovarian cancer cases			
		HGS (N=209) N (%)	Mucinous (N=30) N (%)	Endometrioid (N=28) N (%)	Clear cell (N=32) N (%)
Family history of breast cancer					
No	79,427 (98.1)	133 (85.8)	20 (95.2)	23 (92.0)	27 (100.0)
Yes	1,552 (1.9)	22 (14.2)	1 (4.8)	2 (8.0)	0
Family history of ovarian cancer					
No	80,628 (99.8)	142 (91.6)	21 (95.4)	24 (96.0)	27 (100.0)
Yes	140 (0.2)	13 (8.4)	1 (4.6)	1 (4.0)	0
Family history of breast cancer or ovarian cancer					
No	79,088 (97.9)	124 (79.5)	20 (90.9)	22 (88.0)	27 (100.0)
Yes	1,680 (2.1)	32 (20.5)	2 (9.1)	3 (12.0)	0

	HGS (N=209) OR (95% CI)	Mucinous (N=30) OR (95% CI)	Endometrioid (N=28) OR (95% CI)	Clear cell (N=32) OR (95% CI)
Family history of breast cancer				
No ¹	1.00	1.00	1.00	1.00
Yes	5.92 (3.46-10.12)	2.22 (0.29-16.81)	2.26 (0.37-13.77)	-
No ²	1.00	1.00	1.00	1.00
Yes	5.90 (3.44-10.11)	0.93 (0.21-4.12)	2.25 (0.36-14.02)	-
Family history of ovarian cancer				
No ¹	1.00	1.00	1.00	1.00
Yes	35.13 (13.79-89.48)	21.25 (2.50-180.34)	24.23 (2.98-197.11)	-
No ²	1.00	1.00	1.00	1.00
Yes	34.65 (13.57-88.48)	21.19 (2.48-180.90)	24.42 (2.98-199.99)	-
Family history of breast cancer or ovarian cancer				
No ¹	1.00	1.00	1.00	1.00
Yes	7.98 (4.94-12.89)	3.99 (0.91-17.47)	4.01 (0.98-16.42)	-
No ²	1.00	1.00	1.00	1.00
Yes	8.04 (4.97-13.01)	4.04 (0.92-17.72)	4.03 (0.97-16.65)	-

Abbreviations: HGS, High grade serous; CI, Confidence interval; OR, Odds ratio.

The bold values indicate statistical significance at 95% confidence levels.

The italic values indicate marginal statistical significance at 95% confidence levels.

Low grade serous was not included in the analysis because its number was 7 which was too small to get the values.

1. The OR (95% CI) was estimated in logistic regression adjusted by age and enrollment year.

2. The OR (95% CI) was estimated in logistic regression adjusted by age, enrollment year, breast cancer or ovarian cancer family history, and oral contraceptive use.

† Estimated by performing Cochran-Mantel-Haenszel.

Supplementary Table 8. The distribution and the ORs (95% CIs) of socioeconomic status between cases classified by histological subtype and controls in the Korean Epithelial Ovarian Cancer Study (Ko-EVE), 2009-2016: Restricted data

	Controls (N=80,979) N (%)	Histological subtypes of ovarian cancer cases			
		HGS (N=209) N (%)	Mucinous (N=30) N (%)	Endometrioid (N=28) N (%)	Clear cell (N=32) N (%)
Age (years)					
35-49	29,833 (36.8)	63 (30.1)	6 (26.1)	4 (16.0)	4 (14.8)
50-64	43,658 (53.9)	105 (50.3)	7 (30.4)	7 (28.0)	9 (33.3)
65-79	7,488 (9.3)	41 (19.6)	10 (43.5)	14 (56.0)	14 (51.9)
Education (graduates)					
≤ Middle school	29,703 (37.1)	45 (29.6)	6 (26.1)	4 (16.0)	4 (14.8)
High school	34,218 (42.7)	61 (40.1)	7 (30.4)	7 (28.0)	9 (33.3)
≥ College	16,136 (20.2)	46 (30.3)	10 (43.5)	14 (56.0)	14 (51.9)
Household income (\$)					
< 2,000	26,112 (34.8)	45 (21.5)	8 (26.6)	8 (28.6)	4 (12.5)
2,000 – 3,999	31,429 (41.8)	79 (37.8)	11 (36.7)	8 (28.6)	12 (37.5)
≥ 4,000	17,551 (23.4)	85 (40.7)	11 (36.7)	12 (42.8)	16 (50.0)

	HGS (N=209) OR (95% CI)	Mucinous (N=30) OR (95% CI)	Endometrioid (N=28) OR (95% CI)	Clear cell (N=32) OR (95% CI)
Age (years)				
35-49 ¹	1.00	1.00	1.00	1.00
50-64	1.08 (0.59-2.00)	0.04 (0.01-0.30)	0.43 (0.08-2.28)	0.26 (0.05-1.35)
65-79	1.99 (0.69-5.73)	0.06 (0.01-1.21)	0.79 (0.04-15.20)	0.13 (0.01-3.45)
35-49 ²	1.00	1.00	1.00	1.00
50-64	0.91 (0.44-1.87)	0.12 (0.02-0.96)	0.45 (0.08-2.65)	0.30 (0.05-1.76)
65-79	1.54 (0.45-5.29)	0.26 (0.01-6.37)	0.86 (0.04-18.44)	0.08 (0.01-3.56)
Education (graduates)				
≤ Middle school ³	1.00	1.00	1.00	1.00
High school	1.15 (0.74-1.79)	0.93 (0.29-2.98)	0.94 (0.26-3.49)	0.92 (0.25-3.38)
≥ College	1.78 (1.07-2.97)	3.19 (1.02-10.01)	3.35 (0.91-12.30)	2.01 (0.51-7.87)
≤ Middle school ⁴	1.00	1.00	1.00	1.00
High school	1.04 (0.66-1.65)	0.70 (0.20-2.38)	0.89 (0.24-3.35)	0.85 (0.22-3.25)
≥ College	1.52 (0.89-2.60)	2.30 (0.69-7.73)	3.44 (0.93-12.75)	2.08 (0.51-8.45)
Household income (\$)				
< 2,000 ³	1.00	1.00	1.00	1.00
2,000 – 3,999	1.48 (0.91-2.41)	1.37 (0.51-3.66)	0.53 (0.19-1.49)	1.39 (0.41-4.64)
≥ 4,000	3.16 (1.90-5.27)	3.12 (1.12-8.69)	1.34 (0.48-3.71)	3.36 (1.02-11.03)
< 2,000 ⁴	1.00	1.00	1.00	1.00
2,000 – 3,999	1.49 (0.94-2.37)	1.27 (0.43-3.77)	0.59 (0.20-1.76)	1.11 (0.31-3.97)
≥ 4,000	3.22 (1.96-5.28)	2.69 (0.82-8.77)	1.57 (0.54-4.56)	3.15 (0.91-10.91)

Abbreviations: HGS, High grade serous; CI, Confidence interval; OR, Odds ratio.

The bold values indicate statistical significance at 95% confidence levels.

The italic values indicate marginal statistical significance at 95% confidence levels.

Low grade serous was not included in the analysis because its number was 7 which was too small to get the values.

1. The OR (95% CI) was estimated in logistic regression adjusted by enrollment year.

2. The OR (95% CI) was estimated in logistic regression adjusted by enrollment year, breast cancer or ovarian cancer family history, and oral contraceptive use.

3. The OR (95% CI) was estimated in logistic regression adjusted by age and enrollment year.

4. The OR (95% CI) was estimated in logistic regression adjusted by age, enrollment year, breast cancer or ovarian cancer family history, and oral contraceptive use.

Supplementary Table 9. The distribution and the ORs (95% CIs) of menstrual factors between cases classified by histological subtype and controls in the Korean Epithelial Ovarian Cancer Study (Ko-EVE), 2009-2016: Matched data

	Controls (N=2,124) N (%)	Histological subtypes of ovarian cancer cases			
		HGS (N=209) N (%)	Mucinous (N=30) N (%)	Endometrioid (N=28) N (%)	Clear cell (N=32) N (%)
Age at menarche (years)					
< 13	412 (19.5)	32 (16.6)	7 (28.0)	12 (42.8)	14 (43.8)
14-15	985 (46.7)	76 (39.4)	10 (40.0)	5 (17.9)	12 (37.5)
≥ 16	712 (33.8)	85 (44.0)	8 (32.0)	11 (39.3)	6 (18.7)
Menopausal status					
Premenopause	904 (42.6)	52 (25.0)	11 (36.7)	13 (46.4)	17 (53.1)
Postmenopause	1,218 (57.4)	156 (75.0)	19 (63.3)	15 (53.6)	15 (46.9)
Age at menopause (years)					
Premenopause	904 (44.2)	52 (26.4)	11 (40.8)	13 (48.2)	17 (53.1)
< 49	373 (18.2)	39 (19.8)	8 (29.6)	6 (22.2)	6 (16.8)
49-51	381 (18.6)	53 (26.9)	3 (11.1)	5 (18.5)	5 (15.6)
≥ 52	388 (19.0)	53 (26.9)	5 (18.5)	3 (11.1)	4 (12.5)

	HGS (N=209) OR (95% CI)	Mucinous (N=30) OR (95% CI)	Endometrioid (N=28) OR (95% CI)	Clear cell (N=32) OR (95% CI)
Age at menarche (years)				
< 13 ¹	0.84 (0.52-1.36)	3.00 (0.98-9.21)	1.45 (0.55-3.84)	3.09 (0.99-9.58)
14-15	0.74 (0.51-1.07)	1.50 (0.54-4.15)	0.31 (0.10-0.96)	1.01 (0.33-3.08)
≥ 16	1.00	1.00	1.00	1.00
< 13 ²	1.07 (0.60-1.90)	3.22 (0.96-10.86)	1.04 (0.36-2.97)	6.11 (1.53-24.42)
14-15	0.90 (0.57-1.41)	0.99 (0.29-3.35)	0.25 (0.07-0.83)	1.35 (0.32-5.62)
≥ 16	1.00	1.00	1.00	1.00
Menopausal status				
Premenopause ¹	0.66 (0.41-1.07)	6.13 (1.61-23.37)	1.17 (0.35-3.91)	1.20 (0.34-4.25)
Postmenopause	1.00	1.00	1.00	1.00
Premenopause ²	0.78 (0.43-1.41)	4.46 (0.94-21.21)	0.94 (0.26-3.38)	0.88 (0.21-3.68)
Postmenopause	1.00	1.00	1.00	1.00
Age at menopause (years)				
Premenopause ¹	0.75 (0.43-1.32)	5.04 (1.13-22.47)	0.92 (0.26-3.34)	0.92 (0.23-3.64)
< 49	1.00	1.00	1.00	1.00
49-51	1.25 (0.77-2.03)	0.37 (0.09-1.50)	0.71 (0.20-2.55)	0.75 (0.18-3.10)
≥ 52	1.09 (0.67-1.79)	0.36 (0.10-1.22)	0.37 (0.08-1.69)	0.85 (0.20-3.70)
Premenopause ²	0.85 (0.43-1.67)	2.87 (0.52-15.93)	0.66 (0.17-2.53)	0.67 (0.15-3.03)
< 49	1.00	1.00	1.00	1.00
49-51	1.15 (0.65-2.03)	0.32 (0.06-1.66)	0.66 (0.18-2.40)	0.75 (0.16-3.56)
≥ 52	0.66 (0.36-1.21)	0.35 (0.09-1.37)	0.40 (0.09-1.78)	0.70 (0.13-3.80)

Abbreviations: HGS, High grade serous; CI, Confidence interval; OR, Odds ratio.
 Low grade serous was not included in the analysis because its number was 7 which was too small to get the values.
 The bold values indicate statistical significance at 95% confidence levels.
 The italic values indicate marginal statistical significance at 95% confidence levels.
 1. The OR (95% CI) was estimated in logistic regression adjusted by age and enrollment year.
 2. The OR (95% CI) was estimated in logistic regression adjusted by age, enrollment year, breast cancer or ovarian cancer family history, and oral contraceptive use.
 † Estimated by performing Cochran-Mantel-Haenszel.

Supplementary Table 10. The distribution and the ORs (95% CIs) of parity and breastfeeding factors between cases classified by histological subtype and controls in the Korean Epithelial Ovarian Cancer Study (Ko-EVE), 2009-2016: Matched data

	Controls (N=2,124) N (%)	Histological subtypes of ovarian cancer cases			
		HGS (N=209) N (%)	Mucinous (N=30) N (%)	Endometrioid (N=28) N (%)	Clear cell (N=32) N (%)
Parity					
Never	68 (3.2)	14 (6.7)	5 (16.7)	7 (25.0)	8 (25.0)
Ever	2,056 (96.8)	195(93.3)	25 (83.3)	21 (75.0)	24 (75.0)
Number of parity					
Nullipara	68 (3.3)	14 (6.8)	5 (16.7)	7 (25.0)	8 (25.0)
1	244 (11.7)	26 (12.6)	7 (23.3)	4 (14.3)	5 (15.6)
2+	1,771 (85.0)	166 (80.6)	18 (60.0)	17 (60.7)	19 (59.4)
Breastfeeding					
Nullipara	68 (3.2)	14 (6.7)	5 (16.7)	7 (25.0)	8 (25.0)
Never	349 (16.4)	28 (13.4)	7 (23.3)	4 (14.3)	6 (18.8)
Ever	1,707 (80.4)	167 (79.9)	18 (60.0)	17 (60.7)	18 (56.3)
Breastfeeding duration (months)					
Nullipara	68 (3.2)	14 (6.7)	5 (16.7)	7 (25.0)	8 (25.0)
Never	349 (16.4)	28 (13.4)	7 (23.3)	4 (14.3)	6 (18.8)
< 6	339 (16.0)	34 (16.3)	2 (6.7)	5 (17.8)	2 (6.2)
≥ 6	1,368 (64.4)	133 (63.6)	16 (53.3)	12 (42.9)	16 (50.0)

	HGS (N=209) OR (95% CI)	Mucinous (N=30) OR (95% CI)	Endometrioid (N=28) OR (95% CI)	Clear cell (N=32) OR (95% CI)
Parity				
Never ¹	1.00	1.00	1.00	1.00
Ever	0.33 (0.17-0.63)	0.14 (0.05-0.46)	0.11 (0.04-0.29)	0.16 (0.06-0.47)
Never ²	1.00	1.00	1.00	1.00
Ever	0.27 (0.13-0.57)	0.14 (0.04-0.54)	0.12 (0.04-0.40)	0.17 (0.05-0.55)
Number of parity				
Nullipara ¹	1.00	1.00	1.00	1.00
1	0.42 (0.20-0.91)	0.40 (0.11-1.47)	0.18 (0.05-0.69)	0.28 (0.08-1.03)
2+	0.31 (0.16-0.60)	0.11 (0.03-0.36)	0.10 (0.03-0.27)	0.15 (0.05-0.43)
Nullipara ²	1.00	1.00	1.00	1.00
1	<i>0.43 (0.18-1.01)</i>	0.42 (0.10-1.86)	0.18 (0.04-0.80)	0.34 (0.08-1.40)
2+	0.25 (0.12-0.53)	0.10 (0.03-0.40)	0.11 (0.04-0.35)	0.14 (0.04-0.47)
Breastfeeding				
Nullipara ¹	3.40 (1.59-7.27)	3.26 (0.88-12.07)	8.71 (2.25-33.77)	3.96 (1.12-13.99)
Never	1.00	1.00	1.00	1.00
Ever	1.14 (0.72-1.80)	0.36 (0.14-0.92)	0.91 (0.29-2.92)	0.57 (0.21-1.52)
Nullipara ²	3.40 (1.43-8.08)	4.05 (0.83-19.75)	6.52 (1.59-26.67)	3.28 (0.83-12.96)
Never	1.00	1.00	1.00	1.00
Ever	0.90 (0.53-1.54)	0.49 (0.15-1.59)	0.73 (0.23-2.37)	0.44 (0.15-1.26)
Breastfeeding duration (months)				
Nullipara ¹	3.43 (1.60-7.35)	3.25 (0.88-12.03)	8.78 (2.26-34.05)	3.92 (1.11-13.85)
Never	1.00	1.00	1.00	1.00
< 6	1.47 (0.82-2.60)	0.33 (0.06-1.64)	1.40 (0.35-5.65)	0.35 (0.07-1.79)
≥ 6	1.06 (0.66-1.70)	0.37 (0.14-0.97)	0.78 (0.23-2.63)	0.64 (0.23-1.75)
Nullipara ²	3.45 (1.45-8.19)	3.94 (0.81-19.27)	6.63 (1.62-27.10)	3.27 (0.83-12.92)
Never	1.00	1.00	1.00	1.00
< 6	1.32 (0.68-2.56)	0.23 (0.02-2.26)	1.34 (0.34-5.37)	0.37 (0.07-1.94)
≥ 6	0.80 (0.46-1.39)	0.55 (0.17-1.82)	0.57 (0.16-1.97)	0.46 (0.15-1.38)

Abbreviations: HGS, High grade serous; CI, Confidence interval; OR, Odds ratio.
 Low grade serous was not included in the analysis because its number was 7 which was too small to get the values.
 The bold values indicate statistical significance at 95% confidence levels.
 The italic values indicate marginal statistical significance at 95% confidence levels.
 1. The OR (95% CI) was estimated in logistic regression adjusted by age and enrollment year.
 2. The OR (95% CI) was estimated in logistic regression adjusted by age, enrollment year, breast cancer or ovarian cancer family history, and oral contraceptive use.
 † Estimated by performing Cochran-Mantel-Haenszel.

Supplementary Table 11. The distribution and the ORs (95% CIs) of age of the childbirth and abortions between cases classified by histological subtype and controls in the Korean Epithelial Ovarian Cancer Study (Ko-EVE), 2009-2016: Matched data

	Controls (N=2,124) N (%)	Histological subtypes of ovarian cancer cases			
		HGS (N=209) N (%)	Mucinous (N=30) N (%)	Endometrioid (N=28) N (%)	Clear cell (N=32) N (%)
		N (%)	N (%)	N (%)	N (%)
Age of the first childbirth (years) ¹					
< 24	401 (20.0)	49 (27.2)	4 (18.2)	1 (5.0)	2 (8.7)
24-26	722 (35.9)	59 (32.8)	8 (36.4)	6 (30.0)	9 (39.1)
27-29	604 (30.1)	41 (22.8)	5 (22.7)	9 (45.0)	5 (21.8)
≥ 30	282 (14.0)	31 (17.2)	5 (22.7)	4 (20.0)	7 (30.4)
Age of the last childbirth (years) ¹					
< 29	658 (37.2)	71 (39.4)	10 (43.5)	6 (28.6)	6 (25.0)
29-31	622 (35.2)	47 (26.1)	8 (34.8)	8 (38.1)	6 (25.0)
32-35	363 (20.6)	37 (20.6)	3 (13.0)	7 (33.3)	8 (33.3)
≥ 36	124 (7.0)	25 (13.9)	2 (8.7)	0	4 (16.7)
Spontaneous abortion					
Never	849 (40.0)	71 (34.3)	15 (50.0)	16 (57.1)	18 (56.2)
Ever	1,273 (60.0)	136 (65.7)	15 (50.0)	12 (42.9)	14 (43.8)
Artificial abortion					
Never	1,666 (78.5)	176 (85.0)	24 (82.8)	25 (89.3)	30 (93.8)
Ever	456 (21.5)	31 (15.0)	5 (17.2)	3 (10.7)	2 (6.2)
		HGS (N=209) OR (95% CI)	Mucinous (N=30) OR (95% CI)	Endometrioid (N=28) OR (95% CI)	Clear cell (N=32) OR (95% CI)
Age of the first childbirth (years) ¹					
< 24 ²	1.00	1.00	1.00	1.00	1.00
24-26	0.71 (0.46-1.10)	1.36 (0.39-4.76)	4.10 (0.46-36.61)	2.85 (0.52-15.76)	
27-29	0.61 (0.38-1.00)	0.98 (0.24-3.93)	6.75 (0.78-58.34)	2.11 (0.34-13.302)	
≥ 30	1.11 (0.65-1.90)	2.97 (0.73-11.98)	5.53 (0.54-56.19)	2.95 (0.46-18.90)	
< 24 ³	1.00	1.00	1.00	1.00	1.00
24-26	0.63 (0.37-1.08)	0.94 (0.19-4.60)	4.17 (0.45-38.30)	2.88 (0.34-24.38)	
27-29	0.65 (0.37-1.14)	1.23 (0.25-5.98)	6.46 (0.72-57.86)	2.48 (0.27-22.88)	
≥ 30	0.87 (0.45-1.69)	4.38 (0.91-21.10)	4.29 (0.38-48.25)	3.66 (0.38-35.343)	
Age of the last childbirth (years) ¹					
< 29 ²	1.00	1.00	1.00	1.00	1.00
29-31	0.72 (0.47-1.10)	0.97 (0.37-2.57)	1.47 (0.49-4.38)	1.22 (0.37-4.02)	
32-35	1.10 (0.69-1.75)	0.58 (0.14-2.35)	1.82 (0.56-5.90)	2.43 (0.74-7.93)	
≥ 36	2.03 (1.15-3.59)	1.35 (0.28-6.56)	1.88 (0.24-14.51) [†]	2.21 (0.50-9.79)	
< 29 ³	1.00	1.00	1.00	1.00	1.00
29-31	0.76 (0.46-1.25)	1.27 (0.38-4.22)	1.04 (0.32-3.44)	1.34 (0.38-4.68)	
32-35	1.01 (0.58-1.76)	1.01 (0.22-4.70)	1.90 (0.59-6.15)	1.37 (0.32-5.88)	
≥ 36	1.25 (0.60-2.60)	1.01 (0.11-9.07)	0.98 (0.08-11.80) [†]	2.28 (0.46-11.37)	
Spontaneous abortion					
Never ²	1.00	1.00	1.00	1.00	1.00
Ever	1.28 (0.92-1.79)	0.69 (0.32-1.48)	0.78 (0.34-1.75)	0.46 (0.20-1.04)	
Never ³	1.00	1.00	1.00	1.00	1.00
Ever	1.43 (0.96-2.15)	0.48 (0.19-1.19)	0.87 (0.36-2.08)	0.34 (0.13-0.90)	
Artificial abortion					
Never ²	1.00	1.00	1.00	1.00	1.00
Ever	0.69 (0.45-1.07)	0.91 (0.33-2.47)	0.56 (0.16-1.88)	0.34 (0.08-1.44)	
Never ³	1.00	1.00	1.00	1.00	1.00
Ever	0.74 (0.44-1.23)	0.61 (0.16-2.31)	0.63 (0.18-2.16)	0.22 (0.03-1.64)	

Abbreviations: HGS, High grade serous; CI, Confidence interval; OR, Odds ratio.
The bold values indicate statistical significance at 95% confidence levels.
The italic values indicate marginal statistical significance at 95% confidence levels.
Low grade serous was not included in the analysis because its number was 7 which was too small to get the values.
1. Among parous women 2. The OR (95% CI) was estimated in logistic regression adjusted by age and enrollment.
3. The OR (95% CI) was estimated in logistic regression adjusted by age, enrollment year, breast cancer or ovarian cancer family history, and oral contraceptive use.
[†] Estimated by performing Cochran-Mantel-Haenszel.

Supplementary Table 12. The distribution and the ORs (95% CIs) of history of hormonal use and surgical history of female genital organs between cases classified by histological subtype and controls in the Korean Epithelial Ovarian Cancer Study (Ko-EVE), 2009-2016: Matched data

	Controls (N=2,124) N (%)	Histological subtypes of ovarian cancer cases			
		HGS (N=209) N (%)	Mucinous (N=30) N (%)	Endometrioid (N=28) N (%)	Clear cell (N=32) N (%)
		N (%)	N (%)	N (%)	N (%)
Oral contraceptive use					
Never	1,862 (87.8)	185 (89.8)	27 (90.0)	24 (85.7)	28 (90.3)
Ever	258 (12.2)	21 (10.2)	3 (10.0)	4 (14.3)	3 (9.7)
Oral contraceptive use duration (months)					
Never	1,862 (88.5)	185 (93.0)	27 (90.0)	24 (85.6)	28 (90.3)
< 10	122 (5.8)	9 (4.5)	0	2 (7.2)	2 (6.5)
≥ 10	121 (5.7)	5 (2.5)	3 (10.0)	2 (7.2)	1 (3.2)
HRT ¹					
Never	894 (77.2)	116 (85.3)	16 (88.9)	12 (85.7)	11 (84.6)
Ever	264 (22.8)	20 (14.7)	2 (11.1)	2 (14.3)	2 (15.4)
HRT duration (months) ¹					
Never	894 (77.8)	116 (85.9)	16 (88.8)	12 (85.8)	11 (84.6)
≤ 12	120 (10.4)	8 (5.9)	1 (5.6)	1 (7.1)	1 (7.7)
> 12	136 (11.8)	11 (8.2)	1 (5.6)	1 (7.1)	1 (7.7)
Tubal ligation					
Never	1,681 (79.3)	163 (95.9)	23 (95.8)	21 (95.4)	28 (100.0)
Ever	439 (20.7)	7 (4.1)	1 (4.2)	1 (4.6)	0
Hysterectomy					
Never	1,912 (90.2)	197 (97.5)	25 (92.6)	24 (88.9)	31 (100.0)
Ever	209 (9.8)	5 (2.5)	2 (7.4)	3 (11.1)	0
Oophorectomy					
Never	1,992 (93.9)	204 (98.1)	29 (96.7)	27 (96.4)	27 (84.4)
Ever	129 (6.1)	4 (1.9)	1 (3.3)	1 (3.6)	5 (15.6)

Continued

Supplementary Table 12 Continued

	HGS (N=209)	Mucinous (N=30)	Endometrioid (N=28)	Clear cell (N=32)
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Oral contraceptive use				
Never ²	1.00	1.00	1.00	1.00
Ever	1.00 (0.60-1.68)	1.12 (0.33-3.84)	1.22 (0.37-4.06)	1.48 (0.42-5.13)
Never [†]	1.00	1.00	1.00	1.00
Ever	0.69 (0.34-1.40)	1.03 (0.23-4.58)	0.49 (0.09-2.64)	1.86 (0.52-6.67)
Oral contraceptive use duration (months)				
Never ²	1.00	1.00	1.00	1.00
< 10	0.90 (0.42-1.93)	1.66 (0.33-8.44) [‡]	1.26 (0.25-6.47)	1.83 (0.40-8.24)
≥ 10	0.46 (0.17-1.22)	2.23 (0.64-7.73)	1.20 (0.23-6.22)	1.08 (0.14-8.30)
Never [†]	1.00	1.00	1.00	1.00
< 10	0.63 (0.23-1.76)	1.13 (0.14-9.25) [‡]	0.49 (0.05-5.04)	2.26 (0.48-10.56)
≥ 10	0.50 (0.16-1.54)	2.01 (0.44-9.14)	0.48 (0.05-4.96)	1.40 (0.18-11.00)
HRT ¹				
Never ²	1.00	1.00	1.00	1.00
Ever	0.60 (0.35-1.00)	0.31 (0.07-1.42)	0.59 (0.13-2.74)	0.81 (0.16-4.14)
Never ³	1.00	1.00	1.00	1.00
Ever	0.60 (0.32-1.12)	0.46 (0.09-2.27)	0.61 (0.13-2.90)	1.15 (0.23-5.85)
HRT duration (months) ¹				
Never ²	1.00	1.00	1.00	1.00
≤ 12	0.60 (0.29-1.27)	0.29 (0.04-2.34)	0.67 (0.08-5.36)	1.01 (0.12-8.68)
> 12	0.57 (0.29-1.13)	0.35 (0.04-2.68)	0.54 (0.07-4.29)	0.67 (0.08-5.93)
Never ³	1.00	1.00	1.00	1.00
≤ 12	0.63 (0.26-1.51)	0.43 (0.05-3.95)	0.70 (0.09-5.69)	1.33 (0.16-11.35)
> 12	0.55 (0.24-1.27)	0.49 (0.06-3.94)	0.56 (0.07-4.53)	1.02 (0.12-8.90)
Tubal ligation				
Never ²	1.00	1.00	1.00	1.00
Ever	0.11 (0.05-0.27)	0.17 (0.02-1.29)	0.25 (0.03-1.99)	1.19 (0.42-3.35) [‡]
Never ³	1.00	1.00	1.00	1.00
Ever	0.14 (0.05-0.39)	0.26 (0.03-2.19)	0.35 (0.04-2.84)	1.58 (0.53-4.71) [‡]
Hysterectomy				
Never ²	1.00	1.00	1.00	1.00
Ever	0.26 (0.10-0.64)	0.30 (0.05-1.99)	1.45 (0.42-5.04)	2.08 (0.60-7.24) [‡]
Never ³	1.00	1.00	1.00	1.00
Ever	0.23 (0.07-0.73)	0.34 (0.03-3.30)	1.74 (0.49-6.17)	1.63 (0.38-7.02) [‡]
Oophorectomy				
Never ²	1.00	1.00	1.00	1.00
Ever	0.31 (0.11-0.89)	0.57 (0.08-4.28)	0.74 (0.10-5.57)	3.45 (1.16-10.32)
Never ³	1.00	1.00	1.00	1.00
Ever	0.28 (0.08-0.97)	0.74 (0.09-5.84)	0.78 (0.10-6.11)	1.82 (0.43-7.68)

Abbreviations: HGS, High grade serous; HRT, Postmenopausal hormone replacement therapy; CI, Confidence interval; OR, Odds ratio.

The bold values indicate statistical significance at 95% confidence levels.

The italic values indicate marginal statistical significance at 95% confidence levels.

Low grade serous was not included in the analysis because its number was 7 which was too small to get the values.

1. Among postmenopausal women

2. The OR (95% CI) was estimated in logistic regression adjusted by age and enrollment year.

3. The OR (95% CI) was estimated in logistic regression adjusted by age, enrollment year, breast cancer or ovarian cancer family history, and oral contraceptive use.

† The OR (95% CI) was estimated in logistic regression adjusted by age, enrollment year, and breast cancer or ovarian cancer family history.

‡ Estimated by performing Cochran-Mantel-Haenszel.

Supplementary Table 13. The distribution and the ORs (95% CIs) of cigarette smoking and alcohol drinking factors between cases classified by histological subtype and controls in the Korean Epithelial Ovarian Cancer Study (Ko-EVE), 2009-2016: Matched data

	Controls (N=2,124) N (%)	Histological subtypes of ovarian cancer cases			
		HGS (N=209) N (%)	Mucinous (N=30) N (%)	Endometrioid (N=28) N (%)	Clear cell (N=32) N (%)
Cigarette smoking					
Never	2,052 (96.8)	145 (94.2)	21 (91.2)	25 (100.0)	24 (96.0)
Past smoking	20 (1.0)	7 (4.5)	1 (4.4)	0	1 (4.0)
Current smoking	47 (2.2)	2 (1.3)	1 (4.4)	0	0
Smoking duration (years)					
Never	2,052 (96.8)	145 (94.2)	21 (91.2)	25 (100.0)	24 (96.0)
< 30	65 (3.1)	8 (5.2)	1 (4.4)	0	1 (4.0)
≥ 30	2 (0.1)	1 (0.6)	1 (4.4)	0	0
Smoking frequency (cigarette per day) ¹					
Never	2,052 (96.8)	145 (94.8)	21 (95.4)	25 (100.0)	24 (96.0)
< 10	31 (1.5)	2 (1.3)	0	0	0
≥ 10	36 (1.7)	6 (3.9)	1 (4.6)	0	1 (4.0)
Smoking pack-year (pack-years)					
Never	2,052 (96.8)	145 (94.8)	21 (95.4)	25 (100.0)	24 (96.0)
< 10	49 (2.3)	2 (1.3)	0	0	0
≥ 10	18 (0.9)	6 (3.9)	1 (4.6)	0	1 (4.0)
Alcohol drinking					
Never	1,409 (66.4)	100 (64.9)	12 (50.0)	18 (72.0)	15 (55.6)
Past drinking	28 (1.3)	23 (15.0)	4 (16.7)	4 (16.0)	3 (11.1)
Current drinking	686 (32.3)	31 (20.1)	8 (33.3)	3 (12.0)	9 (33.3)
Drinking duration (year)					
Never	1,409 (66.6)	100 (69.9)	12 (52.2)	18 (78.3)	15 (60.0)
< 21	485 (22.9)	26 (18.2)	7 (30.4)	1 (4.3)	7 (28.0)
≥ 21	221 (10.5)	17 (11.9)	4 (17.4)	4 (17.4)	3 (12.0)
Drinking frequency (times/week)					
Never	1,409 (66.4)	100 (69.9)	12 (50.0)	18 (81.8)	15 (60.0)
< 2	544 (25.6)	30 (21.0)	11 (45.8)	3 (13.6)	8 (32.0)
≥ 2	170 (8.0)	13 (9.1)	1 (4.2)	1 (4.6)	2 (8.0)
Alcohol dose (g/week)					
Never	1,409 (66.4)	100 (69.9)	12 (50.0)	18 (81.8)	15 (60.0)
< 5	432 (20.3)	28 (19.6)	8 (33.3)	2 (9.2)	5 (20.0)
5-14	113 (5.3)	3 (2.1)	3 (12.5)	1 (4.5)	3 (12.0)
≥ 15	169 (8.0)	12 (8.4)	1 (4.2)	1 (4.5)	2 (8.0)

Continued

Supplementary Table 13 *Continued*

	HGS (N=209) OR (95% CI)	Mucinous (N=30) OR (95% CI)	Endometrioid (N=28) OR (95% CI)	Clear cell (N=32) OR (95% CI)
Cigarette smoking				
Never ¹	1.00	1.00	1.00	1.00
Past smoking	5.67 (1.96-16.38)	6.38 (0.75-54.58)	5.00 (0.82-30.33) [†]	0.30 (0.01-83.76)
Current smoking	1.08 (0.25-4.74)	1.07 (0.07-17.18)	5.09 (0.42-61.42) [†]	4.51 (0.76-26.90) [†]
Never²				
Past smoking	6.16 (2.11-18.01)	8.44 (0.95-75.02)	5.69 (0.71-45.46) [†]	0.31 (0.01-79.84)
Current smoking	0.94 (0.20-4.44)	1.11 (0.07-17.88)	1.52 (0.90-25.33) [†]	5.99 (0.77-46.36) [†]
Smoking duration (years)				
Never ¹	1.00	1.00	1.00	1.00
< 30	2.60 (1.12-6.03)	0.73 (0.05-11.15)	4.03 (0.83-19.69) [†]	0.17 (0.01-14.93)
≥ 30	5.70 (0.19-175.14)	45.0 (0.61-3296.87) [†]	-	-
Never²				
< 30	2.70 (1.15-6.39)	0.79 (0.05-12.50)	2.53 (0.39-16.34) [†]	0.17 (0.01-14.35)
≥ 30	2.32 (0.01-391.30)	33.00 (0.44-2470.58) [†]	-	-
Smoking frequency (cigarettes/day)				
Never ¹	1.00	1.00	1.00	1.00
< 10	1.36 (0.30-6.18)	4.11 (0.11-151.56) [†]	5.00 (0.82-30.33) [†]	3.50 (0.45-27.42) [†]
≥ 10	3.33 (1.18-9.37)	0.89 (0.04-21.72)	5.09 (0.42-61.42) [†]	0.25 (0.01-48.08)
Never²				
< 10	1.41 (0.31-6.41)	-	5.69 (0.71-45.46) [†]	4.74 (0.39-57.31) [†]
≥ 10	3.27 (1.08-9.93)	0.88 (0.04-21.96)	1.52 (0.09-25.33) [†]	0.27 (0.01-49.16)
Smoking pack-year (pack-years)				
Never ¹	1.00	1.00	1.00	1.00
< 10	0.81 (0.19-3.54)	4.11 (0.11-151.56) [†]	4.49 (0.91-22.19) [†]	2.72 (0.36-20.42) [†]
≥ 10	8.94 (2.66-30.13)	1.49 (0.04-61.17)	4/78 (0.13-175.43) [†]	6.08 (0.48-77.51) [†]
Never²				
< 10	0.74 (0.16-3.39)	-	2.53 (0.39-16.34) [†]	3.22 (0.29-36.17) [†]
≥ 10	9.59 (2.82-32.63)	1.81 (0.03-96.82)	-	5.74 (0.45-73.16) [†]
Alcohol drinking				
Never ¹	1.00	1.00	1.00	1.00
Past drinking	25.19 (11.08-57.27)	49.91 (12.14-205.24)	7.65 (1.64-35.74)	18.52 (3.08-111.24)
Current drinking	0.89 (0.56-1.41)	1.69 (0.62-4.65)	0.36 (0.10-1.30)	1.46 (0.55-3.84)
Never²				
Past drinking	21.92 (9.60-50.05)	80.74 (17.89-364.51)	6.94 (1.48-32.66)	17.03 (2.81-103.09)
Current drinking	0.85 (0.52-1.37)	2.31 (0.79-6.80)	0.37 (0.10-1.34)	1.44 (0.55-3.81)
Drinking duration (years)				
Never ¹	1.00	1.00	1.00	1.00
< 21	0.96 (0.57-1.62)	2.38 (0.84-6.79)	0.14 (0.02-1.18)	1.25 (0.42-3.72)
≥ 21	1.35 (0.73-2.49)	2.86 (0.83-9.80)	1.45 (0.46-4.61)	1.63 (0.40-6.67)
Never²				
< 21	0.90 (0.52-1.55)	3.20 (1.05-9.75)	0.15 (0.02-1.27)	1.26 (0.42-3.81)
≥ 21	1.34 (0.71-2.53)	3.76 (1.04-13.61)	1.44 (0.45-4.57)	1.69 (0.41-7.03)
Drinking frequency (times/week)				
Never ¹	1.00	1.00	1.00	1.00
< 2	1.15 (0.71-1.85)	3.11 (1.24-7.78)	0.47 (0.13-1.68)	2.33 (0.76-7.13)
≥ 2	1.25 (0.63-2.48)	1.04 (0.13-8.39)	0.41 (0.05-3.21)	0.26 (0.01-6.49)
Never²				
< 2	1.20 (0.74-1.97)	4.45 (1.66-11.95)	0.50 (0.14-1.80)	2.17 (0.72-6.53)
≥ 2	1.04 (0.50-2.15)	1.27 (0.15-10.75)	0.39 (0.05-3.09)	0.51 (0.05-5.36)
Alcohol dose (g/week)				
Never ¹	1.00	1.00	1.00	1.00
< 5	1.40 (0.85-2.28)	3.13 (0.18-8.32)	0.38 (0.08-1.78)	2.66 (0.82-8.61)
5-14	0.43 (0.12-1.56)	3.05 (0.66-14.08)	0.78 (0.10-6.06)	1.48 (0.18-12.21)
≥ 15	1.19 (0.59-2.40)	1.04 (0.13-8.39)	0.41 (0.05-3.21)	0.27 (0.01-6.30)
Never²				
< 5	1.48 (0.89-2.45)	4.50 (1.59-12.74)	0.42 (0.09-1.94)	2.45 (0.77-7.81)
5-14	0.46 (0.13-1.67)	4.29 (0.87-21.29)	0.78 (0.10-6.09)	1.38 (0.16-11.57)
≥ 15	0.96 (0.46-2.04)	1.27 (0.15-10.75)	0.39 (0.05-3.10)	0.52 (0.05-5.35)

Abbreviations: HGS, High grade serous; CI, Confidence interval; OR, Odds ratio.

The bold values indicate statistical significance at 95% confidence levels.

The italic values indicate marginal statistical significance at 95% confidence levels.

Low grade serous was not included in the analysis because its number was 7 which was too small to get the values.

1. The OR (95% CI) was estimated in logistic regression adjusted by age and enrollment year.

2. The OR (95% CI) was estimated in logistic regression adjusted by age, enrollment year, breast cancer or ovarian cancer family history, and oral contraceptive use.

† Estimated by performing Cochran-Mantel-Haenszel.

Supplementary Table 14. The distribution and the ORs (95% CIs) of BMI and regular exercise factors between cases classified by histological subtype and controls in the Korean Epithelial Ovarian Cancer Study (Ko-EVE), 2009-2016: Matched data

	Histological subtypes of ovarian cancer cases				
	Controls (N=2,124) N (%)	HGS (N=209) N (%)	Mucinous (N=30) N (%)	Endometrioid (N=28) N (%)	Clear cell (N=32) N (%)
BMI (kg/m ²)					
< 18.5	63 (3.0)	9 (4.3)	1 (3.3)	1 (3.6)	1 (3.1)
18.5-22.9	1,009 (47.6)	97 (46.4)	12 (40.0)	15 (53.6)	20 (62.6)
23-24.9	504 (23.7)	48 (23.0)	7 (23.3)	5 (17.8)	5 (15.6)
25-29.9	485 (22.9)	49 (23.4)	10 (33.4)	6 (21.4)	5 (15.6)
≥ 30	59 (2.8)	6 (2.9)	0	1 (3.6)	1 (3.1)
Regular exercise ¹					
No	1,036 (48.8)	72 (46.4)	14 (58.3)	19 (76.0)	6 (22.2)
Yes	1,088 (51.2)	83 (53.6)	10 (41.7)	6 (24.20)	21 (77.8)
Exercise time (hours/time)					
0 - < 1	1,237 (59.1)	98 (63.6)	18 (75.0)	23 (92.0)	13 (48.2)
1 - < 1.5	511 (24.4)	36 (23.4)	4 (16.7)	1 (4.0)	9 (33.3)
≥ 1.5	344 (16.5)	20 (13.0)	2 (8.3)	1 (4.0)	5 (18.5)
Exercise frequency (times/week)					
0 - 2	1,265 (60.3)	114 (74.5)	20 (83.3)	23 (95.8)	16 (59.3)
3-4	413 (19.7)	27 (17.7)	3 (12.5)	0	9 (33.3)
5+	420 (20.0)	12 (7.8)	1 (4.2)	1 (4.2)	2 (7.4)
Exercise duration (hours/week)					
0 - < 2	1,300 (62.1)	119 (77.8)	21 (87.5)	24 (100.0)	19 (70.4)
≥ 2	792 (37.9)	34 (22.2)	3 (12.5)	0	8 (29.6)
		HGS (N=209) OR (95% CI)	Mucinous (N=30) OR (95% CI)	Endometrioid (N=28) OR (95% CI)	Clear cell (N=32) OR (95% CI)
BMI (kg/m ²)					
< 18.5 ²	1.49 (0.69-3.21)	1.23 (0.15-10.00)	0.73 (0.09-6.12)	0.18 (0.01-3.68)	
18.5-22.9	1.00	1.00	1.00	1.00	
23-24.9	0.92 (0.62-1.37)	1.32 (0.49-3.56)	0.90 (0.31-2.58)	0.43 (0.13-1.44)	
25-29.9	0.81 (0.54-1.22)	1.48 (0.60-3.67)	0.90 (0.32-2.49)	0.57 (0.19-1.67)	
≥ 30	0.72 (0.27-1.93)	4.00 (0.77-20.93) [†]	1.37 (0.17-10.88)	1.04 (0.13-8.24)	
< 18.5 ³	1.47 (0.60-3.63)	1.66 (0.20-14.20)	0.81 (0.09-7.01)	0.13 (0.01-5.75)	
18.5-22.9	1.00	1.00	1.00	1.00	
23-24.9	0.96 (0.59-1.56)	1.06 (0.30-3.78)	0.81 (0.25-2.64)	0.51 (0.14-1.92)	
25-29.9	0.89 (0.55-1.44)	1.85 (0.65-5.25)	1.09 (0.38-3.11)	0.69 (0.22-2.19)	
≥ 30	0.70 (0.21-2.40)	4.95 (0.48-50.57) [†]	1.68 (0.21-13.65)	4.57 (1.06-19.77) [†]	
Regular exercise ¹					
No ²	1.00	1.00	1.00	1.00	
Yes	1.04 (0.72-1.50)	1.20 (0.42-3.40) [†]	0.46 (0.17-1.23) [†]	1.98 (0.78-5.03) [†]	
No ³	1.00	1.00	1.00	1.00	
Yes	1.03 (0.70-1.51)	1.15 (0.46-2.92)	0.40 (0.15-1.05)	5.98 (1.84-19.50)	
Exercise time (hours/time)					
0 - < 1 ²	1.00	1.00	1.00	1.00	
1 - < 1.5	0.75 (0.47-1.18)	0.45 (0.14-1.46)	0.14 (0.02-1.02)	2.96 (1.09-8.04)	
≥ 1.5	0.75 (0.43-1.32)	0.49 (0.11-2.18)	0.22 (0.03-1.69)	2.54 (0.76-8.43)	
0 - < 1 ³	1.00	1.00	1.00	1.00	
1 - < 1.5	0.76 (0.47-1.21)	0.47 (0.14-1.54)	0.13 (0.02-1.00)	3.03 (1.09-8.38)	
≥ 1.5	0.70 (0.39-1.25)	0.26 (0.03-1.98)	0.20 (0.03-1.56)	2.61 (0.76-8.93)	
Exercise frequency (times/week)					
0 - 2 ²	1.00	1.00	1.00	1.00	
3-4	0.69 (0.42-1.14)	0.57 (0.17-1.99)	0.94 (0.30-2.94) [†]	1.94 (0.73-5.19)	
5+	0.36 (0.19-0.69)	0.16 (0.02-1.25)	0.18 (0.02-1.34)	0.77 (0.16-3.58)	
0 - 2	1.00	1.00	1.00	1.00	
3-4	0.71 (0.43-1.18)	0.35 (0.08-1.56)	1.06 (0.29-3.91) [†]	1.96 (0.74-5.21)	
5+	0.36 (0.19-0.70)	0.39 (0.05-2.85) [†]	0.17 (0.02-1.32)	0.76 (0.16-3.58)	
Exercise duration (hours/week)					
0 - < 2 ²	1.00	1.00	1.00	1.00	
≥ 2	0.46 (0.29-0.71)	0.26 (0.08-0.90)	0.62 (0.22-1.75) [†]	1.04 (0.41-2.65)	
0 - < 2 ³	1.00	1.00	1.00	1.00	
≥ 2	0.47 (0.30-0.74)	0.09 (0.01-0.65)	0.72 (0.49-3.45) [†]	1.05 (0.41-2.71)	

Abbreviations: HGS, High grade serous; BMI, Body mass index; CI, Confidence interval; OR, Odds ratio.
 The bold values indicate statistical significance at 95% confidence levels. The italic values indicate marginal statistical significance at 95% confidence levels. Low grade serous was not included in the analysis because its number was 7 which was too small to get the values. 1. Work up a sweat exercising.
 2. The OR (95% CI) was estimated in logistic regression adjusted by age and enrollment year.
 3. The OR (95% CI) was estimated in logistic regression adjusted by age, enrollment year, breast cancer or ovarian cancer family history, and oral contraceptive use. † Estimated by performing Cochran-Mantel-Haenszel.

Supplementary Table 15. The distribution and the ORs (95% CIs) of family history between cases classified by histological subtype and controls in the Korean Epithelial Ovarian Cancer Study (Ko-EVE), 2009-2016: Matched data

	Controls (N=2,124) N (%)	Histological subtypes of ovarian cancer cases			
		HGS (N=209) N (%)	Mucinous (N=30) N (%)	Endometrioid (N=28) N (%)	Clear cell (N=32) N (%)
		N (%)	N (%)	N (%)	N (%)
Family history of breast cancer					
No	2,070 (97.5)	133 (85.8)	20 (95.2)	23 (92.0)	27 (100.0)
Yes	54 (2.5)	22 (14.2)	1 (4.8)	2 (8.0)	0
Family history of ovarian cancer					
No	2,121 (99.9)	142 (91.6)	21 (95.4)	24 (96.0)	27 (100.0)
Yes	3 (0.1)	13 (8.4)	1 (4.6)	1 (4.0)	0
Family history of breast cancer or ovarian cancer					
No	2,067 (97.3)	124 (79.5)	20 (90.9)	22 (88.0)	27 (100.0)
Yes	57 (2.7)	32 (20.5)	2 (9.1)	3 (12.0)	0

	HGS (N=209) OR (95% CI)	Mucinous (N=30) OR (95% CI)	Endometrioid (N=28) OR (95% CI)	Clear cell (N=32) OR (95% CI)
Family history of breast cancer				
No ¹	1.00	1.00	1.00	1.00
Yes	6.79 (3.55-13.01)	5.46 (0.59-50.58) [†]	5.06 (1.29-19.95)[†]	5.26 (0.90-30.61) [†]
No ²	1.00	1.00	1.00	1.00
Yes	7.01 (3.65-13.47)	0.33 (0.01-16.80) [†]	5.19 (1.31-20.64)[†]	5.53 (0.94-32.79) [†]
Family history of ovarian cancer				
No ¹	1.00	1.00	1.00	1.00
Yes	64.07 (10.81-379.84)	-	28.11 (2.21-356.90)	-
No ²	1.00	1.00	1.00	1.00
Yes	62.76 (10.54-373.77)	-	135.00 (1.92-9503.31)[†]	-
Family history of breast cancer or ovarian cancer				
No ¹	1.00	1.00	1.00	1.00
Yes	8.94 (4.95-16.15)	5.46 (0.59-50.58) [†]	6.96 (1.77-27.42)[†]	5.26 (0.90-30.61) [†]
No ²	1.00	1.00	1.00	1.00
Yes	9.14 (5.05-16.55)	0.33 (0.01-16.80) [†]	7.17 (1.80-28.49)[†]	5.53 (0.94-32.79) [†]

Abbreviations: HGS, High grade serous; CI, Confidence interval; OR, Odds ratio.

The bold values indicate statistical significance at 95% confidence levels.

The italic values indicate marginal statistical significance at 95% confidence levels.

Low grade serous was not included in the analysis because its number was 7 which was too small to get the values.

1. The OR (95% CI) was estimated in logistic regression adjusted by age and enrollment year.

2. The OR (95% CI) was estimated in logistic regression adjusted by age, enrollment year, breast cancer or ovarian cancer family history, and oral contraceptive use.

[†] Estimated by performing Cochran-Mantel-Haenszel.

Supplementary Table 16. The distribution and the ORs (95% CIs) of socioeconomic status between cases classified by histological subtype and controls in the Korean Epithelial Ovarian Cancer Study (Ko-EVE), 2009-2016: Matched data

	Controls (N=2,124) N (%)	Histological subtypes of ovarian cancer cases			
		HGS (N=209) N (%)	Mucinous (N=30) N (%)	Endometrioid (N=28) N (%)	Clear cell (N=32) N (%)
		N (%)	N (%)	N (%)	N (%)
Age (years)					
35-49	881 (41.5)	63 (30.1)	6 (26.1)	4 (16.0)	4 (14.8)
50-64	1,098 (51.7)	105 (50.3)	7 (30.4)	7 (28.0)	9 (33.3)
65-79	145 (6.8)	41 (19.6)	10 (43.5)	14 (56.0)	14 (51.9)
Education (graduates)					
≤ Middle school	530 (25.1)	45 (29.6)	6 (26.1)	4 (16.0)	4 (14.8)
High school	970 (45.8)	61 (40.1)	7 (30.4)	7 (28.0)	9 (33.3)
≥ College	616 (29.1)	46 (30.3)	10 (43.5)	14 (56.0)	14 (51.9)
Household income (\$)					
< 2,000	328 (22.7)	45 (21.5)	8 (26.6)	8 (28.6)	4 (12.5)
2,000 – 3,999	524 (36.3)	79 (37.8)	11 (36.7)	8 (28.6)	12 (37.5)
≥ 4,000	592 (41.0)	85 (40.7)	11 (36.7)	12 (42.8)	16 (50.0)

	HGS (N=209) OR (95% CI)	Mucinous (N=30) OR (95% CI)	Endometrioid (N=28) OR (95% CI)	Clear cell (N=32) OR (95% CI)
Age (years)				
35-49 ¹	1.00	1.00	1.00	1.00
50-64	1.37 (0.97-1.95)	0.48 (0.19-1.22)	0.53 (0.23-1.24)	0.40 (0.17-0.92)
65-79	3.74 (2.27-6.14)	5.08 (2.04-12.66)	1.40 (0.39-5.05)	0.35 (0.05-2.73)
35-49 ²	1.00	1.00	1.00	1.00
50-64	1.24 (0.81-1.90)	0.64 (0.22-1.85)	0.57 (0.23-1.41)	0.46 (0.19-1.15)
65-79	3.44 (1.90-6.22)	5.21 (1.71-15.88)	1.86 (0.50-6.93)	1.31 (0.28-6.22) [†]
Education (graduates)				
≤ Middle school ³	1.00	1.00	1.00	1.00
High school	0.89 (0.55-1.42)	0.62 (0.19-2.00)	0.74 (0.20-2.73)	0.76 (0.20-2.86)
≥ College	1.07 (0.62-1.84)	1.58 (0.51-4.96)	2.13 (0.59-7.70)	1.32 (0.33-5.19)
≤ Middle school ⁴	1.00	1.00	1.00	1.00
High school	0.90 (0.55-1.48)	0.52 (0.15-1.79)	0.78 (0.21-2.93)	0.84 (0.21-3.30)
≥ College	1.00 (0.56-1.76)	1.27 (0.38-4.25)	2.21 (0.61-8.08)	1.53 (0.36-6.54)
Household income (\$)				
< 2,000 ³	1.00	1.00	1.00	1.00
2,000 – 3,999	1.33 (0.86-2.08)	1.09 (0.40-2.93)	0.42 (0.15-1.20)	1.21 (0.35-4.15)
≥ 4,000	1.26 (0.80-1.98)	1.07 (0.38-3.00)	0.45 (0.16-1.24)	1.14 (0.34-3.88)
< 2,000 ⁴	1.00	1.00	1.00	1.00
2,000 – 3,999	1.19 (0.71-2.00)	1.15 (0.37-3.59)	0.63 (0.20-1.96)	0.90 (0.24-3.38)
≥ 4,000	1.00 (0.58-1.72)	0.90 (0.26-3.08)	0.59 (0.19-1.87)	8.88 (0.24-3.24)

Abbreviations: HGS, High grade serous; CI, Confidence interval; OR, Odds ratio.

The bold values indicate statistical significance at 95% confidence levels.

The italic values indicate marginal statistical significance at 95% confidence levels.

Low grade serous was not included in the analysis because its number was 7 which was too small to get the values.

1. The OR (95% CI) was estimated in logistic regression adjusted by enrollment year.

2. The OR (95% CI) was estimated in logistic regression adjusted by enrollment year, breast cancer or ovarian cancer family history, and oral contraceptive use.

3. The OR (95% CI) was estimated in logistic regression adjusted by age and enrollment year.

4. The OR (95% CI) was estimated in logistic regression adjusted by age, enrollment year, breast cancer or ovarian cancer family history, and oral contraceptive use.

† Estimated by performing Cochran-Mantel-Haenszel.

VI. References

1. Reid BM, Permuth JB, Sellers TA. Epidemiology of ovarian cancer: a review. *Cancer biology & medicine*. 2017;14(1):9-32.
2. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Pineros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer*. 2019;144(8):1941-53.
3. Bathesda M. SEER Cancer Stat Review: Ovarian Cancer. National Cancer Institute. 2019.
4. Center NC. Annual report of cancer statistics in Korea in 2016. 2018.
5. Yang H, Dai H, Li L, Wang X, Wang P, Song F, et al. Age at menarche and epithelial ovarian cancer risk: A meta-analysis and Mendelian randomization study. *Cancer Medicine*.0(0).
6. Sung HK, Ma SH, Choi J-Y, Hwang Y, Ahn C, Kim B-G, et al. The Effect of Breastfeeding Duration and Parity on the Risk of Epithelial Ovarian Cancer: A Systematic Review and Meta-analysis. *J Prev Med Public Health*. 2016;49(6):349-66.
7. IARC. List of Classifications by cancer sites with sufficient or limited evidence in humans, Volumes 1 to 124 a. International Agency for Research on Cancer. 2019;1 to 124.
8. Terry KL, Titus-Ernstoff L, McKolanis JR, Welch WR, Finn OJ, Cramer DW. Incessant Ovulation, Mucin 1 Immunity, and Risk for Ovarian Cancer. *Cancer Epidemiology Biomarkers & Prevention*. 2007;16(1):30-5.
9. Cramer DW, Welch WR. Determinants of ovarian cancer risk. II. Inferences regarding pathogenesis. *J Natl Cancer Inst*. 1983;71(4):717-21.
10. Peres LC, Risch H, Terry KL, Webb PM, Goodman MT, Wu AH, et al. Racial/ethnic differences in the epidemiology of ovarian cancer: a pooled analysis of 12 case-control studies. *International journal of epidemiology*. 2018;47(2):460-72.
11. Franceschi S, La Vecchia C, Booth M, Tzonou A, Negri E, Parazzini F, et al. Pooled analysis of 3 European case-control studies of ovarian cancer: II. Age at menarche and at menopause. *Int J Cancer*. 1991;49(1):57-60.
12. Peterson NB, Trentham-Dietz A, Newcomb PA, Chen Z, Hampton JM, Willett WC, et al. Alcohol consumption and ovarian cancer risk in a population-based case-control study. *International Journal of Cancer*. 2006;119(10):2423-7.
13. Ma SH, Kim BG, Choi JY, Kim TJ, Kim YM, Kim JW, et al. Korean epithelial ovarian cancer study (Ko-EVE): protocols and interim report. *Asian Pac J Cancer Prev*. 2012;13(8):3731-40.
14. Health Examinees Study G. The Health Examinees (HEXA) study: rationale, study design and baseline characteristics. *Asian Pac J Cancer Prev*. 2015;16(4):1591-7.

15. Nguyen HN, Averette HE, Janicek M. Ovarian carcinoma: A review of the significance of familial risk factors and the role of prophylactic oophorectomy in cancer prevention. *Cancer*. 1994;74(2):545-55.
16. Frakt AB. An Observational Study Goes Where Randomized Clinical Trials Have Not. *Jama*. 2015;313(11):1091-2.

한국형 난소암 연구 (Ko-EVE)에서의 난소암과 위험 요인의 연관성 연구

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서론

난소암은 여성의 암 사망 원인 중 7 번째에 해당한다. 세계적으로 난소암 관련된 위험 요인에 대한 연구는 발표되어 왔으나 대부분의 연구가 유럽 연구에 해당하며 특히 한국의 경우 난소암에 관한 위험 요인 관찰 연구가 전무하였다. 따라서, 본 연구는 생식, 호르몬 치료, 생활습관, 가족력 등의 다양한 요인과 난소암의 연관성을 확인하고자 하였다.

방법

한국형 난소암 연구 (Ko-EVE)에서의 난소암 환자군 530 명과 도시기반코호트 (HEXA)의 여성 중 80,979 명이 연령과 입적년도에

따라 제한되었다. 환자군에는 일차 난소암 발생자이며 임상병기가 1 기부터 3 기에 해당하는 상피성 난소암 환자가 포함되었다. 선택 편향 최소화 위하여 restriction 과 입적년도와 수입에 따른 빈도 매칭을 사용하였다. Restricted 자료의 오즈비와 95% 신뢰구간을 구하기 위하여 multivariate logistic regression model 을 사용하였으며 매칭된 자료의 오즈비와 95% 신뢰구간을 구하기 위한 통계적 분석 방법에는 conditional logistic regression model 을 사용하였다.

결과

초경 연령이 이른 여성 (OR=1.48, 95% CI=1.05-2.09), 마지막 출산 연령이 늦은 여성 (OR=1.68, 95% CI=1.07-2.64)의 경우 높은 난소암 위험을 보였다. 생활 습관 관련 요인의 분석 결과로는, 과거 흡연자 (OR=3.69, 95% CI=1.75-7.78), pack year 가 10 이상인 여성 (OR=3.14, 95% CI=1.32-7.44), 과거 음주 경험자 (OR=11.20, 95% CI=6.75-18.59), body mass index (BMI)가 18.5 kg/m² 미만인 여성 (OR=1.80, 95% CI=1.04-3.13)이 높은 오즈비를 보였다. 유방암 가족력이 있는 여성 (OR=3.92, 95% CI=2.47-6.21), 난소암 가족력이 있는 여성 (OR=33.65, 95% CI=9.67-117.13) 이 각각의 가족력이 없는 여성에 비교하여 높은 난소암 위험을 보였다.

또한, 감소된 난소암 위험이 출산력이 있는 여성 (OR=0.24, 95% CI=0.16-0.37), 특히 2 명 이상의 아이를 출산한 경험이 있는 여성 (OR=0.23, 95% CI=0.15-0.35) 에서 출산 경험이 없는 여성에 비하여, 인공 유산 경험 (OR=0.66, 95% CI=0.48-0.91)이 있는

경우에도 인공 유산 경험이 없는 경우에 비하여 감소된 난소암 위험을 보였다. 호르몬 관련 요인 분석 결과, 경구 피임약 복용 경험이 있는 여성 (OR=0.59, 95% CI=0.41-0.87), 경구 피임약을 10 개월 이상 복용한 여성 (OR=0.59, 95% CI=0.41-0.87), 난관 결찰/절제술 (OR=0.17, 95% CI=0.10-0.31), 자궁 적출술 (OR=0.34, 95% CI=0.19-0.62)을 받은 적 있는 여성에서 각각의 요인 경험이 없는 여성에 비하여 낮은 오즈비를 보였다. 생활 습관 요인 분석에서는 땀이 날 정도의 규칙적 운동을 한 번에 한 시간 반 이상 (OR=0.60, 95% CI=0.41-0.86), 일주일에 5 번 이상 (OR=0.41, 95% CI=0.28-0.60), 일주일에 2 시간 이상 (OR=0.47, 95% CI=0.35-0.61) 하는 경우에 그렇지 않은 경우보다 난소암 위험이 낮은 것으로 나타났다. 폐경 후 호르몬 대체 치료의 경우, 치료 경험이 있는 경우 (OR=0.51, 95% CI=0.32-0.80) 없는 경우보다 더 낮은 오즈비를 보였지만 충분한 정보 수집이 되지 못했기 때문에 호르몬 대체 치료가 난소암 위험에 대하여 보호 효과를 가지고 있다고 하기는 어렵다.

결론

국내에서 최초로 난소암 위험 요인에 대한 관찰 연구를 시행한 결과, 출산력, 경구피임약 복용, 인공 유산, 난관 결찰/절제술, 자궁 적출술, 규칙적인 운동이 상피성 난소암에 대하여 보호 효과를 가지고 있으며 특히 출산력, 경구피임약, 규칙적 운동의 경우, 출산 아이 수의 증가, 장기간 경구피임약 복용, 긴 시간과 잦은 빈도의 운동에 따라 보호 효과도 함께 커지는 것을 확인 하였다. 반면에 이른 초경, 늦은 마지막

아이 출산 연령, 흡연, 음주, BMI 18.5 kg/m² 미만, 유방암 가족력과
난소암 가족력은 난소암 위험 요인임을 확인하였다.

주요어

난소암, 생식 요인, 위험 요인, 환자-대조군 연구, Frequency
matching, Logistic regression, 역학, 한국