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ORIGINAL ARTICLE

# Risk factors for breast cancer: a hospital-based case-control study

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## Summary

***Purpose:*** *The factors responsible for the genesis of breast cancer remain unclear. A case-control study was undertaken to investigate the possibility of an association between hypothesized risk factors and the development of breast cancer in Serbia.*

***Patients and methods:*** *This hospital-based case-control study comprised 120 new breast cancer cases and 120 hospital controls matched with respect to age (± 2 years). This study used a targeted and detailed questionnaire to obtain information from respondents. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated from multivariate conditional logistic regression models.*

***Results:*** *Five independent predictors of breast cancer were: delayed age at first birth (OR=6.1, 95% CI=4.2-12.4), alcohol consumption (OR=4.8, 95% CI=1.9-12.4), family history of breast cancer in 2nd degree relatives (OR=2.5, 95% CI=1.4-4.3), never having breastfed (OR=5.2, 95% CI=1.4-18.5) and maternal death in childhood (OR=3.3, 95% CI=1.2-8.6).*

***Conclusion:*** *The results of this study confirmed that the aetiology of breast cancer in Serbia, as elsewhere, is complex. More research is needed to understand the interactions between factors that could affect vulnerability to breast cancer.*

**Key words:** breast cancer, epidemiology, risk factors

## Introduction

Although the incidence rates for breast cancer in Europe vary between different countries, it is the most frequently occurring malignant tumor in women and also the leading cause of cancer-related death [1].

Breast cancer is the leading malignancy in females in all Balkan countries including Serbia as well [1]. Incidence rates are lower than in northern or western Europe [1].

Breast cancer in central Serbia constitutes a quarter of all female cancers [2]. The total number of new annual breast cancer cases is 2,846, with standardized incidence rate 60 per 100,000 [2]. Similar breast cancer rates have been observed in some neighbouring ex-Yugoslavian, countries: Slovenia (59), Croatia (62), Bosnia and Herzegovina (59), FYROMakedonia (52) [1].

Breast cancer in central Serbia is the leading cause of cancer deaths in females (19% of all cancer deaths in women) [2] and caused 1,089 deaths in 2003 with standardized mortality rate 24 per 100,000 [2].

There is a constant increase both in incidence and mortality rates of this disease in Serbia [3]. During the period 1970-2000, the standardized mortality rate in Serbia increased 2.4 times, from 8.3 per 100,000 in 1970 to 19.7 per 100,000 in 2000 [3]. During the period 1990-2003, the standardized mortality rate in central Serbia increased 1.5 times, from 16.5 per 100,000 in 1990 to 24 per 100,000 in 2003.

The age and stage distribution at diagnosis is unfavorable, compared to some other countries such as Slovenia, France, Australia and USA [3]. The median age at presentation is 56 years and one third of the patients is under the age of 50 (6% is under the age of 40 and 24% is in the 40-49 age group). More than half of the patients are diagnosed in late stages (53% with re-

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gional and 9% with distant metastases) and only 38% in local stage [4].

In comparison with breast cancer patients from the Belgrade county, women affected with the disease from other parts of central Serbia were younger and with advanced disease stages at diagnosis [3]. The differences in the availability and quality of health services, diagnosis, treatment and education of women regarding breast cancer risk and prevention in different parts of Serbia appear to contribute to the observed variation in age and stage distribution at diagnosis.

In view of breast cancer characteristics and its importance as the cancer most commonly occurring in females in Serbia [2], this study was undertaken to assess the association of hypothesized risk factors with the occurrence of this malignancy.

## Patients and methods

One hundred and twenty new breast cancer cases (within 2 years from diagnosis) and 120 hospital controls (patients from the Clinic of Physical Medicine and the Orthopedic Clinic, with nonoccupational accidental injuries and with no breast cancer and benign breast disease) matched by age (±2 years) were interviewed. They participated in this breast cancer risk evaluation during a one-year period. All respondents were interviewed by a single interviewer, using a targeted questionnaire on a variety of known and suspected risk factors for breast cancer in women.

### *Statistical considerations*

The SPSS statistical package was used and variables were considered to be significant when $p < 0.05$. OR and 95% CI were calculated from multivariate conditional logistic regression models.

According to McNemar's and t-test 21 variables were selected and considered for further analyses. These variables were reproductive variables (age at first and last birth, never having breastfed), somatometric variables (height, weight, body mass index/BMI), habits (alcohol consumption, physical inactivity, cigarette smoking, passive smoking), family history of malignant tumors in 2nd and 3rd degree relatives, personal case history of hormone replacement therapy, personal history of death of mother in childhood. Several conditional logistic regression models were tested, including the variables grouped according to the their nature (model of reproductive variables, model of lifestyle etc.), and only the statistically significant ones entered into the final model of the conditional logistic regression analysis: age at first birth, never having breastfed, height, BMI, alcohol consumption, passive smoking, physical activity, family history of breast cancer in 2nd degree relative, and maternal death in childhood.

## Results

Table 1 summarizes selected characteristics of the study population.

Patients and controls were similar in terms of age, marital status, education, occupation, place of residence and menopausal status.

Both groups of respondents consisted of female patients with median age 50.8 years (range 30-69). Most of them were married (79.2% vs. 81.7%), working (68.3% vs. 73.3%), premenopausal (80.8% vs. 80.0%), urban dwellers (62.5% vs. 56.7%), with primary (37.5% vs. 38.7%) and secondary education (25.8% vs. 26.0%).

Multiple conditional logistic regression analysis revealed 5 independent predictors of breast cancer:

**Table 1.** Selected characteristics of the study population

| *Characteristic* | *Patients (%)* | *Controls (%)* | *p-value*[a] |
|---|---|---|---|
| Age (years) | | | |
| 30-39 | 8.3 | 12.5 | |
| 40-49 | 40.8 | 33.3 | |
| 50-59 | 30.8 | 35.0 | matched |
| 60-69 | 20.0 | 19.2 | |
| Mean age (SD) | 50.8 (8.9) | 50.8 (8.7) | 0.55 |
| Marital status | | | |
| Never married | 2.5 | 4.2 | |
| Married | 79.2 | 81.7 | 1* |
| Widowed | 10.0 | 10.0 | |
| Divorced | 8.3 | 4.2 | 0.27 |
| Education | | | |
| No formal | 8.3 | 3.3 | |
| Primary school | 37.5 | 38.3 | |
| Secondary school | 25.8 | 26.0 | 1* |
| College | 2.5 | 24.0 | |
| University | 5.8 | 8.3 | 0.57 |
| Occupation | | | |
| Working | 68.3 | 73.3 | |
| Housewife | 30.8 | 26.7 | |
| Retired | 0.8 | 0.0 | 0.25 |
| Place of residence | | | |
| Rural | 37.5 | 43.3 | 1* |
| Urban | 62.5 | 56.7 | 0.20 |
| Menopausal status | | | |
| Premenopausal | 80.8 | 80.0 | 1* |
| Postmenopausal | 19.2 | 20.0 | 0.55 |

[a]p value by matched t-test, SD: standard deviation
*risk ratio=1 in baseline category

**Table 2.** Significant predictors of breast cancer

| *Variable* | *OR** | *95% CI§* | *p-value†* |
|---|---|---|---|
| Age at first birth | 6.1 | 4.2-12.4 | 0.00 |
| Alcohol consumption | 4.8 | 1.9-12.4 | 0.00 |
| Family history of breast cancer in 2nd degree relatives | 2.5 | 1.4-4.3 | 0.00 |
| Never having breastfed | 5.2 | 1.4-18.5 | 0.01 |
| Maternal death in childhood | 3.3 | 1.2-8.6 | 0.02 |

*Odds ratio, §95% confidence interval, †p-value estimated by multivariate conditional logistic regression analysis

delayed age at first birth (OR=6.1, 95% CI=4.2-12.4), alcohol consumption (OR=4.8, 95% CI=1.9-12.4), family history of breast cancer in 2nd degree relatives (OR=2.5, 95% CI=1.4-4.3), never having breastfed (OR=5.2, 95% CI=1.4-18.5) and maternal death in childhood (OR=3.3, 95% CI=1.2-8.6) (Table 2).

## Discussion

In our study, the risk of developing breast cancer was positively related to late age at first birth. The younger a woman is when she begins childbearing, the lower her risk of breast cancer [5]. The relative risk of developing breast cancer increases by 3% for each year of delay [6]. For example, a woman who had her first child at 28 would have a 3% lower risk of breast cancer than a woman who had her first child at 29, all other factors being equal.

Although the association between alcohol consumption and breast cancer is still open to discussion, in our study the risk of developing breast cancer was strongly related to alcohol consumption. Results of previous meta-analyses have shown a positive association between alcohol intake and breast cancer [7-9]. However, most of component studies have been conducted among western populations. Alcohol drinking has also been linked to female breast cancer in one recent study: a significant association between alcohol intake and breast cancer has been found in Turkish women [5].

A woman with one affected 1st degree relative (mother or sister) has approximately a 2-fold risk of breast cancer development than a woman with no family history of this disease; if 2 (or more) relatives are affected, her risk increases further [10,11]. With affected 2nd degree relatives (grandmothers, aunts, granddaughters), there is lesser increase in risk [12]. However, more than 85% of women who have one or more first degree relative with breast cancer will never develop the disease, and more than 85% of women with breast cancer do not have affected mother, sister or daughter [11]. In developed countries it is estimated that hereditary factors contribute around a quarter of inter-individual differences in susceptibility to breast cancer, while environmental and lifestyle factors contribute the remaining three-quarters [12]. In our study we failed to observe positive association between family history of breast cancer in 1st degree relatives and breast cancer development. The results of the present study in Serbia suggest that the risk of developing breast cancer was positively related to family history of breast cancer in 2nd degree relatives.

Our study supported the possibility that history of never having breastfed might be associated with an increased risk of breast cancer. Studies in less developed countries, where the total duration of breastfeeding can be very long, have reported substantial protective effects [13]. Breastfeeding women reduce their risk compared with women who do not breastfeed [5]. The longer a woman breastfeeds, the greater the protection: risk is reduced by 4.3% for each year a woman breastfeeds [6].

This study found that maternal death in childhood (until 14 years) increases the risk for breast cancer development. Parental loss in childhood merits investigation as a risk factor for the development of breast cancer since it is an early and intense event that has been associated with breast cancer development in the past; only methodically weak studies not controlling for confounding variables, retrospective in nature, and with small and poorly matched samples etc. are to be found in the relevant literature [14-16]. The Le Shan's [14] early work suggests that parental loss occurred in high frequency among cancer patients. Baltrush and Waltz [15] found in a group of a patients with a variety of cancers that early parental death was significantly higher than in the control group. Scherge and Blohmke [16] found that death of the mother in childhood was the life event that most increased the risk of developing cancer in women. They did not find any significant association between death of the father and cancer. Some of these studies frequently did not adequately control for family history of cancer. Unlike these studies, family history of breast and other cancers was statistically controlled in the study of Jacobs and Bovasso [17]. The authors speculated that increasing vulnerability to cancer is most likely attributed to the depression and trauma due to the loss of the mother, which last for several years and are a well-documented research finding.

The experience of parental loss is a profoundly traumatic event for a child with negative effects that persists for many years [18]. Gersten et al. [19] found that bereaved children were 7 times more likely to have a clinical depression than non-bereaved children and

these depressive symptoms usually continued for 3 to 5 years. When the death of a parent occurred in adolescence, these bereaved adolescents were more likely than adolescents from intact families to be depressed, attempt suicide, and other conduct disorder problems [20]. The death of a parent is not only a profound loss but frequently involves other stressful complications [21] such as more family discord, increased and unsatisfied demands for parental attention and less financial resources.

Lokugamage et al. [22] did not find overall association between parental death, parental divorce or psychiatric disorder and the incidence of breast cancer. A metaanalysis is needed that uses data from all available cohort studies and investigates possible interactive effects on breast cancer risk.

In conclusion, the results of this study confirmed that the aetiology of breast cancer in Serbia, as elsewhere, is complex. Although substantial knowledge has been accumulated about the epidemiology and aetiology of breast cancer, a lot of questions still remain to be solved in this new century. More research is needed to understand the interactions between factors that could affect vulnerability to breast cancer. But it should not be forgotten that breast cancer control could be achieved only by combined efforts directed into primary prevention and early detection, as well as improving the availability of effective treatment.

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