Risk Factors for Ovarian Cancer: Results from a Hospital-Based Case-Control Study

Over Kanseri Risk Faktörleri: Hastaneye Dayalı Vaka-Kontrol Çalışması Sonuçları

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ABSTRACT Objective: Incidence of ovarian cancer varies greatly from one population to another, depending on the prevalent risk factors mostly influenced by menstrual-reproductive events and life style habits. It is hardly possible to present proper and updated data concerning Turkey due to the insufficiency of the statistical records. The aim of this study was to investigate the association between risk factors and ovarian cancer in Turkish women. **Material and Methods:** In a hospital-based case-control study in a university hospital in İstanbul, 217 patients with histologically confirmed ovarian cancer were compared with 1050 controls, who were admitted to the different departments of the same hospital. Data were collected using a structured questionnaire including questions about characteristics (age, education, marital status, body mass index, chronic diseases, smoking and alcohol), menstrual and reproductive history, and family history of cancer in all participants. Odds ratios (OR) and 95% confidence intervals (CI) were obtained from multivariate logistic regression analysis, fitted by the method of maximum likelihood. **Results:** Risk factors for ovarian cancer were found to be the age (p= 0.002), body mass index (BMI) (OR= 1.96, 95% CI: 1.41-2.72) and history of diabetes or hypertension (OR= 2.13, 95% CI: 1.40-3.23), (OR= 2.85, 95% CI: 1.64-4.98). However, when compared with controls, it was found that the OR of non-smokers and the patients with a negative family ovarian cancer history; were 0.29 and 0.33. **Conclusion:** This study indicates that age, BMI and history of diabetes or hypertension and lower parity were strong risk factors for ovarian cancer.

Key Words: Ovarian neoplasms; body mass index; smoking; parity

ÖZET Amaç: Over kanseri insidansı menstrüel-üreme olayları ve yaşam biçimi davranışlarının etkilediği yaygın görülen risk faktörlerine dayalı olarak bir toplumdan diğerine değişiklik göstermektedir. Türkiye'de istatistiksel kayıtların eksikliği sebebi ile düzgün ve güncel verilere ulaşmak çok zordur. Bu araştırma Türk kadınlarında over kanseri ve risk faktörleri arasındaki ilişkiyi değerlendirmek amacıyla planlanmıştır. **Gereç ve Yöntemler:** Bu çalışma İstanbul'daki bir üniversite hastanesinde vaka-kontrol çalışması olarak yapılmıştır. Histolojik olarak over kanseri tanısı alan 217 hasta ile aynı hastanenin farklı bölümlerine müracaat eden 1050 kontrol karşılaştırılmıştır. Veriler katılımcıların özellikleri (yaş,öğrenim, evlilik durumu, beden kitle indeksi, kronik hastalıklar, sigara ve alkol kullanımı), menstrüel ve üreme öyküsü ve ailede kanser öyküsünü içeren yapılandırılmış anket formu ile toplanmıştır. Odds oranı (OR) ve %95 güven aralığı multivariate lojistik regresyon analizi ile elde edilmiş ve maximum olasılık yöntemi ile değerlendirilmiştir. **Bulgular:** Over kanseri için risk faktörleri, yaş (p= 0.002), beden kitle indeksi (BKİ) (OR= 1.96, 95% CI: 1.41-2.72) ve diyabet veya hipertansiyon öyküsü (OR= 2.13, 95% CI: 1.40-3.23), (OR= 2.85, 95% CI: 1.64-4.98) olarak belirlenmiştir. Bununla birlikte kontrol grubu ile karşılaştırıldığında sigara içmeyenler ve ailesinde over kanseri öyküsü bulunmayanların odds oranı 0.29 ve 0.33'tür. **Sonuç:** Sonuç olarak bu çalışma yaş, BKİ, diyabet veya hipertansiyon öyküsünün over kanseri için yüksek risk faktörü olduğunu göstermiştir.

Anahtar Kelimeler: Over kanseri; beden kitle indeksi; sigara içmek; parite

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In developed countries of the world, ovarian cancer is a frequent neoplasm, ranking the 7th and 6th most frequent for incidence and mortality, respectively. The highest incidence areas are in Europe (especially the Nordic countries and the United Kingdom) and North America, with a ratio of approximately four separating rates in the highest and the lowest incidence countries worldwide.[1] Age-standardized incidence rates of ovarian cancer are strongly correlated with 'Westernization' of lifestyle, and are up to 10-fold higher in Western Europe or the USA than in, for example, areas of Asia or Africa.[2] It is hardly possible to present proper and updated data concerning Turkey due to the insufficiency of the statistical records.[3] However, incidence of ovarian cancer varies greatly from one population to another, depending on the prevalent risk factors mostly influenced by menstrual-reproductive events (parity, late menopause) and life style habits (cigarette smoking).[4-7] Traditionally, women in Turkey get married at a young age and do not use oral contraceptives; they also enjoy having many children and breastfeed them as long as possible. However this lifestyle is gradually changing due to internal migration, education and Westernization. Additionally, women get married in their late twenties, use oral contraceptives, have fewer children and breastfeed them for a shorter time.

In literature, it is reported that changing lifestyle is related to ovarian cancer. Epidemiological studies have shown that physical activity, weight change and body mass index (BMI) in increase the risk for ovarian cancer.[6,8] A cohort study in Sweden found that alcoholic women developed ovarian cancer.[9] Two other studies, Zhang et al[10] and Modugno et al[11] found that current cigarette smoking was a risk factor for mucinous epithelial ovarian cancer. In another study, Weiderpass et al suggested that diabetes mellitus was associated with ovarian cancer.[8] Most of the literature reports that ovarian cancer is related to the reproductive life of women, menstrual history and oral contraceptive use.[4,5,12-14] Infertility, and age at menarche and menopause were also studied in associated with ovarian cancer risk.[6,12,14] The results of these studies confirm the protective role of pregnancy on the risk of ovarian cancer. Besides, some epidemiological studies reported that positive family history of cancer has the highest in ovarian cancer but another epidemiological study is not associated with an increased risk of ovarian cancer.[6,15-20]

Early detection is much important in the ovarian cancer, which is a serious woman health problem in the world. The early diagnosis of the illness contributes to recovery, slows down the development of the illness, preventing the complications, restricts the disabilities and improves the life quality and standard.[21] However, although our literature review has shown many epidemiological studies and publications in other countries, we are not aware of any earlier investigations on risk factors for ovarian cancer carried out in our country. Therefore, the present study was carried out in order to determine the risk factors leading to ovarian cancer in Turkish women.

MATERIAL AND METHODS

Between September 2002 and October 2003, we conducted a case-control study of ovarian cancer. Cases included 217 women (age range 29-71 years, median 51) with a histologically confirmed diagnosis of invasive ovarian cancer, who were admitted to the Breast and Gynecologic Policlinic of Oncology Institute of İstanbul University in İstanbul. During that period we visited the outpatient clinic of the hospital two days (Monday and Wednesday) in every week, and had an interview with 217 women who applied to the clinic and who agreed to participate in the study. Having obtained Institutional Review Board approval, data were collected. All the participant patients gave their informed consent. The city of Istanbul, which hosts this Oncology Department, is a very cosmopolitan city having a very advanced level of industry and welcoming a large number of domestic migrates from the whole country. Oncology Institute of Istanbul University located in this city also is a reference hospital to which patients with various oncologic diseases are admitted from all regions of Turkey. This hospital is not the only provider of treatment for various type of cancers, but also routine con-

trols of treated patients are performed in the outpatient clinics regularly. Accordingly, the results of the research are important since they do not reflect a limited part of the country, but the whole country.

The control group consisted of women residing in the same populations and they were admitted to the wards or outpatient clinics of the different departments of the same university's hospital during the same interval. While collecting data, we visited the ward and outpatient clinics two days (Thursday and Friday) in every week and a total of 1050 women were interviewed. Half of the controls had no diseases (50%) and they were the relatives of the patients accompanying them during their stay at hospital. The others had an orthopedic disease, surgical (eye disease) or miscellaneous illnesses, such as disorders of the ear, nose and throat. Women who had a malignant, endocrinal or gynecological disease were not included in the control group. In addition, none of the relatives of the patients applying to the oncology department were admitted to the control group.

DATA COLLECTION

Trained study staff interviewed both case patients and control subjects, and all interviews were conducted in hospitals with the subjects who agreed to take a part in the study. None of the participants (cases and controls) refused the interview. Interviews with the case group were performed at the oncology clinics where they come for their routine medical check-ups and in a suitable room after their control. The patients were provided enough time for each interview. Similarly, the interviews of the control group were performed in a suitable place and in an adequate time.

Data were collected using a structured questionnaire including questions about characteristics (age, education, marital status, body mass index, chronic diseases, smoking and alcohol), menstrual and reproductive history [parity, age at first birth, breast-feeding, age at menarche, oral contraceptive and hormone replacement therapy (HRT) use], and family history of cancer (first and second-degree relatives). Body Mass Index (BMI) was calculated as weight (kg)/height (m^2) as to Quatelet' formula. The information about BMI included the weight and height of the case/control group subjects at the moment of interview. Family history was accepted as positive if a first-degree relative (mother, sister) or a second-degree relative (aunt) had had breast cancer. However, the subjects were not BRCA1/2 tested. Parity was the number of full-term pregnancies, which were defined as pregnancies longer than 6 months regardless of the outcome. HRT use was categorized as follows: non-users (none or less than 6 months of cumulative use), and current users (at least 6 months of use within previous 12 months before the reference date). Analysis according to the type of therapy (estrogen alone or estrogen combined with progesterone) is not presented due to small sample size. Hypertension or diabetes was registered if a woman reported treatment for the condition or said that a physician had diagnosed it. A woman was considered a 'smoker' if she had smoked at least one cigarette/day for at least one year.[22]

STATISTICAL ANALYSIS

Data about all the risk factors were entered into an SPSS 10.0 for Windows computer program, and odds ratios (OR) and 95% confidence intervals (CI) were obtained from multivariate logistic regression analysis, fitted by the method of maximum likelihood.[23] We modeled the probability of disease by means of the following logistic regression model:

The coefficiencies in model were calculated the following:

$$P(Y)=\frac{\exp(\beta_0+\beta_1 X)}{1+\exp(\beta_0+\beta_1 X)}=\frac{1}{1+\exp(-\beta_0-\beta_1 X)}$$

$$Q(Y)= 1 - P(Y)$$

$$\ln\left(\frac{P(Y)}{Q(Y)}\right)=\beta_0+\beta_1 X_1+\beta_2 X_2+\ldots+\beta_p X_p \text{ and}$$

$$\frac{P(Y)}{Q(Y)}=e^{\beta_0+\beta_1 X_1+\beta_2 X_2+\ldots+\beta_p X_p}=e^{\beta_0}e^{\beta_1 X_1}e^{\beta_2 X_2}\ldots e^{\beta_p X_p}$$

As the ratio of probable is calculated as Odds ratios (OR)= P(Y) / Q(Y), the exp(β)'value of each variable is taken up the ratios of probability.

TABLE 1: Distribution of cases and controls according to age and selected general characteristics.

Factor	Ovarian cancer (n= 217)		Controls (N= 1050)		
	Number	(%)	Number	(%)	P values x^2
Age					
≤49	90	(41.5)	560	(53.3)	x^2= 11.036
50-59	73	(33.6)	260	(24.8)	sd= 2
60 ≤	54	(24.9)	230	(21.9)	p= 0.004
Education					
Non-literate	38	(17.5)	168	(16.0)	x^2= 0.786
Literate+Primary School	152	(70.1)	730	(69.5)	sd= 2
Secondary School+University	27	(12.4)	152	(14.5)	p= 0.675
Marital status					
Ever married	186	(85.7)	989	(94.2)	x^2= 19.187
Never married	31	(14.3)	61	(5.8)	sd= 1
					p= 0.000
Body mass index					
Normal (18.5-24.99)	86	(39.6)	291	(27.7)	x^2= 12.157
Obese (25.0 ≤)	131	(60.4)	759	(72.3)	sd= 1
					p= 0.001
Chronic disease					
No	140	(64.5)	821	(78.2)	x^2= 21.509
Diabetes	25	(11.5)	54	(5.1)	sd= 1
Hypertension	52	(24.0)	175	(16.7)	p= 0.000
Smoking					
Never	129	(59.4)	841	(80.1)	x^2= 42.723
Ever	88	(40.6)	209	(19.9)	sd= 2
					p= 0.000
Alcohol					
Never	200	(92.2)	1004	(95.6)	x^2= 4.538
Ever	17	(7.8)	46	(4.4)	sd= 1
					p= 0.039

The statistical analysis of the study was evaluated with regard to 19 variables in Table 1 (age, education, marital status, body mass index, chronic diseases, smoking and alcohol), Table 2 (parity, age at first birth, breast-feeding, age at menarche, oral contraceptive and HRT use), and Table 3 (cancer history in the first and second-degree relatives) to find their associated with ovarian cancer. It was found that age, marital status, BMI, chronic diseases, smoking, alcohol, parity, breast-feeding, age at menarche, HRT use and cancer history in first/second-degree relatives were important for ovarian cancer. Later, multivariate logistic regression model was formed and these variables were examined to figure out which variables increase or reduce the risk factor for ovarian cancer. Variables that had positive β coefficiency and above one of the exp (β)' value were evaluated as factors increasing the risk for ovarian cancer. However, variables that had negative β coefficiency and below one of the exp (β)' value were considered as the risk reducing factors (Table 4). In addition, Hosmer-Lemeshow test was applied that this multivariate logistic model to decide the accommodation. As the result of this test, it was found that the value of Chi-square was 17.326 and Sig. was 0.015. The meaningfulness and truth degree of model was analyzed with Nagelkerke R Square and Classification Plot Percentage. In this analysis, it was found that Nagelkerke R^2 was 0.132 and many variables in Classification Plot

TABLE 2: Distribution of cases and controls according to reproductive history and menstrual factors.

Factor	Ovarian cancer (n= 217)		Controls (N= 1050)		
	Number	(%)	Number	(%)	P values x^2
Parity					
≤ 2	151	(%69.6)	527	(50.2)	x^2= 27.193
≥ 3	66	(30.4)	523	(49.8)	sd= 1
					p= 0.000
Age at first birth					
≤ 20	75	(43.4)	502	(51.3)	x^2= 5.606
21-29	95	(54.9)	446	(45.6)	sd= 2
≥ 30	3	(1.7)	31	(3.2)	p= 0.061
Breast-feeding (1 year at least)					
Yes	185	(85.3)	883	(84.1)	x^2= 821.535
Never	32	(14.7)	167	(15.9)	sd= 1
					p= 0.000
Age at menarche					
≤ 12	89	(41.0)	176	(16.8)	x^2= 65.813
13-14	103	(47.5)	648	(61.7)	sd= 2
≥ 15	25	(11.5)	226	(21.5)	p= 0.000
Oral contraceptive use					
Ever	28	(12.9)	154	(14.7)	x^2= 0.455
Never	189	(87.1)	896	(85.3)	sd= 1
					p= 0.500
HRT use					
Ever	40	(18.4)	58	(5.5)	x^2= 41.995
Never	177	(81.6)	992	(94.5)	sd= 1
					p= 0.000

Percentage were smaller than 0.05. Consequently, this result indicate that formed model has a good meaningfulness degree, accomodatition and truth.

RESULTS

Table 1 presents the distribution of 217 ovarian cancer cases and 1050 controls according to age and selected general characteristic variables (age, education, marital status, body mass index, chronic diseases, smoking and alcohol). Table 2 gives the distribution of ovarian cancer cases and controls according to reproductive history and menstrual factors (parity, age at first birth, breast-feeding, age at menarche, oral contraceptive and HRT use). The distribution of cases and controls according to family history of cancer (first and second-degree relatives) is presented in Table 3. Table 4 presents the results of multivariate logistic regression analyses.

In general, it was found that age was associated with ovarian cancer (p= 0.002). Higher BMI was associated with a positive ovarian cancer risk, compared to normal BMI (18.5-24.99), and the risk was significant (p= 0.000). When compared to people without diabetes and hypertension, those with diabetes and hypertension had an OR of 2.13 (95% CI: 1.40-3.23), an OR of 2.85 (95% CI: 1.64- 4.98) for ovarian cancer. However, compared to the controls, cases that do not smoke had a negative risk; the OR being 0.29. Similarly, cases that have a negative family history in second-degree relatives had a negative risk for ovarian cancer; the OR being 0.33.

DISCUSSION

In this study; age, BMI, chronic disease, smoking and family history of cancer in second-degree relatives were found to be associated with ovarian cancer.

TABLE 3: Distribution of cases and controls according to family history (mother and sister) of ovarian, breast, and endometrial cancer.

Factor	Ovarian cancer (n= 217)		Controls (N= 1050)		
	Number	(%)	Number	(%)	P values x^2
First-degree relatives					
History of breast cancer					
No	201	(92.6)	1030	(98.1)	x^2= 19.481
Yes	16	(7.4)	20	(1.9)	sd= 1
					p= 0.000
History of over cancer					
No	208	(95.9)	1038	(98.9)	x^2= 4.044
Yes	9	(4.1)	12	(1.1)	sd= 1
					p= 0.044
History of endometrial cancer					
No	195	(89.9)	1035	(98.6)	x^2= 885.231
Yes	22	(10.1)	15	(1.4)	sd= 1
					p= 0.000
History of colorectal cancer					
No	186	(85.7)	1011	(96.3)	x^2= 975.506
Yes	31	(14.3)	39	(3.7)	sd= 1
					p= 0.000
Second-degree relatives					
History of breast cancer					
No	187	(86.2)	1016	(96.8)	x^2= 42.025
Yes	30	(13.8)	34	(3.2)	sd= 1
					p= 0.000
History of over cancer					
No	197	(90.8)	1043	(99.3)	x^2= 15.753
Yes	20	(9.2)	7	(0.7)	sd= 1
					p= 0.000

Our study revealed that age of the woman was found to be a significant risk factor for ovarian cancer. Weiderpass et al and Adler et al reported a positive association between the age of woman and ovarian cancer.[8,24] Our finding of increased risk of ovarian cancer with advancing age was consistent with the findings of these studies.

In epidemiological studies it was reported that higher BMI was a risk factor for developing ovarian cancer.[6,25,26] In our study, the risk gradually increased as the weight increased. OR was 1.96 for the ones with BMI ≤ 25.0. The trend was significant (p= 0.000). However, Fairfield et al reported that BMI was not a risk factor.[27]

Case-control studies have usually reported positive associations between history of diabetes or hypertension and gynecologic cancers such as breast, endometrial and ovarian cancer.[28,29] In a population-based case-control study, Augustin et al found hyperinsulinemia as a factor associated with ovarian cancer.[28] Therefore, our results are in accordance with these studies. Conversely, in a population-based cohort study in Sweden it was reported that those results do not support findings of two earlier cohort studies suggesting diabetes as a risk factor for epithelial ovarian cancer.[8] In two other studies, it was also reported that history of diabetes[24] or hypertension[29] was not risk factors for ovarian cancer. However, our result is supportive of the hypothesis that history of diabetes or hypertension was a strong risk factor for ovarian cancer. As seen in Table 1, 60.4 % of the women in case group and 72.3 % of the women in control group

TABLE 4: The results of multivariate logistic regression analyses.

Factor	B	SE	Df	Sig (p)	Exp(B)	95.0% CI for OR	
						lover	upper
Age							
≤ 49 (ref.: no)				0,002	1		
50-59	-0.30	0.23	1	0,19	0,74	0,47	1,16
60 ≤	0.40	0.22	1	0,07	1,49	0,97	2,29
Body mass index							
Normal (18.5-24.99)					1		
Obese (25.0 ≤)	0.67	0.17	1	0.000	1.96	1.41	2.72
Chronic disease							
No (ref.: no)					1		
Diabetes	0.75	0.21	1	0.000	2.13	1.40	3.23
Hypertension	1.05	0.28	1	0.000	2.85	1.64	4.98
Smoking							
Ever (ref: no)					1		
Never	-1.24	0.18	1	0.000	0.29	0.21	0.41
Second-degree relatives							
History of ovarian cancer					1		
Yes (ref: no)	-1.01	0.31	1	0.000	0.33	0.18	0.0.62
No							
Constant	-1.11	0.39	1	0.079	0.90		

Model Summary

-2 Loglikelihood	Cox & Snell R^2	Nagelkerke R^2
1055.118	0.079	0.132

Hosmer and Lemeshow Test

x^2	Sd	P
17.326	7	0.015

Classification Plot
Observed Groups and Predicted Probabilities
320

```
                0
F               0
R      240      0 1
E               0 1
Q               0 0
U               0 0
E      160      0 0
N               0 0
C               0 0  1 1
Y               0 0  0 0  1
       80       0 0 10 0   1
                00  0 100 0 1  0
                00  0 000 0 0  0
                00  00000000  00  00  0  1 1  1
Predicted

  Prob:    0      ,25           ,5           ,75          1
  Group:  000000000000000000000000000001111111111111111111111111111111
     Predicted Probability is of Membership for 1,00
     The Cut Value is ,50
     Symbols: 0 - ,  00
              1 - 1,00
     Each Symbol Represents 20 Cases.
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were in the obese group. It is known that obesity prepares the ground for chronic diseases such as diabetes and hypertension. Predisposition to such chronic diseases puts Turkish women in a risky group with regard to ovarian cancer.

Our study and other studies have reported that cigarette smoking was associated with an increased risk for different types of ovarian cancer. In population-based case-control studies, Pan et al, Marchbanks et al, Zhang et al and Modugno et al found that current cigarette smoking was a risk factor for mucinous epithelial ovarian cancer.[7,10,11,30] However, Goodman and Tung reported that active tobacco smoking was not a risk factor for invasive ovarian cancer.[31] Our results confirm the hypothesis that smoking is a risk factor for ovarian cancer.

The association between family history of ovarian cancer and risk of the disease was recognized.[32] Lubin et al, Dajan et al, Negri et al, Elit et al, Liede et al and Robson found that women with a family history of ovarian or breast cancer had the highest ovarian cancer risk.[6,15-19] In an additional study, Tung et al reported an even stronger increase in the risk of ovarian cancer associated with positive family history for breast, ovarian or colorectal cancers.[33] Another study, Greggi et al also reported that women with a family history of breast, ovarian or endometrial cancer had major risk factors for ovarian cancer.[34] However, in a population-based case-control study, Bosetti et al reported that family history of breast or ovarian cancer was not associated with an increased risk of ovarian cancer.[20] Our results confirm the higher ovarian cancer risk in women with a family history of ovarian and breast cancer. Yet it is still doubtful whether the women with a positive history of cancer in our country will follow a regular medical control. This is mainly because of the insufficiency of the health services offered in our country and the low level of women's education and awareness.

The results from the current study must be considered in the light of certain limitations. Firstly, the study was carried out in a small group of 217 subjects within a year. The smallness of the case group prevented us from studying the histological types of ovarian cancer separately. Another limitation of the study is that all data were obtained from the women's self-reports. Some of the questions were too difficult for them to remember: i.e. pregnancy cases resulting in dead births, the age of menarche and story of cancer in second-degree relatives. The other limitation of the study concerning the control group was that the patients who were hospitalized for orthopedic, surgical, laryngological clinics were included in the study. The complaints of these patients may have resulted from smoking, body mass index or exposure to HTR. However, the findings and limitations of the study are quite useful in that they illuminate the progressive research in this field.

We conclude that this study indicates that age, BMI and history of diabetes or hypertension were strong risk factors for ovarian cancer.

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