RESEARCH ARTICLE

Korean Epithelial Ovarian Cancer Study (Ko-EVE): Protocols and Interim Report

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Abstract

Background: There have been few studies of Asian ovarian cancer and benign tumors. The primary aim of this paper was to report the protocol of the Ko-EVE study to examine epidemiological and molecular factors for ovarian cancer and benign neoplasms and to ascertain the major risk factors for ovarian cancer control in Korea. Methods: This case-control study covers incident epithelial ovarian cancers and benign neoplasms, four major centers participating in enrolling incident cases and 3 hospitals enrolling healthy controls among health examinees. Standardized questionnaires were administered by trained interviewers, including sections on socio-demographics characteristics, past medical history, medication usage, family history, lifetime consumption of alcohol and tobacco, diet, physical activity, and reproductive factors for women. Various biological specimens were collected in the biorepository according to the standardized protocol. Annual follow-up for cancer cases and follow-up at the 1st year for benign tumor cases are performing to evaluate treatment effect and progression. Passive follow to see long-term survival will be conducting using record linkage with national data. Results: The total number recruited in 2010-2011 was 246 epithelial ovarian cancer cases, 362 benign epithelial tumors and 345 controls. We are planning to collect subjects for at least 1,500 sets of ovarian cancer, 2,000 benign tumors and 1,500 controls till 2018. Conclusion: The Ko-EVE will provide unique and important data to probe the etiology and natural history of Korean epithelial ovarian cancer. It will be continued by genomic and proteomic epidemiological analyses and future intervention studies for the prevention of ovarian cancer among Koreans.

Key words: Ovarian cancer - protocol- Ko-EVE study - case - control study

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Introduction

Ovarian cancer is relatively uncommon, with age-standardized incidence rates ranging between 2 and 8 per 100,000 women in most parts of the world (Ferlay et al., 2010). However, it is usually the second most common gynecological cancer in western countries (Ferlay et al. 2010). In Korea, it is the second most common gynecological cancer, next to uterine cervix cancer, but the age-adjusted ovarian cancer incidence in Korea is still much lower than that in many western nations (Ministry of Health & Welfare 2009; Park et al., 2010).

Despite the low incidence of ovarian cancer, population-based incidence rates are increasing steadily with time (Park et al., 2010). In addition, the incidence rate of ovarian cancer will soon exceed that of uterine cervix cancer in Korea when extrapolating the current incidence trend (Park et al., 2010). However, the reasons for this upward trend are unclear. Clinically, women having who are diagnosed with ovarian cancer do not typically feel any symptoms. Moreover, the ovaries are hidden behind the uterus, making earlier detection difficult and hindering the earlier medical process. Therefore, ovarian cancer is often a fatal disease. In fact, the mortality rate for ovarian cancer has an incidence rate of 35-50%, whereas the mortality rate for breast cancer is about 20-30% (Ferlay et al., 2010).

One of the reasons for the upward trend in the incidence of ovarian cancer is the increasing westernization of lifestyles and diet trends. Korea has experienced rapid changes in its overall dietary patterns, going from energy-deficient in the past to an energy imbalance status

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at present characterized by rapidly increasing fat and protein proportions in recent years. Based on national survey data gathered since 1969, the consumption of protein and fat from meat and meat products steeply increased by 19-fold and 7-fold between 1975 and 2009 (2.3% and 6.0% of the total grams of food intake in 1975; and 44.2% and 45.6% in 2009, respectively) (Ministry of Health & Welfare, 2009; Park et al., 2010). It has been alleged that high intake levels of red meats and processed meats are associated with an increased risk for ovarian cancer (Kolahdooz et al., 2010), but this hypothesis as it pertains to meat remains controversial because the other papers have shown no association (Bertone et al., 2002; Larsson et al., 2005; Pan et al., 2004; Schulz et al., 2007). The energy imbalance condition shows a bad effect in the direction of increasing obesity. This is particularly true for obesity in children in Korea, which has increased dramatic from only 1.7-2.6 % in 1979 to 9.0% in 2005 (Park et al., 2010; Park et al., 2004). This obesity problem can greatly increase the future risk of ovarian cancer. Moreover, the reproductive history of Korean women is showing a rapid change toward an increasing risk of ovarian cancer, due to factors such as later marriages and a decreasing fertility rate (Korea National Statistical Office, 2009; Park et al. 2010). In terms of medical utilization and access, Korean has a national health insurance system covering 100% (97% from Medicare and 3% from Medicaid) of the population, with services covering the regular testing of the uterus and ovaries.

These unique environmental factors present an opportunity for a new ovarian cancer study in Korea. In 2009, the Ko-EVE (Korean Epithelial oVarian cancEr) Study initiated by a grant from the National Cancer Institute was started, involving six hospitals. The Ko-EVE study aimed to achieve the following goals. The first goal was to establish large-scale case-controlled study to determine epidemiological risk factors for future prevention strategies at the population level. The second goal was to examine moleculogenetic markers in terms of the etiology, clinical progression and survival rates associated with ovarian cancer. Ovarian epithelial carcinoma is the most frequently diagnosed type of ovarian malignancy, but it is heterogeneous with various histologic subtypes that show different molecular and cytogenetic features, such as the serous, low-grade endometrioid, clear cell, mucinous and transitional carcinomas (Lalwani et al., 2011). Therefore, a moleculogenetic study using biospecimens is needed to classify the heterogeneous disease types of epithelial ovarian cancer and to understand the oncologic signaling pathways of each disease. Third goal is to find some differentiation in the behavior risk factors and molecular factors between malignant and benign epithelial tumors relative to controls. Previous papers showed that a diagnosis of a benign ovarian tumor may be associated with an increased risk of future ovarian cancer during the lifetime of the patient (Jordan et al., 2006). However, the natural history of the development of epithelial ovarian cancer from a benign tumor is unclear. Therefore, to find some epidemiological and molecular distinctions between a benign tumor and a carcinoma is of paramount concern in this study (Lynch et al., 2009). The final aim is to produce evidence-based clinical practice guidelines for epithelial ovarian cancer through study experiences and data accumulated over a period of 10 years.

Materials and Methods

This study was designed and executed to examine epidemiological and moleculogenetic risk factors pertinent to those diagnosed with epithelial ovarian cancer and benign epithelial tumors compared to healthy controls and to investigate the prognostic factors related to survival and the progression of epithelial ovarian cancer.

Design

The Ko-EVE study is a multicenter case-control study of epithelial ovarian cancer and benign epithelial tumors as well as a prospective cohort study for epithelial ovarian cancer. Four university and/or general hospitals are participating in this study. The Institutional Review Boards of the six hospitals approved the study.

Study Subjects

We started to enroll patients in 2010. The enrollment will continue until 2019. The selection criteria for a hospital were as follows: 1) Among the top six hospitals where operations and chemotherapy are mainly performed in Korea, 2) has a considerable amount of experiences in ovarian cancer research, 3) has an existing ovarian cancer patient follow-up rate of 80% or better, and 4) has experience with multicenter network research. Ovarian cancer cases are defined as patients who were admitted to any of the four university or/and training hospitals located in Seoul and its suburban regions in Korea. Eligible criteria of ovarian cancer cases are as follows: 1) incident cases diagnosed as primary ovarian cancer at the time of enrollment, 2) those confirmed histopathologically as epithelial ovarian carcinoma, and 3) subjects with primary ovarian cancer between stages I and III and 4) Subjects must be over 20. Ovarian benign tumor cases are also patients admitted to the same hospitals during the same periods. Eligible criteria are as follows: 1) incident cases, 2) those confirmed histopathologically as epithelial benign ovarian tumors, 3) those with no previous or current history of cancer, and 4) those over 20. Control subjects are selected from three hospitals with a health examinee check-up system in the same locality as the hospitals for case selection. These participants are selected according to the following criteria: 1) those who visit to the hospital for a health check-up at the time of enrollment; and 2) those with no previous history of cancer, benign ovarian tumor, or oophorectomy, and no mass on physical examination. All

participants must agree to participate in this study, with questionnaire interviews and biospecimen storage, and all must have no communication problems.

Pilot study and IRB consent

During 2008 and 2009, an investigating committee composed of gynecologists and epidemiologists set the protocol and then tried to gain the approval from the Institutional Review Boards (IRBs) of the four hospitals about study protocol in 2009. A pilot study was performed in March and April in 2009 in three hospitals for which the respective IRBs had granted consent. In addition, we revised the questionnaire items (types of alcohol beverage drank and the use of tampons and/or sanitary pads) that participants had difficulty in recalling or responding to and deleted an item from the Mini-Mental State Exam (MMSE). The IRBs of other one hospitals approved the study protocol in April of 2010.

The composition of baseline information

We obtained informed consent from all subjects. At the enrollment time, we collected information on the cancer cases and the benign tumor cases using questionnaires, anthropometric measurements, physical examinations, laboratory clinical tests, tumor marker tests, urine tests, ECGs, BMDs, and pelvic and vaginal ultrasonic test. For controls, we used the same questionnaire, anthropometric measurements, physical examinations, laboratory clinical tests, and urine tests (Table 1). Abdominal and pelvic physical examinations were conducted to detect the presence of an abdominal or pelvic mass. The laboratory clinical tests of the cases included the CBC, HBsAg, HBsAb, ESR, and CRP assessments as well as BUN, Creatinine, AST (SGOT), ALT (SGPT) and ALP chemistry tests. The control tests were limited to CBC and CRP assessments and to the BUN, Creatinine, AST (SGOT) and ALT (SGPT) chemistry tests. All subjects were tested with glucose, urine nitrite, leukocyte esterase, blood, and albumin. All cases underwent ECG and BMD tests as well as pelvic and vaginal ultrasonic test results, whereas the controls did not have these specific assessments (Table 1).

Structured questionnaire

The questionnaires are classified into two forms: one questionnaire is composed of general and selected questions about ovarian cancers, and the other is a questionnaire pertaining to diet. The items of the first one included demographical information including the patient's age, education, marital status, social/living status, history of hospitalization, lifestyle factors such as alcohol history, smoking history, physical activity, family history of cancer in general and benign tumors, premenstrual syndrome (cancer and benign cases only), and depression status (Table 2).

The diet questionnaire assessed quantitative information about food, specifically the intake frequency of foods, the intake amounts, the cooking methods of favorite meats, and the types of oils used for cooking. It was proposed by the KCDC and was validated in 2007 (Ahn et al., 2007).

Height and weight were measured in the clinic with participants wearing light clothing and no shoes. Their body mass index (BMI) values were calculated by dividing their weight in kilograms by their height in meters squared. The waist circumference was measured in standing subjects midway between the inferior lateral margin of the ribs and the superior lateral border of the iliac crest. The widest hip circumference was measured.

Table 1. Protocol of Ko-EVE Study at the Time of Baseline Enrollment

Baseline	Ovarian cancer cases	Benign tumor cases	Healthy controls
Informed consent	O	O	O
Questionnaire (Baseline or follow-up)	O	O	O
Anthropometric measurement[1]	O	O	O
Physical examination[2]	O	O	O
Laboratory clinical test[3]	O	O	O
Tumor marker (CA-125, CA19-9)	O	O	-
Urine test[4]	O	O	O
EKG	O	O	-
BMD	O	O	-
Pelvic and vaginal ultrasonic test	O	O	-
Pathologic report	O	O	-
Biospecimen collection[5]	O	O	O

[1]Height, Weight, Waist and hip circumference, [2]Abdominal and pelvic examination, [3]CBC, HBsAg, HBsAb, ESR, CRP and chemistry such as BUN, Creatinine, AST(SGOT), ALT(SGPT), and ALP, [4]Nitrite, glucose, leukycyte esterate, blood, albumin, [5]16cc blood per a subject (8cc at EDTA tube and 8cc at plain tube) is collected and aliquoted as following; 2 plasma, 1 buffy coat, and 1 RBC clot from EDTA tube; and 3 serum from plain tube

Table 2. Collecting Information Using Questionnaires at the Time of Baseline in the Ko-EVE Study

Category	Items
Questionnaires	
All cases and controls	-Demographical information: age, education, marital status, social/living status -History of Sanitary napkin -History of hospitalization, fall down or fracture -Life style factor: alcohol history, smoking history, physical activity -Family history of ovarian cancer and benign tumor, other cancers -Past medical history, medication history, reproductive history -Premenstrual syndrome
Cases only	-Depression status by CES-D*
All cases and controls	-Diet questionnaires (food frequency questionnaire)
Baseline CRF	
All cases	-Results of Laboratory clinical test and urine test -Results of Chest X-ray, EKG and BMD -Gynecologic symptom check -Description of radiologic diagnosis -Report of surgery and pathology

Biological sample collection, processing and storage

Blood samples were collected after at least 8 hours of overnight fasting from the antecubital vein and funneled into Vacutainer tubes. The blood and urine of cases with ovarian cancer and benign tumors were extracted in an operation room before anesthesia. Control's specimens were extracted in the interview room by a trained nurse or by a medical laboratory technologist. Blood samples of 16cc were collected using a 10cc EDTA and a 5cc EDTA along with a 10cc plain tube. 10cc of midstream urine was also collected into a sterilized urine cup for storage. The 5cc EDTA tubes go to a clinical laboratory for a CBC test at each hospital. The specimen from the 10cc EDTA and the 10cc plain tubes are given a study ID which matches the number on the questionnaire and are labeled with barcode stickers. They are kept in a refrigerator at each institution until collection by a courier every day and sent to a commercial laboratory. The laboratory is responsible for all transportation, processing and storage events. 1cc of whole blood is drawn from the 10cc EDTA tube, and using this blood, DNA is first extracted. The remaining 7cc in the 10cc EDTA tube is centrifuged at 3000rpm for 15 minutes and in each case, 1cc of plasma in two 1.5cc screw tubes, 1 buffy coat, and 1 RBC clot are divided. The 10cc plain tube is also centrifuged at 3000rpm for 15 minutes and the specimens from the centrifuged tube are separated into 1cc of serum each in three screw tubes. All biospecimens are transferred and stored in liquid nitrogen (Union Carbide, liquid nitrogen refrigerator) at the Samsung central biobank.

Follow-up

We designed our subjects' follow-up visits as either active or passive follow-up (see Table 3). Active follow-ups are performed during the patients' outpatient clinic visits. Cancer cases are checked annually for 10 years and benign tumor patients are checked only the first visit time. Active follow-ups of controls are not planned.

At the outpatient clinic, doctors check the subjects' survival and progression and nurses measure their height, weight, waist and hip circumferences. Patients report their health status using self-administrated questionnaires containing information about cognitive function, the VAS score of depression, stress and usual health status, and new disease incidences. Also included are exposure changes such as to infections and/or drugs as well as questions about menopause, hormone therapy and chemotherapy, diet and diet supplements, smoking and drinking, physical activity, and a family history of cancer. Information on vital status and disease progression is sourced from hospital charts. Also, from case reports, the following information will be sought: the category of primary therapy, the results of primary therapy including chemotherapy, and information related to progression diagnosis. If patients have the results of repeated laboratory clinical tests and chest x-rays, EKG and BMD, these results are included in the follow-up case report. We are planning to collect repeated biospecimens upon the first and third follow-up years. If patients do not keep their prearranged follow-up visit, the patients are contacted by letter to inform them of the study and are subsequently contacted by phone. In cases of an invalid phone number, a second letter will be sent asking the patient to contact our center to provide a correct phone number.

Passive follow-ups will be planned for all subjects, including the controls. This will involve record linkages with three nationwide databases, specifically the national cancer registry, the death certificate database, and the

Table 3. Follow-up Protocol for Outcome Ascertainment of Ko-EVE Study

	Ovarian cancer cases	Benign neoplasm cases	Controls
Active follow at each hospital			
Interval and duration	Annually for 10 years	The 1st year only	None
Doctors' check-up items	Outcomes such as main therapy effect, progression, and survival		None
Self administrated questionnaire	New disease occurrence	New disease occurrence	None
Follow-up CRF	Category of primary therapy to progression diagnosis and chemotherapy information related to progression diagnosis, medication history, results of laboratory clinical test, chest X-ray, EKG and BMD	Same as cancer cases except information for primary therapy	None
Passive follow-up*	All groups		
Interval and duration	Once per 3 years for 15 years		
Information by passive follow-up	Outcomes such as new cancer ascertainment, cardiovascular attack, stroke, and overall survival,		
Exposure assessment			
Self administrated questionnaire	Cognitive function, VAS scoreof depression, stress and usual health status; Exposure changes such infection, drug, menopause, hormone therapy and chemotherapy, diet and diet supplement, smoking and drinking, physical activity and family history of cancer	Same as cancer cases except information of chemotherapy	None
Follow-up biospecimen plan	The first and third year	The first year only	None

*Record linkage with three nationwide datasets including Nationwide death certificate, Cancer Registry and National Insurance Review and Assessment data (HIRA)

medical claims database of the National Health Insurance Review Agency. Earlier research showed that cohort subjects with new cancer incidence matched by up to 99% from the three data sources. Moreover, the efficiency of the three passive follow-up methods combined was 99.1% and the national death certificate data could estimate nearly 99% of the total certified death instances (Cho et al., 2009). Therefore, the combination of active and passive follow-up methods is expected to increase the follow-up completeness in ascertaining outcomes such as patient deaths and new cancer incidences.

Data editing and quality control procedure

Interviewers are selected from among the nurses in charge of research. They were educated and given complete standardized training regarding the questionnaire and case report form. All questionnaires and case report forms are shipped to the central data entry location once a month. Biospecimens are shipped to a commercial laboratory for quality control using standardized methods.

Errors in the date entry are controlled at the time they are entered initially and are double-checked by two persons: the first person entering the data and the data entry supervisor. After confirming the absence of data entry errors and other errors, the data manager in the data entry and management center sends the relevant data back to the interviewer at each hospital.

Sample size calculation and future plan

Women's smoking prevalence is about 4-7% according to national data from 2008-2010 (Ministry of Health & Welfare) and among the controls in our previous breast cancer case-controlled studies (Cho et al., 2009; Han et al., 2008; Lee et al., 2005; Park et al., 2000). Controls with a family history of breast cancer in the breast case-controlled study amounted to 4-8% of the total (Cho et al. 2009; Han et al. 2008; Lee et al. 2005; Park et al. 2000). In candidate gene studies, the SNPs with minor allele frequencies of < 5% are usually excluded. Therefore, the minimum frequency for this was set to at least 5% (Lee et al., 2009; Ministry of Health and Welfare, 2012; Qie et al., 2002). We also assumed a minimum exposure frequency among the controls of 4-10%. When the minimum target odds ratio, alpha error and cancer case-healthy control ratio are assumed to be 1.5, 0.05, and 1:1, respectively, the total number of the target population to account for 80% statistical power ranges from 957 to 2,185 using PASS 2000 (Power Analysis and Sample Size) software. We collected 98 ovarian cancer cases and 143 benign cases over a course of 8 months in 2009 (cancer: benign case ratio=1:1.55) as well as 148 cancer cases and 219 benign cases (cancer : benign case ratio=1:1.48), whereas the questionnaire-based number was 187 : 251 for 2009-2010 (cancer : benign case ratio=1:1.35). Thus, the future enrollment cancer-to-benign-tumor ratio is expected to be about 1.4. In Korea, nearly 1,350-1,660 new ovarian cancer cases were registered with the Korea Central Cancer Registry program between 1999 and 2006, and about 1,750-1,800 cases were registered between 2007 and 2008 (Ministry of Health and Welfare,2012). Annually, at least 150 cancer cases based on the recent increasing tendency of ovarian cancer incidence and our capacity for enrollment and at least 210 benign tumor cases at a 1:1.4 ratio of cancer: benign cases can be enrolled in our Ko-EVE study from 2012. Therefore, we expect to enroll about 1,500 ovarian cancers and the same number of controls, as along with least 2,000 benign cases by 2019. The exposure fraction among benign tumor cases, the minimum odds ratio, the cancer case : benign case ratio, and the alpha error are assumed to be 0.05, 1.5, 1:4, and 0.05, respectively. The target number to obtain 80% statistical power is 1,503 cancer cases and 2,105 benign casesß.

Results

From April of 2010 to December of 2011, we collected the biospecimens of 246 ovarian epithelial cancer and 362 benign tumor cases and from 345 normal controls (Table 4). Past medical history including medication and reproductive histories were collected from 100% of the subjects. Lifestyle factors and family and diet questionnaires were collected for only 76% of the cancer cases and 73% of the benign tumor cases, while this information was collected from 99% of the controls.

The distribution of the selected characteristics of all of the participants is shown in Table 5. The patients with ovarian cancer were older than the controls, while those with benign tumors were younger than the controls. BMI is slightly higher in normal controls than both of the cancer cases. Age at menarche and age at menopause in the cancer cases are higher than the controls and the benign tumor cases, while age at first full-term pregnancy

Table 4. Participating Rate of Each Process for Collecting Information at the Time of Baseline from April 2010 to December 2011

	Ovarian cancer cases	Benign ovarian tumor cases	Healthy controls
Blood collection	246	362	345
Enrollment year			
2010	98	143	267
2011	148	219	78
Questionnaires (Past medical history, Medication history, Reproductive history)	246	362	345
Questionnaires including diet and lifestyle and family history factors	187	251	342
Case report form	246	362	345
Clinical test and physical examination	189	265	342

Table 5. General Characteristics for Participants in Each Group from 2010 to 2011

	Ovarian cancer Mean (SD)	Benign ovarian tumor Mean (SD)	Normal control group Mean (SD)
Age	52.6 (11.6)	42.3 (13.6)	48.7 (10.5)
Height	156.4 (6.1)	158.3 (5.3)	156.7 (5.8)
Weight	56.0 (9.4)	56.7 (7.7)	57.9 (8.2)
BMI	22.9 (3.6)	22.7 (3.3)	23.6 (3.3)
Age at menarche	15.5 (1.9)	14.4 (1.7)	14.8 (2.0)
Age at first fullterm pregrancy	26.4 (4.7)	26.7 (3.3)	25.6 (3.7)
Age at menopause	50.1 (5.2)	48.8 (7.3)	49.3 (4.5)
Smokers (%)	8	4	5
Drinkers (%)	19	44	43
Regular exercise (%)	59	63	57
Postmenopausal women (%)	40	21	48

is lower in the cancer cases than in the controls and benign tumor cases. Smoking prevalence is higher but drinking prevalence is lower in the cancer cases as compared to the control and benign cases. The proportion

Table 6. Previous Ovarian Cancer Case-control and Cohort Studies among Asians

Reference	N of cases/ Controls/	Source of cases and controls	Country	Results of paper	Comments
1) Hospital based case-control studies					
Non-genetic factor related case-control study					
(Mori et al. 1984)	80/160	Hospital	Japan	Reproductive and lifestyle factors	
(Mori et al. 1988)	110/220	Hospital	Japan	Reproductive, genetic and dietary factors	
(Kato et al. 1989)	417/8920	Hospital	Japan	Alcohol, smoking, residence and occupation	Age
(Shu et al. 1989)	172/172	Hospital	China	Dietary factors	Education, ovarian cyst and parity and
(Chen et al. 1992)	112/224	Hospital	China	Reproductive factors and mumps past infection, talc power exposure	
(Yun et al. 1995)	22/22	Hospital	Korea	Ginseng intake	Age, sex, education, marriage, smoking, and alcohol drinking
(Nandakumar et al. 1995)	97/97	Hospital	India	Smoking, alcohol, reproductive history and dietary practices	
(Mori et al. 1998)	141/2016	Hospital	Japan	Anthropometric factors	1112 among 2016 controls had benign tumor (141 ovarian tumor)
(Hirose et al. 1999)	99/25,488	Hospital	Japan	Reproductive factors and body mass index	Age
(Zhang et al. 2002)	254/652	Hospital	China	Tea consumption Dietary factors	Age, education, residence, family income, menopause, parity, tubal oral contraceptives, family history of ovarian cancer, and total energy intake
(Zhang et al. 2003)	254/652	Hospital	China	Physical activity	Age, education, residence, family income, menopause, parity, tubal ligation, interview season, oral contraceptives, family history of ovarian cancer, and total energy intake
(Zhang et al. 2004)	254/652	Hospital	China	Reproductive and Dietary factors	Age, education, residence, family income, BMI, smoking, alcohol, coffee, income, marriage, menopause, parity, oral contraceptives, and family history of ovarian cancer
(Zhang et al. 2004)	254/652	Hospital	China	Sedentary behaviours	Age, education, residence, family income, BMI, smoking, alcohol, coffee, income, marriage, menopause, parity, oral contraceptives, family history of ovarian cancer, and total energy intake
(Zhang et al. 2004)	254/652	Hospital	China	Soy and isoflavone (FFQ)	Age, education, residence, family income, menopause, parity, oral contraceptives, family history of ovarian cancer, and total energy intake
(Zhang et al. 2004)	275/623	Hospital	China	Lactation	Age, residence, full term pregnancy, oral contraceptives, and family history of ovarian cancer
(Zhang et al. 2005)	275/623	Hospital	China	Body weight and body mass index	Age, residence, smoking, alcohol, menopause, parity, hormone replacement therapy, family history of ovarian cancer, and total energy intake
(Zhang et al. 2007)	254/652	Hospital	China	Carotenioid intake (FFQ)	BMI, Smoking, tea consumption, parity, oral contraceptives, hormone replacement therapy, menopause, physical activity, family history of ovarian cancer, and total energy intake
(Fujita et al. 2008)	89/323	Hospital	Japan	Lifestyle factors	Including smoking and reproductive factors
(Kim et al. 2009)	116/114/[74]	Hospital	Korea	Symptom index	

of those engaging in regular exercise is higher in the benign group than in the cancer cases and the control group. The proportion of postmenopausal women is similar between the cancer cases and the normal controls but the proportion of benign tumor is lower than it is in the other two groups.

Discussion

Detailed information on the risk factors of ovarian cancer and benign tumor and the long-term survival and prognosis for cancer patients remains scarce among Asians. Although many studies of risk factors in Asian ovarian cancer case-controlled studies have been reported, there are few studies designed specifically for behavior-related modifiable risk factors and moleculogenetic risk factors for ovarian cancer.

As shown in Table 6, 47 Asian case-control studies and 8 cohort studies have been published thus far. However, most of these studies had a small sample size for the ovarian cancer cases (about 300 and below). In particular, most of the studies of genetic

Table 6 (cont). Previous Ovarian Cancer Case-control and Cohort Studies among Asians

Reference	N of cases/ Controls/	Source of cases and controls	Country	Results of paper	Comments
Genetic polymorphism related case-control studies					
(Yang et al. 2009)	165/120	Hospital	China	Family history and ARLTS1 genetic variants	85 familial ovarian cancer, 80 sporadic ovarian cancer vs 120 controls
(Aktas et al. 2002)	117/202	Hospital	Turkey	CYP1A1 gene	
(Qie et al. 2002)	15/20	Hospital	China	p53 codon 72 polymorphism	
(Li et al. 2002)	39/131	Hospital	China	p53 codon 72 polymorphism (C/G) and the risk of human papillomavirus	
(Sugawara et al. 2003)	46/31	Hospital	Japan	CYP1A1 polymorphism	
(Kang et al. 2004)	124/128	Hospital	China	p53 codon 72 and p53 intron 3 (PIN3) polymorphism	
(Kang et al. 2004)	257/257	Hospital	China	Microsomal epoxide hydrolase polymorphism	
(Ueda et al. 2006)	68/95	Hospital	Japan	p53 codon 72 polymorphism	
(Li et al. 2006)	122/138	Hospital	China	The promoter region of the matrix metalloproteinases-1 -1607bp1G/2G, matrix metalloproteinases-3 -1171bp5A/6A, matrix metalloproteinases-7 A-181G and matrix metalloproteinases-9 C-1562T	
(Yang et al. 2006)	202/266	Hospital	China	Single nucleotide polymorphisms (SNPs) Thr307Ala and Asn680Ser	
(Jo et al. 2007)	94/329	Hospital	Korea	The C19007T polymorphism of ERCC1	
(Zhang et al. 2008)	56/20	Hospital	China	Tissue samples, mismatch repair gene hMLH1 and hMSH2	
(Li et al. 2008)	207/256	Hospital	China	The -160C/A, -347G/GA polymorphism within the promoter region and 3'-UTR +54C/T polymorphism of E-cadherin	
(Zhang et al. 2010)	96/115	Hospital	China	Interleukin-23 receptor gene polymorphisms	
(Li et al. 2010)	303/303	Hospital	China	VEGF gene polymorphisms	
(Liu F 2010)	34/45	Hospital	China	CYP1A1 Ile/Val polymorphisms	
(ZY et al. 2010)	78/90	Hospital	China	CYP1A1 gene polymorphism	
(Ma et al. 2011)	218/285	Hospital	China	CASP8 gene	
Biomarker related case-control study					
(Xie et al. 2004)	32/16/[16]	Hospital	China	IL-7	
(Woong-Shick et al. 2005)	35/15	Hospital	Korea	Hemoglobin alpha and beta subunit	
(Zhen et al. 2010)	30/76/[12]	Hospital	China	LyGDI	30 ovarian cancer, 12 benign vs 76 healthy controls
(Kim et al. 2011)	78/78	Hospital	Korea	HE4/CA125	
(Zou et al. 2010)	42/46/[42]	Hospital	China	YKL-40, CA125	Controls: 42 benign diseases and 46 healthy
(Jeong et al. 2009)	45/135	Hospital	Korea	β-carotene, lycopene, zeaxanthin plus lutein, retinol, α-tocopherol, and γ-tocopherol	
2) Population-based case-control studies					
(Yen et al. 2003)	86/369	Population	Taiwan	Reproductive factors, diet frequency, smoking and alcohol drinking	
(Chiu et al. 2004)	933 /933	Population	Taiwan	Using linkage with environmental and death certificate data	Age, urbanization, and calcium level or magnesium level in drinking water
(Sokal et al. 2010)	262/755	Population	Vietnam	Using cases from linkage with hospital record and controls from population registry. Quinacrine sterilization procedures	

3) Cohort study	Ovarian cancer/total cohort	Source of population	Country	Purposes	Comments
General cohort					
(Niwa et al. 2005)	39 death /34639	Japan Collaborative Cohort (JACC) in 1988-1990	Japan	Smoking	
(Niwa et al. 2005)	38 death /36456	Japan Collaborative Cohort (JACC) in 1988-1990	Japan	Body mass index	Age, study area, BMI, height, family history of ovarian cancer, age at menarche, age at menopause, parity, alcohol and education
(Inoue et al. 2006)	74/51223	Japan Public Health Center-Based Prospective Study	Japan	Diabetes history, age, study area	
(Sakauchi et al. 2007)	77 death/64,327	Japan Collaborative Cohort (JACC) in 1988-1990	Japan	Dietary habits, reproductive history, BMI, physical activity, smoking and alcohol	Age
Specific exposure (occupational) cohort					
(Chang et al. 2003)	7 death/70735	Chlorinated organic solvents exposed workers	Taiwan	Standardized mortality ratio	
(Wernli et al. 2008)	4/267,400 (8 exposed subcohort)	Textile workers cohort	China	Occupational exposure	
Specific exposure (patient) cohort					
(Kobayashi et al. 2007)	46/6398	Ovarian endometrioma diagnose in 1985-1995	Japan	Standardized incidence ratio	
(Lin et al. 2011)	90/203,808	Pelvic inflammatory disease population from health insurance database	Taiwan	Pelvic inflammatory disease	Age, income, urbanization, cardiovascular disease, diabetes mellitus, chronic liver disease, rheumatic disease, endometriosis

polymorphisms and biomarkers were performed without information about ovarian cancer risk factors using hospital records and specimens. Thus, the studies did not appropriately control for confounding variables. As the number of ovarian cancer cases was small while there were many healthy controls in the Hospital-based Epidemiologic Research Program in the Aichi Cancer Center (HERPACC) case-controlled study using health examinees (Hirose et al., 1999; Kato et al., 1989), the statistical power could be increased. This study appears to be a prototype of Japan cohort studies for ovarian cancer (Inoue et al., 2006; Niwa et al., 2005; Niwa et al., 2005; Sakauchi et al., 2007).

Most knowledge of ovarian cancer risk factors for Asians is based on the work of Zhang et al. (Zhang et al., 2002a; 2002b; 2003; 2004; 2004a; 2004b; 2004c; 2005; 2007). Their research group studied the relationships pertaining to the most commonly alleged risk factors for ovarian cancer, such as lifestyles and reproductive and diet factors, using 254 ovarian cancer cases and 652 controls. Recently, three population-based studies from Taiwan and Vietnam were published, but Yen's study (Yen et al., 2003) appears to be a unique, epidemiologically predesigned study using a health screening program covering several localities in Vietnam. It is an ideal case-controlled study, but there were still a small number of cancer (n=86) and control (n=369) participants (Yen et al. 2003) due to difficulty of the population-based study design itself (e.g., funding, effort, time, availability). Two other population-based case-controlled studies were based on hospital records, population registries, or linkages with environmental measurement data. Therefore, there were limits in terms of controlling confounding variables. Four papers describing Japan cohort studies starting in 1988 were published (Inoue et al. 2006; Niwa et al. 2005; Niwa et al. 2005; Sakauchi et al. 2007), but some ovarian cancer cases were ascertained from death certificate data (Niwa et al. 2005; Niwa et al. 2005; Sakauchi et al. 2007). Two specific occupation exposure cohort studies showed a relationship between occupational exposure and ovarian cancer in China (Chang et al., 2003; Wernli et al., 2008); however, a few cases were ascertained using mortality data (7 cases in (Chang et al. 2003)and 4 cases in (Wernli et al. 2008), respectively). Other specific patient cohort studies showed interesting results in which ovarian endometrioma and pelvic inflammatory disease were associated with ovarian cancer risk (Kobayashi et al., 2007; Lin et al., 2011), but they were insufficient in terms of how they controlled confounding factors, as these were also based on hospital records or health insurance claims data. Among these previous studies, only four considered the differences among cancer cases, benign tumor cases and controls (Kim et al., 2009; Xie et al., 2004; Zhen et al., 2010; Zou et al., 2010). Moreover, they all had small sample sizes that were under 150.

Although the Ko-EVE study was launched relatively lately in 2009, the program was designed before the study and the limitations on operation were improved beforehand by a pilot study. Strong elements of our study are the inclusion of ovarian cancer and benign ovarian tumor patients, the very long follow-up (up to 10 years), its sample size of over 1500 potential participants with ovarian cancer and 2000 benign ovarian tumor patients, and the availability of baseline data for all consecutive patients in the same area. In addition, this is a case-control study which investigated risk factors for epithelial ovarian cancer relative to controls and a prospective study which examined prognostic factor for ovarian cancer. In terms of biomarkers, we think that there are some differences from healthy controls to those with ovarian benign tumors and to those who are actual cancer cases. Thus, we are also collecting data on benign tumor cases. The study will be continued to include genomic and proteomic epidemiological cases and future intervention studies for the prevention of ovarian cancer among Koreans.

It is hoped that the Ko-EVE study will provide unique and important data on the etiology and natural history of epithelial ovarian cancer in Koreans. We feel that the completion of our study may contribute to a better understanding of the pathogenesis of this disease on a continuum from healthy status, benign tumor, to cancer status.

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