

# Hormonal risk factors for ovarian cancer in the Albanian case-control study

Edlira Pajenga<sup>1\*</sup>, Tefta Rexha<sup>2</sup>, Silva Çeliku<sup>3</sup>, Gazmend Bejtja<sup>4</sup>, Mimoza Pisha<sup>5</sup>

<sup>1</sup>Department of Biology, Faculty of Natural Science, "A. Xhuvani" University, Lagja 11 Nentori, street Rinia, 3000 Elbasan, Albania.

<sup>2</sup>Department of Biology, Faculty of Natural Science, University of Tirana, Blv. Zogu I, 1000 Tirana, Albania. <sup>3</sup>Division of Gynecology, Oncology Hospital "Mother Tereza", Dibra 372, 1000 Tirana, Albania. <sup>4</sup>Division of Public Health, B. Curri 1, 1000 Tirana, Albania. <sup>5</sup>Medical Center, lagja 5 Maj, 3000 Elbasan, Albania.

## ABSTRACT

The role of reproductive factors in the aetiology of ovarian cancer had been evaluated in hospital-based case-control study conducted in Albania, providing a total dataset of 283 cases and 1019 controls. Logistic regression models were used to obtain relative risk (OR) estimates. The present results showed that parity had protective effects which increased until the fourth birth and the trend in risk was significant ( $p < 0.01$ ). In each stratum and overall, nulliparous women appeared to be at highly increased risk compared to those who had different number of births (OR=12.5, 95% CI: 2.4-63.8). Evaluation of early age at menarche and late age at menopause, showed statistically significant increased risk. Furthermore, increased risk was observed between pre-menopausal women and never-married nulliparity women, respectively (OR=1.44 95% CI: 0.88-2.36; OR=8.98, 95% CI: 1.44 - 56.14), but ovarian cancer risk was reduced for hysterectomized women. These findings suggest that Albanian women have risk factors similar to women in western countries.

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KEY WORDS: ovarian cancer, reproductive factors, menstrual factors, multivariate analysis

## INTRODUCTION

Cancer of the ovary is among the most common female genital tract cancers and has the worst prognosis. This is largely caused by the fact that these cancers are detected at late stage of disease, because of absence of early clinical symptoms. Consequently, early events in ovarian carcinogenesis remain remarkably unknown [1]. Most established hormone-related risk factors such as parity, oral contraceptive use and hysterectomy [2-10] are associated with only a modest to moderate protective effect on ovarian cancer risk, whereas others (e.g., age at first birth) show no consistent association. Although the modest and inconsistent associations may be attributable to variation in study design, it is also possible that they result from disease heterogeneity. In few studies age at menarche was a strong predictor of ovarian cancer risk [11] and late age at menopause increased risk modestly in some [12, 13]. In other epidemiological studies, differences were found,

although specific findings had not been consistent across studies. Associations reported in some studies for family history of ovarian cancer [8, 14] seems to increase risk. Albanian women have a number of different reproductive experiences and lifestyle habits compared with those of other populations. A fertility rate in 1950 of 6.1 children per woman of child-bearing age has changed to 3 children in 1990 [15]. While the nature of over-nutrition in the urban dwellers does not seem much different from the situation in richer European countries where it is rooted in an increasing sedentary lifestyle, together with a "diet of affluence". In Albania, the incidence of ovarian cancer is lower than in western countries, with the incidence rate per 100 000 women being 7.2 in 2008 compared to 9.7 in western union countries [16]. However, incidence rates are rising, and the epidemiology of ovarian cancer in Albania, remains undefined, without any previously investigation undertaken. Thus, to evaluate the influence of risk factors in Albania and to determine if factors in this lower-incidence area differ from those estimated in other western countries, we conducted a case-control study in Albania.

## MATERIALS AND METHODS

### Patients

We began collecting data for ovarian cancer cases from 1 January 2000 through 31 December 2005, identifying 283

\* Corresponding author: Edlira Pajenga, Department of Biology, Faculty of Natural Science, University A. Xhuvani, Elbasan, Lagja 11 Nentori, street Rinia, 3000 Elbasan, Albania, Phone: +35567 20 488 22 Fax: +355 542 52593 e-mail: eda@enet.al

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women aged 24-74 years old with a primary diagnosis ovarian cancer as potentially eligible subjects for this study.

### Procedures

Using data from a population-based case-control study, we examined risk factors for ovarian cancer after subdividing cases to replicate analyses from previous studies and to evaluate these hypotheses. Hormone-related risk factors of ovarian cancer available for analysis included the following: age at menarche, age at menopause, number of children born, age at first full-term pregnancy, history of abortion and hysterectomy. A pregnancy was classified as full-term if it resulted in a livebirth or lasted 7 or more months; otherwise, it was considered a spontaneous or induced abortion. We, also, tested family history of ovarian cancer for which the relevance of hormones is less established. First, we evaluated various forms of defined variables and then we concluded in results reported here for variables determinate by using the fewest categories that reached relevant associations. Women not having menstrual cycles were considered as perimenopausal and were grouped with premenopausal women. The remaining women were considered postmenopausal if their cycles ended naturally or from surgery in which both the uterus and ovaries were removed, or from surgery in which one ovary remains intact but age at diagnosis was more than 55 years. Cases were identified from the files of the Albanian Central Cancer Registry belonging to the Oncology Hospital. Diagnoses were confirmed histologically, through a biopsy. Controls were used in another population-based case-control study of breast cancer in Albania. Controls were obtained from other hospitals through random selection for non-neoplastic, non-gynecological conditions. These women were outpatients receiving primary care, in the same source area as the cases. The main reasons for the selected controls visiting the outpatient clinic were gastrointestinal upsets (31%), respiratory infections (23%), and skin diseases (17%), among others. The team of interviewers was previously trained in the logistic aspects of this study. Controls answered a standardized questionnaire on age (5-year categories), marital status, age at menarche (<=12, 13,14, 15, >=16 years), number of abortions, number of children (0, 1-2, 3-4, 5-6, >6 or full-term pregnancies), age at menopause (premenopausal, <50, or ≥ 50 years), hysterectomy (no or yes), and family reproductive history of ovarian cancer. The study protocol was approved by the institutional Review Board of Tirana University in February 2007.

### Statistical analysis

We had first analyzed frequency and distribution and then we used Pearson correlation coefficient (R) to measure the strength of linear dependence between dependent and independent variables. Chi square test of Pearson and *p*-

value were done to see if the connection is statistically significant. Then, the relationship between case-control status and all variables were estimated in univariate analysis and in multivariate analysis using binary logistic regression for dependent variable was dichotomous case-control [17]. All primary exposure variables were included in the models to account for potential confounding effects. Women for whom values for one or more of the variables in the models were missing were eliminated from the analyses.

### Statistical analysis

These analyses were performed using software SPSS 15. We used 95% confidence intervals (CIs) testing to evaluate whether variations in risks by these categories were statistically significant. All statistical tests were two-sided, and *p* values of 0.05 or less were considered significant.

## RESULTS

To our knowledge, this is the first nationwide epidemiologic study in Albania, to evaluate ovarian cancer risk in relation to reproductive and menstrual factors. The median age at diagnosis for cancer of the ovary was 48 years of age. Approximately 2.9% were diagnosed between age 19-25 years; 5.4% between 26 and 35 years; 8.6% between 36 and 40 years; 6.8% between 41 and 44 and 76% 45+years of age. Selected characteristics of patients divided by risk factors are presented in Table 1. Age at first birth was similar in cases and controls. Statistically significant differences were only observed in the number of children born in women with ovarian cancer (2.8 children) and the controls (3.17 children); in the age at menarche (14.1 for cases and 14.7 for controls) and in the age at menopause (49 for cases and 42 for controls) with *p*<0.001. Table 2, shows odds ratios for ovarian cancer according to reproductive factors and family history. Among the 283 cases, 54 women (19 percent) had ever been pregnant; among the 1019 controls, the corresponding number was 9 women (0.9 percent). In our study, parous women were consistently at a lower risk of ovarian cancer compared with nulliparous women. The level of protection increased with the number of childbirths, but pregnancy after the fourth one did not decrease the risk further. There were insufficient numbers

**TABLE 1.** Baseline characteristics of case patients and control subjects of Albanian population, 2000-2005

	Cases		Controls		<i>p</i> (chi square)
	Mean	SD	Mean	SD	
Age at menarche	14.14	1.439	14.65	1.534	<0.05
Age at first birth	22.29	4.73	22.46	3.052	<0.5
Number of births	2.78	2.212	3.17	1.427	<0.05
Age at menopause	48.85	6.238	42.2	15.48	<0.05

**TABLE 2.** Odds ratios and 95% confidence intervals of ovarian cancers according to selected reproductive factors and family history, Albania, 2000-2005.

	Multivariate Model			
	Cases	Controls	OR	95% CI
<b>Number of births</b>				
>6	19	0.41	1.00	Referent
5-6	33	118	0.41	0.16-1.06
3-4	88	503	0.31	0.13-0.73
1-2	89	357	0.59	0.24-1.44
0	54	9	12.52	2.4-63.01
p for trend				<i>p</i> =0.002
<b>Age at first birth</b>				
<20	26	40	1.00	Referent
20-24	160	181	1.21	0.4-3.62
25-29	81	57	0.74	0.21-2.56
>=30	16	5	0.34	0.07-1.74
<b>Abortions</b>				
No	195	725	1.00	Referent
Yes	88	294	1.24	0.86-1.79
<b>Marriage</b>				
Yes	253	1014	1.00	Referent
No	30	4	8.98	1.44-56.14
<b>Hysterectomy</b>				
Yes	36	78	0.59	0.41-1.39
No	257	941	1.00	Referent
<b>Family history</b>				
No	270	739	1.41	0.66-3.01
Yes	13	52	1.00	Referent

Legend: Adjusted for age, age at menarche, age at marriage, number of births, family history, abortions, menopause status.

to permit a multivariate analysis among more categories of parity (e.g., parity six or more). Women with 1-2 births had the excess risk 28% compared to women with 3-4 births (OR= 0.59 95% CI =0.24-1.44) and a test for trend by number of births was statistically significant (*p*=0.002). Compared with parous women, nulliparous women had a twelve-fold significant elevated risk of developing ovarian cancer. Age at first birth did not indicate any risk for ovarian cancer. In addition, history of hysterectomy offer protection against ovarian cancer (OR=0.59, 95% CI=0.41-1.39). The sample size limits further analyses according to histologic subtype comparisons. The risk of ovarian cancer was higher among never-married women than ever-married women. The results of the present study revealed that, compared with women who ever-married, women who never-married were at about, significantly nine-fold elevated risk of ovarian cancer in multivariate analysis. Incomplete pregnancies (spontaneous and induced abortions) modestly increased the risk of ovarian cancer (OR=1.24, 95% CI=0.86-1.79). In this study relative risk of ovarian cancer for family history is 41% lower comparing with women without family history as shown in Table 2. Decreased risks appeared with older age at menarche (*p*=0.009). Overall, age at menarche of 16 years or older re-

**TABLE 3.** Odds ratios and 95% confidence intervals of ovarian cancers according to menstrual factors, Albania, 2000-2005.

	Multivariate Model			
	Cases	Controls	OR	95% CI
<b>Age at menarche*</b>				
<=12	38	55	2.88	1.4-5.92
13	34	160	1.12	0.59-2.13
14	128	325	2.88	1.78-4.66
15	44	222	1.11	0.62-1.99
>=16	39	260	1.00	Referent
p for trend				<i>p</i> =0.009
<b>Menopause*</b>				
No	128	605	1.44	0.88-2.36
Yes	155	414	1.00	Referent
<b>Age at menopause**</b>				
<50	61	312	1.00	Referent
>=50	94	154	2.13	1.27-3.59

Legend: \* Adjusted for age, age at menarche, age at marriage, number of births, family history, abortions. \*\*Adjusted for age at menarche, age at marriage, number of births, family history, abortions, menopause status.

duced the risk 2.8 times comparing to the age 14 years and the results were statistically significant as shown in Table 3. As for the state of menopause, a relative risk of about 1.4 was found in those women who were in the still menstruating age-groups compared with those no longer menstruating. A more than two-fold risk (OR=2.13, 95% CI= 1.27-3.29) was found for women whose menopause occurred after age 49 compared to menopause before age 50 years. Late age at menopause was found to be associated with increased risk of ovarian cancer.

## DISCUSSION

Although, risk factors for ovarian cancer have been studied in high incidence areas, epidemiological characteristics remain relatively unexplored elsewhere. In Albania, the incidence of ovarian cancer is lower than in most western countries. However, ovarian cancer rates have been rising in Albania in recent years and ovarian cancer ranks ninth by neoplasm among women. Despite this rising incidence rates, the epidemiology of ovarian cancer in Albania, remained undefined. When all cases were compared with controls, and after adjustment for potential confounding effects, an increased ovarian cancer risk was associated with nulliparity, early age at menarche and late age at menopause. The strengths of our study include its nationwide, population-based design and reliable ascertainment of cases. We can not exclude as a potential source of bias recall of early events. Women over 55 years might have reported improperly any reproductive or hormonal factor such as age at menarche while pregnancies are expected to have been reported accurately. The results are based on data from the Albanian national registers. However, it was not possible to get detailed individual data. There-

fore, the role of confounding factors, e.g. lifestyle, using of oral contraceptive and hormone replacement therapy etc., could not be evaluated. Our results discovered a strong association between nulliparous women and ovarian cancer risk. Nulliparous women had 12.5 times higher risk comparing to parous women. Excessive stimulation of hormones such as pituitary gonadotropins, estrogens and androgens is suggested to increase ovarian cancer risk [18]. Pregnancies suppress pituitary gonadotropin secretion and increase circulating progesterone levels. We, also, have seen a difference between the number of never-married women and nulliparous-married women, which may reflect difficulties in conceiving, but we cannot form any reliable conclusion regarding effect of subfertility, which needs to be studied further. In other studies, parity is the factor associated with ovarian cancer, which is the best documented. Studies carried out in China, USA and Sweden [2, 3, 4, 7, 9, 10, 11, 19, 20, 21, 22, 23] have found that the number of children significantly reduces the risk of ovarian cancer. The protective effect of parity is also confirmed in the present investigation. Further analyses on parous women showed that there was no evidence of an association with age at first pregnancy. In other studies increasing age at first birth reduced the risk of ovarian cancer [2, 9, 10, 22, 23] or found no association [24]. A moderate risk of ovarian cancer was found for abortion but insignificant. Some studies found negative association between risk of ovarian cancer and history of abortion [2, 10] or even no association [9, 19]. Family history appeared not to be related to ovarian cancer risk. In addition, the number of cancer cases in this group was low (approximately 5% of all patients) supposing that hereditary factors are not important in the aetiology of ovarian cancer. In other studies, family history is associated with the risk [8, 14]. In our study, age at menarche has a negative association with ovarian cancer risk while in others the relationship between age at menarche and ovarian cancer is controversial. A younger age at menarche increased the risk of ovarian cancer in several studies [7, 11], whereas others [9, 21, 23, 25, 26] found little or no association. Early menarche is associated with early onset of ovulatory cycles and with higher concentrations of estradiol level during the puberty before the menarche and after the menarche [27]. Excessive exposure of ovarian tissue by estrogens increased ovarian cancer risk [18], thus a protective effect of late age at menarche is in accordance with the incessant ovulation [28] and hormonal hypothesis [29, 30]. Late age at menopause was found to be associated with two-fold significant increased risk of ovarian cancer. Epidemiological studies have suggested that age at menopause is an important factor in ovarian cancer risk. Analyses in Europe [12, 13, 31, 32] indicated a significant increase, whereas in Asia, Africa and United States [7, 11, 21, 23, 25] studies showed no relationship. The finding of the present

study showed that premenopausal women had an increased risk of ovarian cancer compared with postmenopausal women. The 44 % increased risk among premenopausal women who are still exposed to higher level of estrogens indicates the influence of sex hormones in the risk of ovarian cancer. The risk of ovarian cancer decreased at the group of women with history of hysterectomy as seen in other studies [5, 6, 10, 33].

## CONCLUSIONS

We observed that parity, late age at menarche, younger age at menopause and hysterectomy reduced risk against ovarian cancer, while age at first birth and family history had no influence on ovarian cancer risk. These data show that risk factors for Albanian women are similar to those found in western countries, although great differences in incidence rates between them.

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## DECLARATION OF INTEREST

The authors declare no conflict of interest for this study.

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