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Ovarian Cancer Risk Factors in a Defined Population Using Rare Event Logistic Regression

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Abstract

Background: This study evaluated the role of family history of cancer and gynecologic factors in relation to the etiology of ovarian cancer in a low socioeconomic population in Iran.

Methods: From 2007-2009 we conducted a screening program on women with insurance coverage provided by the Imam Khomeini Relief Foundation. A total of 26788 women participated in this study of whom 76 cases had ovarian cancer and 26712 were considered as controls. We used rare event logistic (ReLogit) regression analysis with a prior correction method that used the Zelig package in R to obtain odds ratio estimates and confidence intervals.

Results: Ovarian cancer was more frequent among postmenopausal than premenopausal (odds ratio: 2.30; confidence interval: 1.17-4.49) women. We observed increased risk for this disease in women with histories of hormone replacement therapy compared to those with no history (odds ratio: 2.36; confidence interval: 1.13-4.91). A greater increase in ovarian cancer was observed in women with family histories of breast (odds ratio: 2.88; confidence interval: 1.44-5.77), ovarian (odds ratio: 11.27; confidence interval: 5.63-22.54) and all cancer sites (odds ratio: 2.95; confidence interval: 1.71-5.08). However, the use of oral contraceptive pills was significantly associated with lower risk for ovarian cancer (odds ratio: 0.47; confidence interval: 0.28-0.79). There was no association between ovarian cancer and age, marital status, occupation, education level, age at menarche, age at first pregnancy and number of pregnancies.

Conclusion: Ovarian cancer was considered a rare event. Thus we deemed it necessary to explore the associated risk factors using ReLogit with a prior correction method. The risk factors for ovarian cancer were menopause, history of hormone replacement therapy and family history of cancer of the breast, ovaries and other sites. Oral use of contraceptive pills showed a protective effect on risk for ovarian cancer.

Keywords: Ovarian cancer, Screening program, Risk factor, Logistic regression, ReLogit

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Introduction

Ovarian cancer is a common gynecological malignancy, ranking sixth in frequency and seventh for mortality among females worldwide. There were 204,000 cases and 125,000 deaths in 2002.[1] The number of cases diagnosed with ovarian cancer has increased from 137,600 in 1980 to 225,000 in 2008.[2]

The incidence of ovarian cancer varies widely among different populations worldwide with the highest rates reported in Scandinavia, Eastern Europe, Canada, and Africa. The lowest rates have been reported from Asia, with the exception of Japan.[3]

In Iran, ovarian cancer is the 8th most frequent in incidence, 12th in mortality and 16th among all cancers.[4] In Iran the age-standardized incidence rate (ASR) of ovarian cancer in all age groups is much lower than developed countries.[5] Overall, the rate of ovarian cancer in Iran has been reported as 3.9 per 100,000.[5]

An evaluation of median age and most common age group afflicted with ovarian cancer has indicated that this disease in developed countries is observed a decade earlier than other regions, including Iran.[5] However, the five-year survival rate in patients with ovarian cancer in Iran has been reported in 61% of cases which is better than other regions.[4]

Comprehensive studies with consistent findings have shown that infertility, low age at menarche, menopause, first pregnancy after 30 years of age and no breastfeeding increase the risk of ovarian cancer.[6-13] Furthermore, according to several reports, ovarian cancer is associated with obesity, cigarette smoking, alcohol consumption and family history of cancer.[14-20] Although numerous epidemiologic studies have been conducted in relation to the risk factors associated with ovarian cancer, population-based research is sparse, especially among low socioeconomic classes in Iran. Therefore, the aim of the present study is to determine the risk factors associated with ovarian cancer in a low socioeconomic population of Iran.

Materials and Methods

A screening population-based study of breast cancer was conducted from 2007 until 2009. The participants in this study were under insurance coverage sponsored by the Imam Khomeini Relief Foundation (IKRF) and required to declare if they had any history of ovarian cancer.

A total of 26788 women participated in the screening program of whom 76 had ovarian cancer. The control group included 26712 subjects. The IKRF was founded in 1980 to support and increase self-sufficiency of the under-privileged in Iran. Women in this study were mainly from poor and low socioeconomic classes. The present study was conducted on women who resided in Tehran and other Iranian provincial capitals such as Shiraz, Mashhad, Kerman, Kermanshah, Bushehr, Qom, Isfahan, Gorgan, Rasht, and Yazd.

This study was approved by the Ethics Committee of Shiraz University of Medical Sciences. Initially all women were interviewed in order to collect data on general characteristics that included age, educational level, marital status, occupation, socioeconomic status, body mass index, and menstruation and reproductive histories in relation to menopause, age at menarche, age at marriage, age at first pregnancy, number of pregnancies, the use of hormone replacement therapy (HRT), past history of ovary cancer and history of cancer among first degree relatives.[21,22]

Logistic regression has been extensively applied to identify risk factors in observational studies. This popular statistical procedure is unreliable in rare events. A screening program conducted on an apparently healthy population and in a relatively large sample that shows a low incidence of ovarian cancer indicates that this disease is a rare event. In relation to a rare event, the logistic regression method is biased and sharply underestimates the probability of infrequent episodes.[23] Certain corrections are needed to empower the application of logistic regression. King and Zeng[23] have suggested the use of rare event logistic regression with weighting or a prior correction method in rare event data. They designed a simulation program for rare

event data that used the usual logistic regression. The results obtained were compared with those of rare event logistic regression. It was suggested that rare event logistic regression led to less bias coefficient and standard errors compared to logistic regression.

Correction for selecting the dependent variable is made after generating the sample via a case-control design. The slope coefficients are approximately unbiased, whereas the constant term may be significantly biased. The prior correction method adjusts the intercept term and is a rectifying procedure applied to correct the case control design. The corrected intercept is β_0 expressed by the following equation:

$$\beta = \hat{\beta}_0 - \ln\left[\left(\frac{1-\tau}{\tau}\right)\left(\frac{\bar{y}}{1-\bar{y}}\right)\right]$$

Where γ and τ are the disease prevalence in the sample and population, respectively. The slope coefficients are biased in the sample of rare events data and are corrected for rare-events bias ($\tilde{\beta}$) as follows:

$$\tilde{\beta} = \hat{\beta} - bias(\hat{\beta})$$

Where the bias term is expressed by:

$$bais(\hat{\beta}) = (x'wx)^{-1}x'w\xi$$

in which

$$\xi_i = 0.5\,Q_{ii}[(1+w_1)\hat{\pi}_i - w_1],\ Q_{ii}$$

are the diagonal elements of

$$Q = x(x'wx)^{-1}x',\quad w = diag\{\hat{\pi}_i(1-\hat{\pi}_i)w_i\},$$

$$w_i = w_1 y_i + w_0(1-y_i),\quad w_1 = \frac{\tau}{\bar{y}},\quad \text{and}$$

$$w_0 = \frac{1-\tau}{1-\bar{y}}.$$

The prevalence of ovarian cancer has not been reported in Iran and most Asian countries. Therefore, we used the ovarian cancer prevalence in Albania whose incidence was close to the frequency in Iran. The following formula was used to estimate the prevalence of ovarian cancer: Prevalence rate = Incidence rate×duration of the disease which was estimated at 45.5/100000 among Iranian females.[24]

Statistical analysis was performed using statistical analysis software SPSS version 11.5 (SPSS Inc., Chicago, IL, USA). Rare events logistic regression model (ReLogit) analysis with a prior correction was performed using package Zelig in R to determine ovarian cancer risk factors. In the univariate model we calculated both odds ratios (ORs) and confidence intervals (CIs). Covariates with a p-value of less than 0.25 were included in the multiple ReLogit model to determine risk factors.

Results

Of 26788 women who participated in this study, 76 had ovarian cancer. This population-based study consisted of women aged 30 to 88 years. The mean±SD age of subjects with ovarian cancer was 48±10.41 years; for healthy controls it was 45.73±10.15 years.

Table 1 shows the distribution of 76 ovarian cancer cases and 26712 controls according to demographic and clinical features. Table 2 reports univariate ReLogit analysis results. Postmenopausal women were at a higher risk compared to those with menstruation (P<0.01). There was a significantly higher ovarian cancer risk in women who had HRT in the past and in those with histories of breast, ovarian and all other types of cancers in their first-degree relatives. There were no statistically significant differences between cases and controls in terms of age, marital status, occupation, educational level, body mass index, and reproductive factors. Rare event logistic analysis with a prior correction method was performed for variables with a P-value of less than 0.25 on the univariate analysis. Of 15 variables, 10 were selected for the multiple ReLogit model.

The multiple ReLogit result for selected variables is summarized in Table 3. A strong inverse association was observed between oral

Table 1. Demographic results of case and control groups analyzed by the chi-square test.

Variable		Case (n=76) No (%)	Control (n=26712) No (%)	*P*-value	Variable		Case (n=76) No (%)	Control (n=26712) No (%)	*P*-value
Age (years)									
	30-39	14 (0.2)	7656 (99.8)	0.12	**Age at first pregnancy (years)**	≤18	36 (0.3)	12435 (99.7)	0.89
	40-49	30 (0.3)	9781 (99.7)			19-25	31 (0.3)	9958 (99.7)	
	≥50	32 (0.3)	9241 (99.7)			≥26	5 (0.3)	1984 (99.7)	
Marital status									
	Married	17 (0.3)	5048 (99.7)	0.71	**No. of pregnancies**	0-2	15 (0.2)	7882 (99.8)	0.06
	Single	1 (0.2)	663 (99.8)			3-5	39 (0.4)	10217 (99.6)	
	Divorced	23 (0.3)	7588 (99.7)			≥6	21 (0.3)	7807 (99.7)	
	Widowed	32 (0.3)	12578 (99.7)						
Occupation									
	Housewife	65 (0.3)	24082 (99.7)	0.37	**Hormone therapy**	Yes	11 (0.7)	1566 (97.3)	<0.01
	Non-manual	6 (0.5)	1299 (99.5)			No	65 (0.3)	25146 (99.7)	
	Manual	5 (0.4)	1331 (99.6)						
Educational level									
	Illiterate	19 (0.2)	9420 (99.8)	0.17	**Oral contraceptive pills (OCP)**	Yes	30 (0.2)	13576 (99.8)	0.07
	Primary school	37 (0.3)	12144 (99.7)			No	41 (0.3)	11968 (99.7)	
	High school -university	14 (0.3)	3823 (99.7)						
Menopause									
	Yes	40 (0.4)	9280 (99.6)	<0.01	**Breast cancer in first degree relative**	Yes	15 (1.8)	801 (98.2)	<0.01
	No	35 (0.2)	12217 (99.8)			No	61 (0.2)	25911 (99.8)	
Age at menarche (years)									
	≤13	39 (0.3)	13617 (99.7)	0.54	**Cancer in first-degree relative**	Yes	33 (0.8)	4289 (99.2)	<0.01
	≥14	36 (0.3)	10893 (99.7)			No	43 (0.2)	22423 (99.8)	
Age at marriage (years)									
	≤18	55 (0.3)	17509 (99.7)	0.35	**Ovarian cancer in first-degree relative**	Yes	15 (5.5)	258 (98.5)	<0.01
	19-25	55 (0.3)	6904 (99.7)			No	61 (0.3)	26454 (99.7)	
	≥26	1 (0.1)	1187 (99.9)						

contraceptive pills (OCP) and ovarian cancer. There was a 53% risk reduction among women who used OCP compared to those with no OCP use (OR: 0.47; CI: 0.28-0.79). The risk of ovarian cancer was higher among postmenopausal than premenopausal women. In the present study there was an OR of 2.30 in women with no menstruation compared with those in the menstruating age groups.

A positive history of ovarian cancer among first-degree relatives was associated with an increased risk for ovarian cancer (OR: 11.27; CI: 5.63-22.54). A similar relationship was observed between women with positive family histories of breast cancer and increased risk for ovarian cancer (OR: 2.88; CI: 1.44-5.77). There was a significant relationship observed between women with family histories of cancer in all sites (OR: 2.95; CI: 1.71-5.08) and the risk for ovarian cancer. The probability of ovarian cancer among women with a positive history of hormone therapy was approximately 2.5 times higher than those with no history (OR: 2.36; CI: 1.13-4.91). There was no significant relationship between age, occupation, education level and number of pregnancies to ovarian cancer.

Discussion

Ovarian cancer is the most common cause of female mortality among gynecological cancers. According to the American Cancer Society, annually 23400 new cases of ovarian cancer are reported with 3900 deaths.[25]

In Iran, ovarian cancer is the eighth most common cancer among women. Its incidence is rising in recent years.[4] Although predictors for

Table 2. Univariate ReLogit results.

Variable		Odds ratio (95% confidence interval)	*P*-value	Variable		Odds ratio (95% confidence interval)	*P*-value
Age (years)	30-39	1		**Age at first pregnancy (years)**	≤18	1	
	40-49	1.64 (0.87-3.10)	0.12		19-25	1.08 (0.67-1.74)	0.76
	≥50	1.85 (0.99-3.48)	0.05		≥26	0.95 (0.37-2.42)	0.91
Marital status							
	Married	1		**No. of pregnancies**	0-2	0.71 (0.37-1.39)	0.32
	Single	0.97 (0.09- 5.39)	0.75		3-5	1.40 (0.82-2.39)	0.21
	Divorced	0.89 (0.48-1.67)	0.72		≥6	1	
	Widowed	0.75 (0.41-1.34)	0.33				
Occupation							
	Housewife	1		**Hormone therapy**	Yes	2.82 (1.49-5.36)	<0.01
	Non-manual	1.84 (0.80-4.27)	0.15		No	1	
	Manual	1.53 (0.61-3.80)	0.36				
Educational level							
	Illiterate	1		**Oral contraceptive pills (OCP)**	Yes	0.65 (0.40-1.04)	0.07
	Primary school	1.49 (0.86-2.59)	0.16		No	1	
	High school -university	1.83 (0.92–3.66)	0.08				
Menopause							
	Yes	2.12 (1.34-3.33)	<0.01	**Breast cancer in first-degree relative**	Yes	8.16 (4.61-14.41)	<0.01
	No	1			No	1	
Age at menarche (years)	≤13	1.15 (0.72-1.82)	0.53	**Cancer in first-degree relative**	Yes	4.03 (2.55-6.34)	<0.01
	≥14	1			No	1	
Age at marriage (years)							
	≤18	1		**Ovarian cancer in first-degree relative**	Yes	25.84 (1.45-46.07)	<0.01
	19-25	0.89 (0.53-1.50)	0.66		No	1	
	≥26	0.44 (0.06-3.17)	0.41				

ovarian cancer have been investigated in developed countries, the epidemiological risk factors remain unexplored in other parts of the world. Evaluation of factors involved in ovarian cancer prognosis will assist with early disease detection and improve quality of life when considering the lack of changes in long-term survival of patients.

We conducted this population-based screening study in a low socioeconomic population. This study aimed to investigate the importance of socio-demographic and reproductive risk factors in relation to ovarian cancer susceptibility among Iranian women with insurance coverage sponsored by IKRF. The impetus for conducting this study was as follows. As ovarian cancer is a rare event in population-based screening, the present study has attempted to use ReLogit analysis with a prior correction, which was more precise in estimating the ovarian cancer risk factors than logistic regression.

Our findings showed that OCP use was associated with decreased risk of ovarian cancer in Iranian women. However, menopause, history of HRT and family history of breast and ovarian cancers in addition to cancer of all sites were associated with increased ovarian cancer risk. In contrast we observed no association between age, occupation, education level and other reproductive factors.

Our study revealed that positive family histories of ovarian and breast cancers in addition to a familial background of cancer of all sites were significant risk factors for ovarian cancer.

Table 3. Multiple ovarian cancer risk factors modeled with ReLogit analysis.

Variable		Odds ratio (95% confidence interval)	*P*-value
Age (years)	30-39	1	
	40-49	1.17 (0.35- 2.59)	0.70
	≥50	1.31 (0.50- 3.42)	0.58
Occupation			
	Housewife	1	
	Non-manual	1.23 (0.40- 3.74)	0.72
	Manual	0.87 (0.26- 2.90)	0.82
Educational level			
	Illiterate	1	
	Primary school	1.81 (0.95- 3.43)	0.07
	High school -university	2.04 (0.80- 5.22)	0.14
No. of pregnancies			
	0-2	0.82 (0.34-1.97)	0.66
	3-5	1.45 (0.76-2.79)	0.26
	≥6		
Menopause			
	Yes	2.30 (1.17- 4.49)	0.01
	No	1	
Oral contraceptive pills (OCP)			
	Yes	0.47 (0.28- 0.79)	<0.01
	No	1	
Hormone therapy			
	Yes	2.36 (1.13- 4.91)	0.02
	No	1	
First-degree relative with cancer			
	Yes	2.95 (1.71-5.08)	<0.01
	No	1	
First-degree relative with breast cancer			
	Yes	2.88 (1.44- 5.77)	<0.01
	No	1	
First-degree relative with ovarian cancer			
	Yes	11.27 (5.63- 22.54)	<0.01
	No	1	

Moorman et al. and Salehi et al. reported that ovarian or breast cancers in relatives was associated with increased risk for ovarian cancer.[26,27] In a case-control study, positive familial backgrounds of ovarian and breast cancers were associated with heightened risk for ovarian cancer among Italian women.[17] Studies performed by Greggi et al. and Nesrin et al. also reported a higher risk of ovarian cancer among women with positive family histories of ovarian cancer.[28,29] Breast cancer in relatives was considered an increased risk factor for ovarian cancer among women aged 11 to 71 years in Iran.[30] Negri et al. and Tung have reported that family history of cancer of all sites augmented the probability of developing ovarian cancer.[17,31] In contrast, a case control study conducted by Soegaard et al. showed no relationship between breast cancer in a first degree relative and the risk for ovarian cancer.[20] Pasalich also reported no association between a family history of ovarian and breast cancer and risk for ovarian cancer.[32]

Numerous epidemiological studies[3,7,27,32-35] reported strong evidence of a negative association between OCP and ovarian cancer. Our findings were fully compatible with these studies. A pooled analysis of 45 cohort and case control studies from 21 countries reported an overall relative risk of 0.73 for women who used oral contraceptives compared to those who never used

this method of contraception. There was a protective association observed between duration of OCP consumption and ovarian cancer risk in most previous studies.[25,36,37] In a cohort study, Tsilidis et al. reported a significantly lower risk of 45% for ovarian cancer in women who used OCP for 10 or more years compared to those who used OCP for one year or less.[12] Unfortunately, in the current study, information about duration of OCP use was not available.

Data from this study indicated that menopause was associated with an increased risk for cancer. Yen et al., in a case control study in north Taiwan, reported an approximately two-fold risk for ovarian cancer that was significantly higher in postmenopausal compared with premenopausal females.[6] However, Pasalich et al. reported no significant association between menopausal status and risk of ovarian cancer.[32]

An excessive risk for ovarian cancer has been established among women with a history of HRT.[38,39] In our study there was a greater than two-fold risk in women with histories of HRT compared to those with no history. In a meta-analysis of 42 cohort, case control, clinical trial and cancer registry studies, Greiser et al. reported that estrogen (ET) therapy increased the risk for ovarian cancer by 28% and estrogen/progestin therapy (EPT) increased this risk by 11%.[40] Fernandez et al. investigated the relationship between HRT and the risk of various cancers in women aged 45 to 79 years. They found no significant association between HRT and ovarian cancer risk, but observed a heightened risk for HRT-related gallbladder, breast, endometrial and urinary bladder cancers.[41] Another study reported no significant association between HRT and the risk for ovarian cancer among women in Southern China.[32]

Contradictory results have been reported on the relationship between menarche and the risk for ovarian cancer. Several epidemiological studies suggested that early menarche increased the risk of ovarian cancer[11,26,42,43] whereas others reported no significant association between menarche and ovarian cancer risk.[1,12] In the present study we have observed no significant relationship between age at menarche and ovarian cancer risk. Therefore, larger studies are needed to evaluate the effect of age at menarche on ovarian cancer.

Several studies detected a decreased risk for ovarian cancer with increasing parity number.[32,43] Pajenga et al. and Le et al. observed a significantly higher risk for ovarian cancer in nulliparous women compared to those with multiple births.[1,42] Unexpectedly, in the present study there was no significant association detected between parity and disease risk. The present study showed that reproductive factors, with the exception of menopause, were not significantly associated with ovarian cancer. The subjects were from a low socio-economic class, therefore reproductive factors showed a similar distribution in both case and control groups.

The limitation of this study was that the results obtained could not be extended to the general population. We explored the risk factors involved in ovarian cancer in low socioeconomic classes in Iran. Therefore the risk factors might differ for women from other populations in Iran.

In conclusion, our findings supported the protective effect of OCP on risk for ovarian cancer. Menopause, history of HRT, family history of breast and ovarian cancers in addition to a family background of cancer at multiple sites raised the risk for ovarian cancer. These data showed that with the exception of menopause, reproductive factors were less important than other conditions for developing ovarian cancer in a low socioeconomic population in Iran.

Conflict of Interest

No conflict of interest is declared.

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