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ORIGINAL ARTICLE

Maternal and paternal age at birth and the risk of breast cancer in Greek women: a case-control study

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Summary

Purpose: *To investigate the possible association between maternal and paternal age and breast cancer in Greek women.*

Methods: *This study enrolled 238 women with breast cancer and 153 healthy women as control group. All participants were examined clinically and with breast ultrasound and those older than 40 years, also with digital mammography.*

Results: *A statistically significant positive correlation was observed between the age of the father (x^2=52.985, p<0.001) and the mother (x^2=34.838, p=0.001). More specifically, in breast cancer patients, the majority of their mothers (45.4%) was over 30 years of age and their fathers' age (48.3%) was over 37 years of age.*

Conclusions: *Our study found that as the age of the father and mother increases, the incidence of breast cancer increases in parallel. Further studies with larger number of patients are necessary in order to clarify the real role of parental age as a risk factor of breast cancer.*

Key words: *breast cancer, maternal age, paternal age, parental age*

Introduction

A number of epidemiologic researches on the etiology of breast cancer focused on the prenatal factors [1,2]. Interestingly, it has been hypothesized that these factors may affect breast cancer risk by affecting the cumulative frequency of germ cell mutations [3,4] or by altering the hormonal environment of the fetus [5].

Older maternal age has been hypothesized to increase breast cancer risk in female offspring due to higher levels of endogenous estrogen concentrations [5,8]. In particular, there is some evidence that high prenatal estrogen cells may affect the mammary's gland structure. Moreover, the larger number of epithelial and stromal cells may offer a greater probability for genetic and epigenetic events that increase the risk of breast cancer.

Furthermore, older paternal and maternal age may increase breast cancer risk in later-born daughters because of germ cell mutations at older parental ages [9,10]. However, the results from previous studies are inconsistent possibly due to several factors such as the study design, the subject selection or the small number of breast cancer cases [6].

The purpose of this article was to analyze data from a case-control study in order to further investigate the parental age in relation to breast cancer risk.

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Methods

Study design

This research was a case-control retrospective study. Included was the data of patients who consulted in two breast clinics (Alexandroupolis University Hospital and Rea Hospital in Athens) between 2016 and 2019. Four hundred participants were enrolled in the study, but 19 had incomplete information and were excluded. Finally, the case-group included 238 women with histologically confirmed breast cancer after breast surgery, while the control group included 153 women without breast cancer and who were examined with clinical examination, breast ultrasound and/or bilateral digital mammography. The two groups were examined in the same period of time. All participants provided written informed consent.

Statistics

The obtained information regarding maternal and paternal age and the presence or absence of breast cancer was analysed with SPSS 20 statistical package software. Chi-square test (x^2) was used for statistical analysis and $p<0.05$ was considered as statistically significant.

Results

Our study consisted of 391 women, of whom 238 were breast cancer patients and 153 were healthy controls.

Of the 238 breast cancer patients who gave information of their mother age at their birth, 108 (45.4%) had mothers >30 years of age at their birth, 78 (32.8%) mothers aged 24-30 years, while only 52 (21.8%) had mothers <23 years old. On the other hand, from the 153 healthy participants, 64 (41.8%) had mothers <23 years of age at their birth and 62 (40.5%) had mothers aged 24-30 years, with only 27 (17.6%) having mothers >30 years old at their birth (Table 1).

Moreover, we noted that from the 238 breast cancer patients who gave information of their father age at their birth, 115 (48.3%) had fathers >37 years of age at their birth, 93 (39.1%) fathers aged 27-36 years, while only 30 (12.6%) had fathers <26 years old. On the other hand, from the 153 healthy participants, 50 (32.7%) had a father <26 years of age at their birth and 81 (52.9%) had fathers aged 27-36 years, with only 22 (14.4%) having fathers >37 years old at their birth (Table 2).

A statistically significant positive correlation was observed between the age of the father ($x^2=52.985$, $p<0.001$) and the mother ($x^2=34.838$, $p=0.001$). More specifically, in breast cancer patients, the majority of their mothers (45.4%) were over 30 years of age and their fathers' age (48.3%) was over 37 years of age. In general, we noticed that as the age of the father and mother increased, the incidence of breast cancer increased in parallel.

Table 1. Mother's age crosstab

	Mother's age (years)			
	<23	*24-30*	*30+*	*Total*
Cancer				
YES				
Count	52	78	108	238
% within cancer	21.8%	32.8%	45.4%	100.0%
NO				
Count	64	62	27	153
% within cancer	41.8%	40.5%	17.6%	100.0%
Total				
Count	116	140	135	391
% within cancer	29.7%	35.8%	34.5%	100.0%

	Chi-square test for mother's age		
	Value	*df*	*Asymp. Sig. (2-sided)*
Pearson x^2	34.838[a]	2	0.000
Likelihood ratio	36.491	2	0.000
Linear-by-Linear Association	33.063	1	0.000
N of valid cases	391		

[a]0 cells (0.0%) have expected count less than 5. The minimum expected count is 45,39.

Table 2. Father's age crosstab

	Father's age (years)			
	<26	*27-36*	*37+*	*Total*
Cancer				
YES				
Count	30	93	115	238
% within cancer	12.6%	39.1%	48.3%	100.0%
NO				
Count	50	81	22	153
% within cancer	32.7%	52.9%	14.4%	100.0%
Total				
Count	80	174	137	391
% within cancer	20.5%	44.5%	35.0%	100.0%

	Chi-square test for father's age		
	Value	*df*	*Asymp. Sig. (2-sided)*
Pearson x^2	52.985[a]	2	0.000
Likelihood ratio	56.443	2	0.000
Linear-by-Linear Association	50.779	1	0.000
N of valid cases	391		

[a]0 cells (0,0%) have expected count less than 5. The minimum expected count is 31,30.

Discussion

Positive relationship between maternal age at birth and breast cancer risk in female offspring was first described by Standfast in 1967 [10]. Subsequently, several studies have attempted to evaluate this possible association, however until now the results are controversial.

Only a few studies presented a slightly statistically significant increased risk [11,14], however none of them found a strong association [6]. Specifically, some studies found weak positive associations between older maternal age and breast cancer in offspring [1,11,13,14-21] and stronger associations in younger women [11,17,22].

In 2000, Innes et al found the biggest risk for breast cancer in women whose mothers were >35 years old at their birth [11]. Moreover, several studies found an increased breast cancer risk due to the increasing maternal age up to the intermediate (30-34 years old) which was then reduced for older than 35 years old women [1,2,12-14,21,23]. Interestingly, several researchers attributed this relationship to a possible association between maternal age and estrogen level during pregnancy [2,8,24,25]. Specifically, some researchers believe that in the intermediate maternal age there was a peak of estrogen levels, while after that there was a reduction [2]. They even support that because of a perimenopausal change in estrogens, women whose mothers were oldest at their birth were not in a high risk for breast cancer [2,24,25].

This inconsistent association between breast cancer risk and maternal age may be explained by taking into account differences in other maternal factors (such as pregnancy complications and maternal reproductive history) and ethnicity [2].

Overall, there is limited data about the possible association of paternal age and the risk for breast cancer in their female offspring. Some studies concluded that there was an increasing trend of breast cancer risk in women whose fathers were older in their birth [2,11,14,17,19]. Moreover, some previous studies found a significant linear trend between older paternal age and breast cancer risk in female offspring only in young cancer cases [17,19].

Additionally, other researchers concluded that this positive association relates only to African-Americans and that it was not associated with breast cancer for white women [26]. Moreover, some studies concluded that despite maternal age may have a little or no relation with breast cancer in female offspring, paternal age is not associated to risk of breast cancer [13,27].

Furthermore, the largest report about parental ages and breast cancer in Asian women found a 1.6-fold increased breast cancer risk in women whose fathers were ≥ 40 years old in contrast to

the fathers aged <30 years old. Over and above that, there was no statistically significant association for the maternal age in this study [2].

Conclusion

In our series of 391 Greek participants, we found that as the age of the father and mother increases, the incidence of breast cancer increases in parallel. Further studies with larger number of patients are necessary in order to clarify the real role of parental age as a risk factor of breast cancer.

Moreover, men and women should be better informed about their decision to become fathers and mothers at a high age and the possible dangers of such a decision to their offspring.

Conflict of interests

The authors declare no conflict of interests.

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