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DETERMINANTS OF OVARIAN CANCER RISK. REPRODUCTIVE EXPERIENCES AND FAMILY HISTORY.
DETERMINANTËT E RISKUT TË KANCERIT TË OVAREVE. EKSPERIENCAT RIPRODHUESE DHE HISTORIA FAMILJARE.

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ABSTRACT

The role of reproductive factors in the aetiology of ovarian cancer has been evaluated in hospital-based case-control study conducted in Albania, providing a total dataset of 283 cases and 1019 controls. Logistic regression model were used to obtain relative risk (OR) estimates. The risk decreased with increasing number of births (till 6 births) and the trend in risk was significant (p less than 0.01). In each stratum and overall, nulliparous women appear to be at highly increased risk compared to those who have different number of births (OR=12.5, 95%, CI: 2.4-63.8). In this study, the OR of abortions and ovarian cancer risk was 1.24 (95%, CI: 0.8-1.7). Evaluation of the relationship between early age at menarche and late age at menopause, shows increased risk. Effects of parity, late age at menarche, early age at menopause and absence of abortions induce biological mechanisms which offer protection from ovarian cancer risk.
Key words: ovarian cancer; reproductive factors; menstrual factors; family history; multivariate analysis.

PËRMBLEDHJE

Roli i faktorëve riprodhues në etiologjinë e kancerit të ovareve është analizuar në një studim rast-kontroll të realizuar në Shqipëri, me 283 raste dhe 1019 kontrolle. Regresioni logjistik është përdorur për të vlerësuar riskun relativ (OR). Risku ulet me rritjen e numrit të lindjeve (deri në 6) dhe tendenca është sinjifikante (p më i vogël se 0.01). Krahasuar me të gjitha kategoritë, gratë pa fëmijë kanë risk më të lartë krahasuar me ato që kanë numër të ndryshëm lindjesh (OR=12.5, 95%, CI: 2.4-63.8). Në këtë studim, OR e aborteve dhe risku i kancerit të ovareve është 1.24 (95% IC: 0.8-1.7). Vlerësimi i marrëdhënies midis moshës së re në menarke dhe moshës së vonët në menopauzë tregon rritje të riskut. Lindja e fëmijëve, mosha e vonët në menarke, mosha e re në menopauzë dhe mungesa e aborteve induktojnë mekanizma biologjikë të cilët ofrojnë mbrojtje ndaj kancerit të ovareve.

Fjalët kyçe: kanceri i ovareve; faktorët riprodhues; faktorët menstrualë; historia familjare; analiza shumëfaktorialëshe.

INTRODUCTION

A consistent finding of epidemiologic studies on ovarian cancer is a reduced risk with increasing parity (1, 2, 4, 16, 17). In few studies age at menarche was a strong predictor of ovarian cancer risk (17) and late age at menopause increased risk modestly in some (7, 10). Family history of ovarian cancer (11, 16) seems to increase risk .

The "incessant ovulation" in which the ovarian epithelium is recurrently repaired and exposed to estrogen-rich follicular fluid (5) and gonadotropin hypotheses indicates higher risk of ovarian cancer after elevated levels of gonadotropins, which may stimulate the ovarian epithelium, (12, 14) have been central to the discussion of ovarian carcinogenesis and have been supported by both epidemiologic findings and recent advance in molecular biology. Still, the cause of ovarian

cancer remains obscure, and the hypotheses are not consistent with all epidemiologic findings.
The focus of this nationwide case-control study is how reproductive events and family history relate to the risk of ovarian cancer with regard to etiologic hypotheses.

MATERIALS AND METHODS

A case-control design of 283 women with ovarian cancer and their 1019 female controls was held during 2000 till 2005. Cases were identified from the files of the Albanian Cancer Registry belonging to the Oncology Hospital. Diagnoses were confirmed histologically, through a biopsy. Controls were obtained from other hospitals through random selection for for acute, non-neoplastic, non-gynecological conditions. They were selected from Elbasan Central Hospital (305 patients), Tirana Surgical Hospital (409 patients) and Durres Polyclinic (305 patients). Controls answered a standardized questionnaire on age, marital status, age at menarche, number of abortions, number of children, age at menopause, and family history of ovarian cancer.
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 sqaure 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 (taking into account the effects of all variables more than one dependent variable to be analyzed simultaneously) using binary logistic regression for dependent variable was dichotomous case-control (Breslow & Day). OR (odds ratio) measured the value of the risk and if the odds ratio was greater than one and the lower bound of the confidence interval did not go below 1, then the proposed risk factor acted as a significant risk to disease. These analysis were performed using software SPSS 15.

RESULTS AND DISCUSSION

The results observed in this low-risk population are consistent with those found in high-risk western population and support the etiological hypothesis of "gonadotropin" mechanism (6).
To our knowledge, this is the first nationwide epidemiologic study in Albania, to evaluate ovarian cancer risk in relation to reproductive and menstrual factors.

Number of births *			Multivariate	Model	
	Cases%	Control %	OR	95% CI	
> 6	6.8	3.1	1.00	P=0.002	
5. – 6	11.6	11.6	0.41	0.16	1.06
3. – 4	31.1	49.4	0.31	0.13	0.73
1. – 2	31.5	35.0	0.59	0.24	1.44
0	19.1	0.9	12.524	2.46	63.83
Family history *					
No	95.3	93.4	1.41	0.66	3.01
Yes	4.7	6.6	1.00		
Aborts *					
No	69.0	71.1	1.00		
Yes	31.0	28.9	1.24	0.86	1.79

*Adjusted for age, age at menarche, age at marriage, number of births, family history, aborts, menopause status.

TABLE 1. Odds ratios and 95% confidence intervals of ovarian cancers according to *selected* reproductive factors and family history, *Albania, 2000-2005*

Table 1, shows odds ratios for ovarian cancer according to reproductive factors and family history. 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 (fig. 1), but pregnancy after the sixth one did not decrease the risk further. 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). Nulliparious women had 12.5 times higher risk comparing to parious women which indicates that events during reproductive years may be determinant in the risk of ovarian cancer.

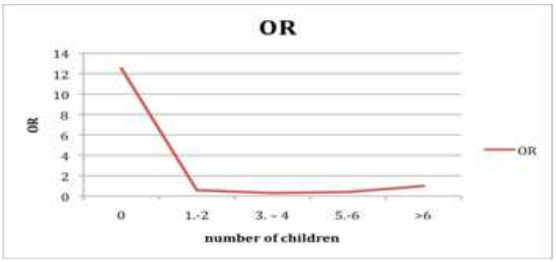

Figura 1. OR and number of children in ovarian cancer

In other studies, parity is the factor associated with ovarian cancer, which is the best documented. Studies carried out in China, USA and Sweden (1, 2, 4, 15, 17, 18) have found that the number of children significantly reduces the risk of Ovarian Cancer.

The decreased risk of ovarian cancer associated with multiparity support Fathalla's theory, and suggest preventing ovulation can protect against ovarian cancer (17, 19).

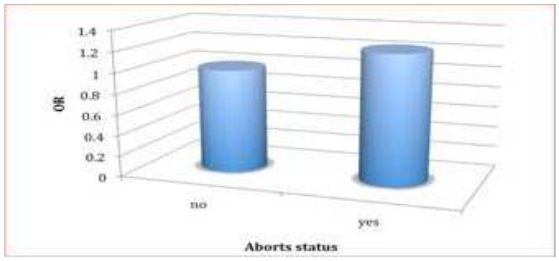

Figura 2. OR and status of aborts in ovarian cancer.

Incomplete pregnancies (spontaneous and induced abortions) modestly increased the risk of ovarian cancer (OR=1.24 95% CI=0.86-1.79) (Table 1; fig. 2). Several studies show negative (1,18) or even no association (4).

Age at menarche *			Multivariate Model		
	Cases%	Control %	OR	95% CI	
<=12	13.5	5.1	2.875	1.40	5.92
13	12.0	15.7	1.122	0.59	2.13
14	45.0	31.9	2.88	1.78	4.66
15	15.5	21.8	1.11	0.62	1.99
>=16	13.9	25.5	1.00	P=0.009	
Menopause *					
No	45.1	59.4	1.44	0.88	2.36
Yes	54.9	40.6	1.00		
Age at menopause**					
< 50	39.6	67.0	1.00		
>= 50	60.4	33.0	2.13	1.27	3.59

* Adjusted for age, age at menarche, age at marriage, number of births, family history, aborts
* *Adjusted for age at menarche, age at marriage, number of births, family history, aborts, menopause status.

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

In this study relative risk of ovarian cancer for family history is 41% lower comparing with women without family history (table 1) in addition, the number of cancer cases was low supposing that hereditary factors are not important in the etiology of ovarian cancer. In other studies, family history is associated with the risk (11, 16).

Decreased risks appeared with older age at menarche, Overall, age at menarche of 16 years or older reduced the risk 2.8 times comparing to the age 14 years and the results were statistically significant (table 2 , fig. 3).

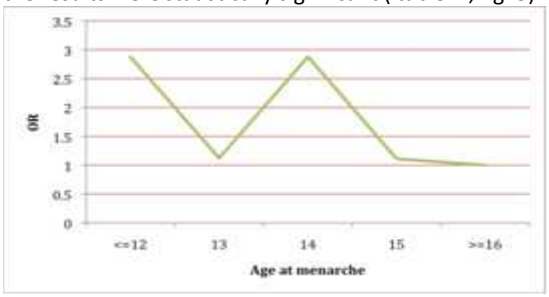

Figura 3. OR and age at menarche of ovarian cancer.

In our study, age at menarche has a negative association with ovarian cancer risk while in others the relationship between the age at menarche and ovarian cancer is controversial. A younger age at menarche increased the risk of ovarian cancer in several studies (8,17), whereas others (9,19) found little or no association.

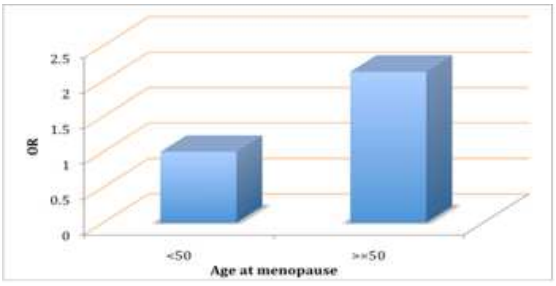

Figura 4. OR and age at menopause of ovarian cancer.

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 mentruating. This elevation in risk, indicates that tumours in women who are still being exposed to premenopausal levels of sex hormones may be growing faster (table 2, fig. 5).

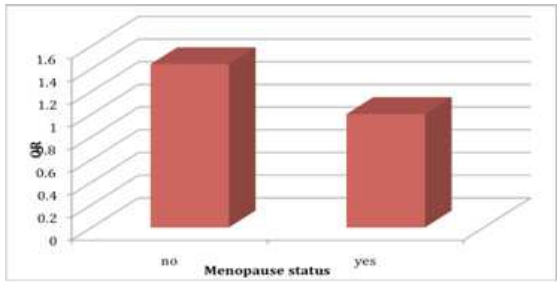

Figura 5. OR and menopause status in ovarian cancer .

A young age at menopause reduced about 2 times the risk of ovarian cancer (OR=2.13 95% CI= 1.27-3.29)(table 2, fig 4) while analyses in Europe (7, 10) indicate a significant increase (OR =1.9), whereas in Asia and United States (8, 9,17, 19) studies show no relationship.

Ovulatory trauma remains an important mechanism for initiating ovarian carcinogenesis, but endogenous hormones will play an important role in the development of these tumor. During the abortion, high levels of circulating estrogens not opposed by progresterone will explain elevated risk with incomplete pregnancies.

Suppression of circulating estrogens levels, may represent a biological mechanism accounting for the protective effects of pregnancy, late menses and early menopause against carcinogenesis of ovarian cancer.

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