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ORIGINAL ARTICLE

# The influence of reproductive factors on breast cancer risk in women with pathogenic mutations

Iulian Gabriel Goidescu[1]*, Gabriela Caracostea[1]*, Ioana Cristina Rotar[1], Dan Tudor Eniu[2], Georgiana Irina Nemeti[1], Gheorghe Cruciat[1], Florin Stamatian[1], Daniel Muresan[1]

[1]Department of Obstetrics and Gynecology I, University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj Napoca, Romania; [2]Department of Surgical Oncology and Oncological Gynecology, University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj Napoca, Romania

*These authors contributed equally to this work.

## Summary

***Purpose:*** *To assess the influence of reproductive factors in the occurrence of breast cancer in women, taking into account the presence/absence of genetic predisposing mutations.*

***Methods:*** *100 patients with breast cancer were included. The genetic testing was conducted through a multigene panel. Reproductive characteristics were noted for all patients: age of menarche, age of the patient at first full term pregnancy, number of pregnancies, number of full-term pregnancies, breastfeeding interval, number of abortions, and menopausal status at the time of diagnosis. The patients were divided into three groups according to their mutations: BRCA1, positive for mutations other than BRCA1 and negative.*

***Results:*** *The risk of breast cancer was not influenced by the number of abortions, parity, age at first pregnancy, age at menarche and menopausal status, or by oral contraceptive use in carriers of pathogenic mutations group in the BRCA1 group. The present study has demonstrated the protective effect of breastfeeding only in patients without genetic risk (p=0.0344). In contrast, breastfeeding did not influence breast cancer occurrence in BRCA1 mutation carriers' group (p=0.2321).*

***Conclusions:*** *Breastfeeding represents a protective mechanism only in patients without genetic breast cancer predisposing mutations. Environmental and reproductive factors can impact the risk and the age of onset of breast cancer in patients carrying pathogenic mutations, but the mechanisms of action are not fully understood.*

***Key words:*** *breast cancer, breastfeeding, pathogenic variants, reproductive factors*

## Introduction

Breast cancer is the most common malignancy diagnosed in women in Europe [1]. It represents the second cause of cancer-related mortality after colorectal cancer [1], the other reproductive system cancers occupying the fourth position (corpus uteri), fifth (ovary) and seventh (cervix), taking into account their contribution to the mortality rates [1-3].

It is well-known that patients carrying pathogenic germline mutations in BRCA1 and BRCA2 genes are at risk for developing breast and ovarian cancer, with early onset. Also an increased risk for breast cancer has been found in the presence of other pathogenic mutations in breast cancer predisposition genes such as TP53, CDH1, STK11, PALB2, CHEK2, ATM [4].

*Corresponding author:* Ioana Rotar, MD, PhD. Department of Obstetrics and Gynecology I, University of Medicine and Pharmacy "Iuliu Haţieganu", Clinicilor 3-5, 400006 Cluj Napoca, Romania.
Tel: +40264450115, Email: cristina.rotar@umfcluj.ro
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Besides the genetic factors, the risk of breast cancer is attributed to reproductive and hormonal factors. Current studies showed that factors such as early menarche [5-7], late menopause [6,7], the large interval between menarche and menopause [8,9], nulliparity, prolonged interval between menarche and the first pregnancy [6], lack of breastfeeding [10,11], repeated abortions [12] and first pregnancy after 35 years [10] are positively associated with the risk of breast cancer, but the results are often contradictory.

The use of combined oral contraceptives was previously linked to an increased breast cancer incidence, but data is often contradictory, the risk being dependent on the duration of administration, the age at which the treatment is initiated and the hormonal concentration from the pills [13,14].

It seems that these reproductive and hormonal factors can influence the risk, but also the age of onset of breast cancer in patients with pathogenic mutations. There are only a few studies that have examined the associations between reproductive factors and the risk of breast cancer in carriers of pathogenic mutations in high-risk genes, most of the data being limited to BRCA1/2 genes [14].

The purpose of this study was to analyze the influence of reproductive factors in the occurrence of breast cancer in patients with pathogenic mutations BRCA1, BRCA2 and other breast cancer predisposition genes and to compare them with the breast cancer patients without mutations. A secondary goal - the influence of the reproductive factors on breast cancer occurrence - was analyzed in a subgroup of patients with pathogenic BRCA1 variants, compared to BRCA1 negative patients.

## Methods

*Ethics*

This study was approved by of the ethics committee of the "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania no.369 / 14.10.2016. Informed consent was signed by all patients at the first medical evaluation.

*Population*

137 consecutive patients were enrolled in this study after being diagnosed with breast cancer in the Surgical Oncology Clinic, Cluj-Napoca, Romania. All patients met the 2016 National Comprehensive Cancer Network (NCCN) criteria for genetic testing [13]. The study took place between between January 2015 and July 2017. Thirty-seven patients have been excluded from the study due to lack of information on reproductive factors or because of variant of uncertain significance (VUS) mutations.

Reproductive characteristics were registered for all patients, as follows: age at menarche (≤12, 13-14, ≥15 years), age of the patient at first full term pregnancy (<25, 25-29, 30-34, ≥35 years), number of pregnancies (1, 2, 3, 4 etc.), number of full-term pregnancies (1, 2, 3, 4, etc.), breastfeeding interval (≤3, 4-6, 7-11, ≥12 months), number of abortions (1, 2, 3, 4 etc.) and the menopausal status at the time of diagnosis (Yes, No). Other parameters were also registered: patient age at diagnosis, height, weight and demographic parameters (rural, urban).

*Genetic testing*

A blood sample was obtained from each patient from which DNA was extracted later on. Genomic DNA was prepared and analyzed using an multigene panel (25 genes) as described in our previous research [16]. The analyzed genes were: ATM, BARD1, BLM, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, FAM175A, MEN1, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D, STK11, TP53, XRCC2.

All genetic tests were performed by GeneKor Laboratories, Greece.

The patients were then divided into 3 groups: pathogenic mutations group, negative mutations group and BRCA1 positive mutations group.

*Statistics*

Data was analyzed with Statistica 8® (STAT Soft, USA) at a significance level of 5%. Categorical data were summarized descriptively using simple statistics such as absolute and relative frequency (expressed as percentage). Metric data were summarized as mean ± standard deviation whenever proved normally distributed (Shapiro-Wilks test). Otherwise, median and the values of first and third quartiles were reported. The association

**Table 1.** Breast cancer patient characteristics

| *Characteristics* | *BRCA1 (n=24)* | *Other mutations (n=26)* | *Without mutations (n=50)* |
|---|---|---|---|
| Age (years)[a] | 42.17±0.11 | 45.38±11.69 | 43.30±10.01 |
| Urban origin[b] | 21 (87.50) | 21 (80.77) | 37 (74.00) |
| BMI, kg/m$^2$ [a] | 25.53±4.27 | 24.55±4.08 | 23.90±3.81 |
| BMI classb | | | |
| Overweight | 8 (33.33) | 6 (23.08) | 14 (28.00) |
| Obese | 5 (20.83) | 3 (11.54) | 2 (4.00) |

[a] mean±standard deviation, [b] no. of cases (%). BMI: body mass index

between categorical data were tested with Fisher exact or $x^2$ test. The comparisons between groups on metric data were done with one-way ANOVA test when more than two groups were compared or Student's t-test for independent sample for normally distributed data. Mann-Whitney U test was applied to compare metric data among groups whenever data proved not to follow the normal distribution. A p value less than 0.05 was considered statistically significant.

## Results

One hundred subjects, 50 with a deleterious mutation and 50 without any mutation, with age ranging between 24 and 71 years met the inclusion criteria and were analyzed. Their mean age was 43.57±10.45 years, while the body mass index (BMI) was 24.46±4.01 kg/m$^2$. No significant differences were observed in terms of age between the subjects with BRCA1 mutations, those with other types of mutations and those without mutations (ANOVA test, p=0.5400). Most of the patients included in the study had normal weight, and 5 of them were underweight (one in the group with other mutations and 4 in the group without any mutations). Absence of significant difference was also observed when BMI was compared between the three investigated groups (ANOVA test, p=0.2577).

In the pathogenic mutations group, the following mutations have been diagnosed: 25 BRCA1 mutations, 9 BRCA2 mutations, 2 TP53 mutations, 5 PALB2 mutations, 6 CHEK2 mutations and 3 ATM mutations (Table 1).

*Comparisons between subjects with and without mutations*

The comparison in terms of reproductive characteristics among subjects with breast cancer with and without mutations has shown that breastfeeding was statistically significant, associated with a protective effect only among breast cancer patients without genetic risk (p<0.05, Table 2). No other significant associations or significant differences between groups were identified (Table 2).

Two subjects underwent assisted reproductive techniques, one woman in the group with mutations and the other one in the group without mutations (p>0.9999).

No significant association has been identified between the consumption of combined oral contraceptives and mutations (p=0.4142). Eighteen subjects in the group with mutations and 22 in the group without mutations have reported consumption of combined oral contraceptives. No significant differences were observed between groups regarding the duration of combined oral contraceptives consumption (with vs. without mutations: 2.00 (1.00-3.00) years vs. 2.00 (1.00-5.00), Mann-Whitney U test, p=0.4797).

*Comparisons between subjects with positive BRCA1 mutations and those without mutations*

A significant lower percentage of subjects with BRCA1 mutations (12.5%) were from rural regions compared with the subjects without mutations (26%;p=0.0077), without significant differences between groups with regard to age (p=0.5715) or BMI (p=0.5866).

The percentage of obese subjects among positive BRCA1 mutation group was higher (20.88%) compared with that of subjects without mutations (4.00%), but without significant difference between groups (p=0.1917).

Interestingly, no significant associations or differences have been observed with regard to reproductive characteristics when the subjects with positive BRCA1 mutations were compared with those without mutations (Table 3).

Two subjects followed assisted reproductive techniques, one woman in the group with the positive BRCA1 mutation (4.17%) and the other one in the group without mutations (2.00%) without significant difference between groups (p>0.9999).

Moreover, no significant association has been identified between the consumption of combined oral contraceptives and BRCA1 mutations (p=0.3816). Eight subjects in the group with mutations and 22 subjects in the group without mutations have reported consumption of combined oral contraceptives. No significant differences were observed between groups regarding the duration of combined oral contraceptives consumption (with vs. without mutations: 1.75 (0.48-3.00) years vs. 2.00 (1.00-5.00), Mann-Whitney U test, p=0.4454).

## Discussion

In the present study no statistically significant difference was established among the three groups (patients without mutations, patients with pathogenic mutations or patients carriers of BRCA1 mutations) regarding the age of menarche or menopause. In contrast, previous studies have linked early menarche to increased risk of hormonal-dependent breast carcinoma, this risk being highest in patients whose menarche occurred before 12 years of age [6,7]. Moreover, patients without family aggregation seems to benefit from the protective effect of the late menarche (>12 years) from breast cancer [17,18].

**Table 2.** Reproductive characteristics: patients with vs. without mutations

| *Characteristics* | *With mutations (n=50) n (%)* | *Without mutations (n=50) n (%)* | *p value* |
|---|---|---|---|
| Menarche (year) [a] | 12.76±1.20 | 13.04±2.28 | 0.4453 |
| Menarche, years [b] | | | 0.2240 |
| ≤12 | 23 (46.00) | 15 (30.00) | |
| 13-14 | 23 (46.00) | 28 (56.00) | |
| ≥15 | 4 (8.00) | 7 (14.00%) | |
| Gestations [c] | | | 0.2482 |
| 0 | 10 (20.00) | 15 (30.00) | |
| 1 | 13 (26.00) | 9 (18.00) | |
| 2 | 16 (32.00) | 15 (30.00) | |
| 3 | 5 (10.00) | 5 (10.00) | |
| 4 | 2 (4.00) | 3 (6.00) | |
| 5 | 3 (6.00) | 1 (2.00) | |
| 6 | 1 (2.00) | 1 (2.00) | |
| 7 | 0 (0.00) | 1 (2.00) | |
| Births [c] | | | 0.4188 |
| 0 | 13 (26.00) | 17 (34.00) | |
| 1 | 21 (42.00) | 19 (38.00) | |
| 2 | 14 (28.00) | 13 (26.00) | |
| 3 | 0 (0.00) | 1 (2.00) | |
| 4 | 1 (2.00) | 0 (0.00) | |
| Missing data | 1 (2.00) | 0 (0.00) | |
| Delivery | | | 0.5941 |
| Preterm | 1 (2.63) | 2 (6.06) | |
| Term | 37 (97.37) | 31 (93.94%) | |
| Abortions [c] | | | 0.5419 |
| 0 | 28 (56.00) | 31 (62.00) | |
| 1 | 17 (34.00) | 11 (22.00) | |
| 2 | 1 (2.00) | 5 (10.00) | |
| 3 | 2 (4.00) | 2 (4.00) | |
| 4 | 2 (4.00) | 0 (0.00) | |
| 6 | 0 (0.00) | 1 (2.00) | |
| Breast feeding, months | | | 0.0344 |
| No | 6 (12.00) | 17 (34.00) | |
| ≤3 | 11 (22.00) | 12 (24.00) | |
| 4-6 | 6 (12.00) | 8 (16.00) | |
| 7-11 | 9 (18.00) | 7 (14.00) | |
| >11 | 9 (18.00) | 6 (12.00) | |
| Missing data | 9 (18.00) | 0 (0.00) | |
| Menopause, yes [b] | 14 (28.00) | 8 (16.00) | 0.1475 |
| Age of first birth, years [d] | 27 (24.25-28.75) | 25 (23.00-28.00) | 0.4677 |
| Class of age at first birth [b], years | n=37[#] | n=33[#] | 0.1866 |
| <25 | 10 (26.32) | 12 (36.36) | |
| 25-29 | 23 (60.53) | 15 (45.45) | |
| 30-34 | 5 (13.16) | 3 (9.09) | |
| ≥35 | 0 (0.00) | 3 (9.09) | |
| Risk of cancer, yes [b] | 25 (50.00) | 17 (34.00) | 0.2223 |

[a] mean±standard deviation; Student's t-test for independent samples; [b] no. of cases (%); $x^2$ test; [c] no. of cases (%); $x^2$ test on 2×2 contingency table (present/absent); [d] median (Q1-Q3), where Q=quartile; Mann-Whitney U test. [#] From the total number of pregnancies (50 for each category), 37 gave birth in the mutation category and 33 in the category without mutation.

**Table 3.** Reproductive characteristics: BRCA1 vs. without mutations

| *Characteristics* | *BRCA1 (n=24)* *n (%)* | *Without mutations (n=50)* *n (%)* | *p value* |
|---|---|---|---|
| Menarhe (year) [a] | 13 (12-13) | 13 (12-14) | 0.0462 |
| Menarhe [b], years | | | 0.1077 |
| ≤ 12 | 11 (45.83) | 15 (30.00) | |
| 13-14 | 13 (54.17) | 28 (56.00) | |
| ≥15 | 0 (0.00) | 7 (14.00) | |
| Gestations [c] | | | 0.9415 |
| 0 | 7 (29.17) | 15 (30.00) | |
| 1 | 6 (25.00) | 9 (18.00) | |
| 2 | 6 (25.00) | 15 (30.00) | |
| 3 | 3 (12.50) | 5 (10.00) | |
| 4 | 0 (0.00) | 3 (6.00) | |
| 5 | 1 (4.17) | 1 (2.00) | |
| 6 | 1 (4.17) | 1 (2.00) | |
| 7 | 0 (0.00) | 1 (2.00) | |
| Births [c] | | | 0.6707 |
| 0 | 9 (37.50) | 17 (34.00) | |
| 1 | 7 (29.17) | 19 (38.00) | |
| 2 | 7 (29.17) | 13 (26.00) | |
| 3 | 0 (0.00) | 1 (2.00) | |
| Missing data | 1 (4.17) | 0 (0.00) | |
| Delivery | | | > 0.9999 |
| Preterm | 0 (0.00) | 2 (6.06) | |
| Term | 15 (100.00) | 31 (93.94) | |
| Abortions [c] | | | 0.7623 |
| 0 | 14 (58.33) | 31 (62.00) | |
| 1 | 8 (33.33) | 11 (22.00) | |
| 2 | 0 (0.00) | 5 (10.00) | |
| 3 | 1 (4.17) | 2 (4.00) | |
| 4 | 1 (4.17) | 0 (0.00) | |
| 6 | 0 (0.00) | 1 (2.00) | |
| Breast feeding [b], months | | | 0.2321 |
| No | 3 (12.50) | 17 (34.00) | |
| ≤3 | 4 (16.67) | 12 (24.00) | |
| 4-6 | 1 (4.17) | 8 (16.00) | |
| 7-11 | 3 (12.50) | 7 (14.00) | |
| >11 | 7 (29.17) | 6 (12.00) | |
| Missing data | 6 (25.00) | 0 (0.00) | |
| Menopause, yes [b] | 5 (20.83) | 8 (16.00) | 0.7456 |
| Age of first birth, years [a] | 26 (22.5-28)* | 25 (23-28)** | 0.9911 |
| Class of age at first birth [b], years | | | 0.7811 |
| <25 | 5 (33.33) | 12 (36.36) | |
| 25-29 | 8 (53.33) | 15 (45.45) | |
| 30-34 | 2 (13.33) | 3 (9.09) | |
| ≥35 | 0 (0.00) | 3 (9.09) | |
| Risk of cancer, yes [b] | 9 (37.50) | 17 (34.00) | 0.5845 |

[a] median (Q1-Q3), where Q=quartile; Mann-Whitney U test; [b] no. of cases (%); Fisher exact test; [c] no. of cases (%); $x^2$ test on 2×2 contingency table (present/absent). *n=15, **n=33

Late menarche in BRCA1 mutations carriers results in a reduction of breast cancer risk ranging from 34 to 54% if the first menstruation occurred after 14-15 years, information which has not been validated in our study [17,18]. This may be due to the small number of patients, but also can be caused by the error in remembering the correct age at menarche.

Literature data regarding the risk of breast cancer in BRCA1 mutations carriers and the age of menopause is contradictory. There are studies that associate an increased risk of breast cancer in menopausal patients after 50 years, but there are also studies that have shown the opposite, namely the protective effect of late menopause in BRCA mutations carriers [17].

When analyzing the influence of pregnancies on breast cancer risk, three parameters were studied more carefully: the number of abortions (or miscarriages), the parity and the age at which the first pregnancy occurred.

No association has been found between the number of abortions and breast cancer risk in the group of patients with BRCA1 pathogenic positive mutations when compared with patients from the group without mutations. The results are similar to those of other studies conducted by Beral et al. and Toss et al. [14,19] who invalidated older results which claimed that the risk of breast cancer is directly proportional to the number of abortions [12] because of a higher susceptibility of breast tissue to carcinogenic agents [20].

Moreover, no association has been detected between parity and breast cancer risk in pathogenic mutations carriers of BRCA1 our results being similar to those of other studies that have analyzed this association [17,21]. Numerous previous studies have demonstrated an inverse association between the number of pregnancies and the risk of developing premenopausal breast cancer [22,23], however, in patients with a family history of breast carcinoma or pathogenic mutations, it appears that parity can be directly associated with breast cancer risk [24,25].

Nevertheless, in an article published in 2016 by Rieder et al. in which the authors analysed the influence of reproductive factors on the age of onset of breast cancer in BRCA1 and 2 mutations carriers, they showed that a full-term pregnancy may delay the onset of this disease with 4.5 years on average compared with nulliparous women [26]. Also, they proved a direct association between the number of pregnancies and delaying the age of breast cancer occurrence in these women [26]. These correlations are more likely due to the fact that Rieder et al. analyzed the influence of full-term pregnancies on the age of breast cancer onset only in the BRCA1 and BRCA2 mutations group.

It is known that a pregnancy before 30 years has a dual effect on the breast: first, causing a transient increase in breast cancer risk, and then after a few years this risk decreases gradually and the protective effect installs [27,28]. Also a late pregnancy after 38 years increases both the short-term and long-term risk of developing breast cancer [28]. In the current study no statistically significant relationship has been found between the risk of developing breast cancer and the age at which the first pregnancy occurred in the mutations carrier group, nor in the BRCA mutations carrier group. The data in the literature is conflicting. Two studies reported that for the BRCA1 mutation carriers the protective effect of the pregnancy against breast cancer occurrence is only validated if pregnancy occurs after the age of 40 years [21,27].

A protective effect of breastfeeding in patients without mutations has been confirmed (p=0.0344) in the present study. Interestingly, no association was found when comparing the same group with BRCA1 mutations carriers group (p=0.2321). This difference may be due to the fact that in the group with positive BRCA1 mutations were included more nulliparous women compared to the group of patients without mutations. Breastfeeding was longtime considered to be one of the most important protective factors against breast cancer [30], but this effect appears to be validated especially for premenopausal and hormone receptor-positive breast cancers types [30,31]. There are numerous studies that have attempted to demonstrate the validity of this information also for the patients with pathogenic mutations and especially in the BRCA mutations carriers, but the results are contradictory, some claiming that there is no relationship [21,32], others validating the protective effect of breastfeeding in these patients [17,33,34]. Furthermore, some studies suggesting that longer breastfeeding is beneficial, especially for more aggressive forms of breast cancer, such as those caused by BRCA1 mutations, have shown that these tumors are usually triple-negative, but the exact mechanisms which makes this possible is not fully understood [35].

The use of combined hormonal contraceptives (CHC) did not influence the risk of breast cancer in patients with BRCA1 mutations nor in the group with pathogenic mutations in other genes, the results being similar to those obtained from other recent studies [14,36]. Narod at al. have reported the association of early onset breast cancer in BRCA1 mutations carriers taking oral CHC; the association was only for patients who took oral CHC treatment

before 1975 [37], when the hormonal doses were higher and when the treatment was initiated before 20 years of age [38].

Environmental and reproductive factors can influence both the risk and the age of onset of breast cancer in patients carrying pathogenic mutations. New molecular insight seems to challenge previous classic affirmations: in the present study breastfeeding had a protective effect against breast cancer occurrence only in patients without mutations. The risk of breast cancer is not affected in carriers of pathogenic mutations or in BRCA1 carriers by the number of abortions, parity, age at which the first pregnancy occurs, age at menarche and menopause, or by oral contraceptive use.

## Conflict of interests

The authors declare no conflict of interests.

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