

POPULATION-BASED CASE-CONTROL STUDY OF BREAST CANCER IN ALBANIA

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Abstract - In Albania, breast cancer is an important cause of death among women, with increasing incidence from 65 cases in 1970, to 400 cases in 2007. This is the first study concerning breast cancer risk factors in Albania. We used a population-based case-control study of 948 women with breast cancer compared with 1019 controls recruited from other hospitals through random selection. Early age at menarche was found to be a significantly strong risk factor during the pre- and postmenopausal groups with OR 10.04 and 12.1, respectively. In addition, nulliparity is associated with higher risk while abortion did not indicate any influence in the multivariate model. The findings from this study have shown that reproductive and menstrual variables are significant predictors of breast cancer risk in Albanian women, as seen in studies of other western countries.

Key-words: Breast cancer, reproductive factors, menstrual factors, multivariate analysis.

INTRODUCTION

Risk factors for breast cancer (BC) are widely analyzed in countries with high incidence rates, while the epidemiology of breast cancer in Albania, a country characterized by low incidence, remains unclear. Thus, in Albania, the incidence of breast cancer is much lower than in other European countries, with the incidence rate per 100,000 women being 48.2 compared to 89.7 in Western Europe (Ferlay et al., 2010).

Nevertheless, breast cancer rates have been rising in Albania, accounting for 22.9% of all cancer cases, and it is the most common malignancy in women and fourth leading cause of mortality (Ferlay et al., 2010). Albanian women have a number of different reproductive experiences and lifestyle habits com-

pared with those of other populations. The fertility rate in 1960 of more than 5 children per woman of childbearing age has changed to 1.4 children in 2010, while the number of abortions has doubled during 2010 compared to 1993 (Bregu et al., 2010). The nutrition situation is optimal, mainly in urban areas, which affects major sections of the resident population.

Epidemiological risk factors for BC include hormonal factors (Timothy et al., 1999) such as early menstruation (Claver-Chapelon et al., 2002; Gao et al., 2000) and late menopause (Hsieh et al., 1990; Fioretti et al., 1999), nulliparity (Miller 1993; Layde et al., 1993) and pregnancy at an advanced age (Bruzzi et al., 1988; Kvale et al., 1987), all of which indicate prolonged estrogenic exposure (Kesley and

Hilderth, 1983; Key, 1995; Timothy et al., 1999; Gao et al., 2000).

The age at which a woman gives birth to her first live child is predictive of breast cancer risk and the risk increases with age at first birth. The importance of age at first birth as a risk factor was first established by MacMahon et al. in 1970, from a large international case-control study. Since then, many epidemiologic studies have revealed that, on average, the younger a woman is when she has her first-full term pregnancy, the lower is her risk of breast cancer (Lubin et al., 1982; Hinkula et al., 2001; Palmer et al., 2003). Parity has influence in levels of circulating hormones such as estradiol, PRL and GH and in the differentiation of epithelial cells that are less susceptible to transformation. In postmenopausal women, obesity, which is positively correlated with plasma estrogen and estradiol levels, is associated with an increased risk of breast cancer.

To analyze the reason for the increased breast cancer rate in Albania and to determine if factors in this low-incidence country differ from those identified in other countries, we conducted a population-based case-control study of 948 breast cancer patients, during the period 1998 to 2006.

MATERIALS AND METHODS

Data collection

A case-control design of 948 women with breast cancer and their 1019 female controls was carried out from 1998 till 2006. All women between 20 and 74 years of age who were diagnosed with a primary, invasive breast cancer between September 1, 1998, and December 31, 2006, were eligible as cases and were identified using the Albanian Central Cancer Registry. This center compiles information from reports of all malignant tumors and is a part of the Oncology Hospital, which is the only institution offering these services within the health sector in Albania.

After exclusion of nine women who had incomplete information on many risk factors of interest,

information from 948 cases was available for analysis. Of the 1204 eligible women, 185 (15%) declined to participate. Thus, information from 1019 controls was available for analysis, for an overall cooperation rate of 85%. Diagnoses were confirmed histologically, through a biopsy.

In the present study, cases were defined as women that were interviewed at the oncology services of the hospital, who presented clinical and cytological reasons to suspect the presence of breast cancer. Women in the same range and residential area but without a history of breast cancer were eligible as controls. Controls were obtained from other hospitals through random selection for a variety of acute conditions unrelated to the hypotheses in the study. 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. Interviewers administered a structured questionnaire in which they were asked to answer questions related to their (a) age, marital status, age at menarche, number of abortions, age at first delivery, number of children, age at menopause and family history of breast cancer; (b) diagnosis year, per year (1998 referent); (c) tumor stage (stage 1 referent); (d) tumor size (0 to <1 cm [referent], 1 to <2, 3 to <4, 4 to <5, 5 to <10, ≥ 10); (e) axillary nodal positivity (0 [referent], 1 to 3, 4 to 10, ≥ 11); for all cases, consent for access to medical documentation was obtained. A pregnancy was classified as full-term if it resulted in a live birth or lasted 7 or more months; otherwise, it was considered an abortion.

Women were classified as postmenopausal if their cycles ended naturally or from radiation therapy (prior to diagnosis for cases), from surgery in which both the uterus and ovaries were removed, or from surgery in which at least one ovary remained intact but age at diagnosis or selection was more than 55 years. Also considered postmenopausal were women who mentioned experiencing menopausal symptoms

after surgery or receiving hormone replacement therapy, although they had never stopped menstruating and were older than 55 years of age. The remaining women who reported not having menstrual cycles were considered perimenopausal and were grouped with premenopausal women for analysis.

We started obtaining information on tumor histology from the pathology report in the medical record since 2002. Four hundred and sixty three cases were classified according to the invasive component, as being ductal ($n = 287$), lobular ($n = 176$) or of other types (82). We analyzed only ductal and lobular cases and all other cases were excluded from the analyses. The study protocol was approved by the Institutional Review Board of Tirana University in February 2007.

Data analysis

Odds ratios and 95% confidence intervals comparing each case subgroup with controls were calculated for risk factors to estimate relative risks. All primary exposure variables, as well as age, were included in the models to account for potential confounding effects. The collected data were initially cleaned through an analysis of the range and distribution of study variables and their mutual consistency. Distribution of study factors was then calculated for cases and controls, as well as the respective odds ratios, 95% confidence intervals, and significance tests. Binary logistic regression models were run by using Statistical software SPSS Incorporation 15 for Windows. All statistical tests were two-sided, and p values of 0.05 or less were considered significant. Data were then submitted to multivariate analyses, employing logistic regression (Breslow and Day, 1980).

RESULTS

Of the 981 case subjects diagnosed with breast cancer during the 9 years of follow-up, 503 were premenopausal and 478 were postmenopausal women. The mean age of cases was 49.5 years and 50.2 years among controls. The baseline distribution of parity, age at first birth, number of children born, age at

menarche and menopause for the 981 breast cancer cases and 1019 controls are given in Table 1. The age distribution of cases was as follows: 7.2% < 35 years, 30.8% from 36 to 45 years, and 59.9% 45 to 60 years. The age distribution of controls was 10.5% < 35 years, 20.7% from 36 to 44 years, and 72.1% from 45 to 60 years. The proportion of these types increased with age to a maximum at 44-54 years and decreased in the following decade.

Among premenopausal women, 19.3 % were nulliparous and 49.8% had had one to two births. Among postmenopausal, 14.6% were nulliparous and 32.3% had had one to two births.

Multivariate analysis was performed separately for premenopausal and postmenopausal women. Compared to premenopausal women whose age at first childbirth was below 20 years, women at 30 years or more (Table 2) had a risk OR=15.7 (95% CI=4.8-50.7). This variable remained insignificant for postmenopausal women.

Most of the parous women had had their first full term pregnancy at an early age: 60% of premenopausal and 72% of postmenopausal women had had their first full term pregnancy before age 25. Compared to women with a parity of five children and more, women with no children were at a 20% insignificant risk; this was the same risk only in the postmenopausal group. Parity and abortion did not indicate any protection in the multivariate model even in the menopausal groups (Table 2).

An early age at menarche was found to be a strong risk factor. Age 12 years or younger increased the risk 10.04-fold in premenopausal and 12-fold in postmenopausal women (Table 2) and an older age at menarche was associated with a significant reduction in the risk of breast cancer in the two groups accordingly. Compared to postmenopausal women, premenopausal women had a 68% increased risk for breast cancer. Age at menopause was found to have a 2.3-fold higher risk for women aged 50 and more compared with those under 50 years (95% CI = 1.1-3.2).

Table 1. Comparison of reproductive variables in breast cancer in Albanian women.

Variables	Mean (cases)	SD	Mean (controls)	SD	p-value
Age	47.05	9.019	52.4	52.4	<0.01
Age at first birth	23.51	3.721	22.46	3.052	0.000
Number of children	2.48	1.926	3.17	1.427	0.000
Age at menopause	50.41	5.403	42.2	15.481	0.000
Age at menarche	13.38	1.691	14.65	1.534	0.000

*student t-test

Table 2. Odds ratios in multivariate analysis for breast cancer according to selected risk factors in Albanian women, 1998-2006.

	Cases/Controls	All women		Premenopausal		Postmenopausal	
		OR	95%CI	OR	95%CI	OR	95%CI
Age at menarche*							
<=12	320/52	8.30	4.6-15.4	10.0	5.6-17.9	12.0	6.5-22.1
13	206/160	1.79	1.0-3.1	2.9	1.7-4.8	2.3	1.3-3.8
14	212/325	1.07	0.6-1.8	1.4	0.9-2.2	2.0	1.2-3.2
15	98/222	0.66	0.3-1.1	1.1	0.6-1.8	0.8	0.4-1.5
>=16	112/260	1.0		1.0		1.0	
Age at first full-term pregnancy (years)*							
<20	104/142	1.0		1.0		1.0	
20-24	429/652	1.28	0.5-2.9	1.3	0.7-2.5	0.7	0.4-1.1
25-29	234/208	1.69	0.6-4.2	2.0	1.0-3.9	1.0	0.5-1.7
>=30	46/17	2.06	0.6-6.7	15.7	4.8-50.7	0.3	0.1-1.0
Parity*							
0	156/9	1.48	0.4-4.5	0.5	0.1-2.4	1.19	0.5-2.3
1-2	390/357	0.61	0.2-1.8	0.3	0.1-1.4	0.5	0.2-1.0
3- 4	285/503	0.76	0.2-2.4	0.4	0.1-2.1	0.7	0.3-1.3
>=5	117/150	1.0		1.0		1.0	
Menopausal status**							
Premenopausal women	503/551	1.68	1.0-2.6				
Postmenopausal women	478/468	1.00					
Postmenopausal women >50 year	144/313	1.0					
Postmenopausal women ≥50 year	334/155	2.3	1.1-3.2				
Abortions*							
Yes	212/294	1.0		1.0		1.0	
No	736/725	1.6	1.1-2.4	1.2	0.8-1.7	1.7	1.1-2.5
Family history*							
Yes	96/68	1.4	0.8-2.6				
No	852/951						

*Adjusted for age, age at first birth, age at menarche, age at marriage, interval between menarche and age at first birth, number of births, family history, abortions, menopause status. **Adjusted for age at first birth, age at menarche, age at marriage, interval between menarche and age at first birth, number of births, family history, abortions.

In our study, there was differential protection against subtypes of breast cancer. Increased age at menarche reduced risk in lobular cancer but increased risk in ductal. Early menopause was a protective factor only for ductal cancer and had an opposite effect on the lobular type. A positive family history of breast cancer is associated positively with ductal but not with lobular cancer.

Multiparity, early age at first delivery, and late age at menarche significantly reduced the frequency of ER+, PR+ cancers and did not influence ER-, PR-cancers.

DISCUSSION

For the past one and a half decades, Albania's society has witnessed rapid economic growth and major demographic change along with a sizable rural-urban population migration that are associated with significant reproductive and lifestyle changes. Therefore, in this study we intended to clarify the role of breast cancer risk factors in the Albanian population, and since there is a shortage of data on breast cancer risk factors among women in low-risk countries, the results are of interest, particularly when compared with studies in other areas of the world.

The age at menarche indicated a positive association with breast cancer risk. Late age at menarche offered strong protection in premenopausal and postmenopausal years. A significant reduction in the risk of breast cancer was found in some studies (Nagata et al., 1995; Gao et al., 2000; Claver-Chapelon and E3N-Epic Group, 2002). Several studies carried out in a high-risk population found no association between age at menarche and the risk of breast cancer (Adami et al., 1978; Talamini et al., 1996). Negative association was found between increasing age at menarche and breast cancer risk in women born before 1925, but not after (Magnusson et al., 1999).

In multivariate analysis, a young age at first birth was protective against breast cancer only in premenopausal women. A 15-fold elevated risk of breast cancer was observed when the age at first childbirth

was after 29 years. A consistent finding reported in many epidemiologic studies was that the younger a woman is when she has her first childbirth; the lower is her risk of breast cancer (Leon et al., 1989; Paffenbarger et al., 1980; Negri et al., 1988; Okobia et al., 2006). An excess risk ranged from 2-5-fold or increase in risk by 3-5% per year of delay in age at first birth for women with a birth after 30 years compared to those with a birth prior to 18 years, has been reported by several studies (Nagata et al., 1995; Hinkula et al., 2001). Some studies found no positive association between age at first birth and the risk of breast cancer (Ewertz et al., 1988; Huo et al., 2008). The influence of age at first birth and age at menarche may indicate that events early in life matter most in determining breast cancer risk. Recall bias was not considered to be a major source of error because it was unlikely that healthy women or women with breast cancer would misreport the years of birth of their children.

Low parity was found to be significantly associated with an increased risk of breast cancer (Gomes et al., 1995; Romieu et al., 1996; Magnusson et al., 1999). Nulliparity was associated with an increased risk of 27-30% compared with parous women (Ewertz et al., 1990; McCredie et al., 1998). A protective effect of high parity was found only for postmenopausal women (Claver-Chapelon F and E3N-Epic Group, 2002). In our study, parity did not emerge as a risk factor for breast cancer. The significant risk found in premenopausal and postmenopausal nulliparous women observed in univariate analysis disappeared in the multivariate model.

Premenopausal women have an increased risk compared to postmenopausal women. This elevation in risk indicates that existing tumors may have an increased growth rate at the time of menopause. Among postmenopausal women, late age at menopause was found to be associated significantly with the risk of breast cancer, suggesting that late menopause has higher risk of breast cancer.

A large number of epidemiological studies have suggested that age at menopause is an important de-

terminant in breast cancer. Late age at menopause was found to be associated with an increased risk of breast cancer (Schatzkin et al., 1987; Bruzzi et al., 1988; Talamini et al., 1996; Fioretti et al., 1999) which points out the quality of our study. It is possible that the two factors, early age at menarche and late age at menopause, indicate an influence of the total numbers of years of menstrual activity (Henderson et al., 1988). In our study, cases more commonly reported a familial cancer history, although reproductive cancers did not predominate. Familial cancer history was positively related to BC risk and thus it would appear that heredity is a contributing factor to the etiology of breast cancer in Albania.

Young age at first birth and late age at menarche may affect the hormonal characteristics of breast cancer, as each of them was associated with a reduced frequency of ER+PR+ breast cancer (Ursin et al., 2005; Britt et al., 2007).

In conclusion, we established protection from breast cancer as early age at first birth among premenopausal women, late age at menarche in both groups, and early age at menopause. The risk of breast cancer was not associated with parity. In general, the results show that risk factors for Albanian women are similar with those found in western countries, although there are also considerable differences in the incidence rates.

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