The possible role of allergic status as risk factor of breast cancer

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S u m m a r y. **Purpose:** *To investigate a possible risk factor for breast cancer: allergic status. This relation has not been explored very much in the literature.*
Material-Methods: *391 women who consulted in two breast clinics were enrolled in this study. From these, 238 had breast cancer and 153 had benign breast diseases or normal breast exams. All participants were examined clinically and with breast ultrasound, while those ≥40 years old, also with bilateral digital mammography. The statistic method used was x^2 (Chi-square test).*
Results: *Our study showed statistically significant positive correlation between allergic status and breast cancer (p<0.001).*
Conclusion: *This study pointed out that more than the "classic" risk factors for developing breast cancer, there are probably another "non-classic" risk factor represented by allergic status of the patient.*

INTRODUCTION

In 2018 it was estimated that approximately 9.6 million people died from cancer **(1)**. For this reason, cancer is a major threat to health population. Breast cancer is the world's most common malignant neoplastic disease in the female population under the age of 60 and is responsible for more than one in every 10 deaths in developed countries **(2-3)**.

Most cases of breast cancer are associated to factors related to menstrual history such as the early age of the first menstruation, obstetric factors

such the advanced mother's age in the first delivery, lifestyle factors such postmenopausal obesity, alcohol consumption and probably tobacco intake, among many others **(4)**. In 20 percent, breast cancer patients have a family history with a first-degree female relative with breast cancer, including cases with BRCA1 and BRCA2 gene mutations **(5-6)** in about 10% of the cases.

The topic about cancer's allergic background is not unusual **(7)**. The role of allergies in reducing or increasing the risk of developing cancer remains controversial **(8)**. Several epidemiological studies have assessed the relationship of allergic history with the occurrence of neoplastic diseases and have concluded that its onset depends on the immune function of each organism **(9-10)**.

In general, four possible mechanisms have been proposed to describe this relationship, which are based on either allergic inflammation or IgE antibodies. The four mechanisms are 1) the chronic inflammation, 2) the immune reaction related to the destruction of neoplastic cell's apoptosis, 3) the inappropriate T2 - helper immune skewing and 4) the immune system prophylaxis **(10)**. However, in some cohort studies, cancer patients appeared to have fewer IgE-background allergies than in the control population **(11)**.

However, the association between breast cancer and allergies remains unknown as a variety of studies confirm the negative or the positive relationship between them, while others reject this position **(8, 12-13)**. The main objective of this study was to investigate the possible association between history of allergies and breast cancer.

MATERIAL AND METHODS

Study design: This study is a case-control study. 391 women, who consulted in two breast clinics in Greece, were enrolled in this study and were divided in two groups. The case-group included 238 women with breast cancer confirmed by the histopathological analysis. On the other side, the control group included 153 healthy women who consulted in the breast clinics and were examined clinically, with breast ultrasound and/or bilateral digital mammography. The two groups were evaluated in the same period of time and all women had written an informed consent. We report if they presented in their medical history allergy reaction. We classified the allergy reaction in 3 stages: slight (simple reaction which did not need medication), mild (needed antihistaminic

medication) and severe (needed corticosteroids drugs and/or hospitalization).

Statistical analysis: The information regarding history of allergy and the presence of breast cancer or not, was analyzed using SPSS 20 software. Moreover, Chi-square test and Crosstabulation were performed in order to calculate the p-value. A statistical significant result was considered if p-value <0.05.

RESULTS

In our series consisted of 391 women, of who 238 were patients with breast cancer and 153 were without breast cancer: control group, the mean age of the patients at the time of onset of the disease was 58 years. The maximum age of the patients at the time of the disease was 94 years, while the minimum age was 26 years. For the women in the control group, the mean age was 56 years, the maximum age was 82 years, and the minimum age was 20 years.

Of the 391 participants in this study, 333 (85.2%) had no history of allergies and 58 (14.8%) had allergy. Of the participants without allergy, 191 (57.4%) were breast cancer patients, while the 42 (42.6%) were in the control group.

Regarding the patients with breast cancer, 191 from the 238 women (80.3%) had no history of allergies, while 47 (19.7%) had allergy. Regarding the 153 healthy women in the study, 142 (92.8%) had no history of allergies, while 11 (7.2%) had got **(Table 1)**. Moreover, Chi-square statistical test showed that there was a statistically significant positive correlation between allergy history and the risk of breast cancer (p<0.001) **(Table 2)**.

Furthermore, from the 47 breast cancer patients who had also allergy history, 32 (68.1%) had slight allergy, 13 (27.7%) had mild allergy and 2 (4.2%) had severe allergy who needed hospitalization. On the other hand, from the 11 participants of the control-group, 7 (63.6%) reported slight allergy, 3 (27.3%) mild allergy and 1 (9.1%) severe allergy who needed hospitalization **(Table 3)**. According to these results, there is no difference in the degree of allergy between the two groups.

Therefore, this study showed that women with a history of allergy are more likely to link to breast cancer than patients without this history: 4.5 times more independently of the degree of the allergy.

DISCUSSION

It is well known that breast cancer is dependent of genetic causes such as mutations in BRCA1 and BRCA2 oncogenes in about 10% of patients.

Moreover, environmental and demographic factors, patient habits, medical history, obesity, etc play a role with more than 80%-90% **(6, 14)**. The role of allergy status as risk factor in the development of breast cancer remains controversial **(8, 15-16)**.

Many studies **(2, 7, 10, 17-18)** reject the possible association of allergy status with breast cancer. This topic began in 1970 when scientists suggested that allergies were related to hyperstimulation of the immune system, so it would reduce the relative risk of cancer **(7)**. The same opinion was confirmed by Sherma et al where, after a cohort study, they concluded that IgEs protect against carcinogenic antigens before the neoplastic tissue is formed **(17)**. In fact, Zhang et al in 2016 concluded that patients with lower serum IgE levels < 32.6 IU / ml were more likely to develop breast cancer. Moreover, some authors showed low IgE levels in contrast to allergic individuals **(8, 19)**. In addition, the meta-analysis of Vojtechova et al, published in 2009, concluded that asthma or any other form of allergy is not associated with breast cancer as an aggravating factor **(16)**. Same results were published and in other studies **(18, 20)**.

In contrast, other studies concluded that the patient's allergic history increases the relative risk of breast cancer. Furthermore, the Sadeghi F et al study conducted in January 2019 concludes that breast cancer is associated with the pathological function of T2 helper rather than the increased Ig E levels and the relative risk of occurrence increases significantly in patients with allergic rhinitis, atopic dermatitis **(8)** or food allergies **(8, 19)**. Patients with atopic dermatitis, based on the study from Wang et al., had p = 0.92 while the weight-status increases the significant risk **(14)**. Joseph et al suggested four possible hypotheses for how cancer is related to allergies, two of which were the elevated IgE levels and the pathological function of T2 helpers and the common factor was the hypersensitivity of the immune system **(10)**.

In the most recent study by Kantor et al, published in June 2019, it appeared that certain types of cancer have an allergic background, e.g. lung cancer associated with asthma **(21)**. This, however, may not be the case with breast cancer **(22)**, since the basis of the study is p<0.19 for patients with allergies and p<0.56 for patients without allergies **(21)**. Furthermore, Hedderson MM et al, in their research study, including women aged 45 or younger, concluded that the relative risk of developing breast cancer in a patient with an allergic history is reduced in women older than 35 years old, while the age at which the allergy first appeared also played an important role **(23)**.

In our study, patients with the history of allergies appeared to be linked to develop breast cancer (p<0.001). Finally, the history of allergies has not been sufficiently proposed as a risk factor for breast cancer, this result is similar to other studies **(8)**.

CONCLUSION

In our study, of 391 participants Greek native, we found that patients with history of allergy presented more frequently breast cancer in contrast with patients without allergy. This study pointed out that beyond the "classic" risk factors for developing breast cancer, there are other "non-classic" risk factors, like history of allergy. Further studies with larger number of patients are necessary in order to confirm our findings: the possible role of allergy as a risk factor of breast cancer, and to explore the complex mechanisms of this association.

Conflicts of Interest: The author declares no conflicts of interest regarding the publication of this paper.

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Table 1. Table of participants with or not breast cancer and with or not allergy.

History of allergy * CASE/CONTROL Crosstabulation					
			CASE/CONTROL		Total
			Breast cancer patients	Healthy women	
History of allergy	NO	Count	191	142	333
		% within History of allergy	57.4%	42.6%	100.0%
		% within CASE/CONTROL	80.3%	92.8%	85.2%
		% of Total	48.8%	36.3%	85.2%
	YES	Count	47	11	58
		% within History of allergy	81.0%	19.0%	100.0%
		% within CASE/CONTROL	19.7%	7.2%	14.8%
		% of Total	12.0%	2.8%	14.8%
Total		Count	238	153	391
		% within History of allergy	60.9%	39.1%	100.0%
		% within CASE/CONTROL	100.0%	100.0%	100.0%
		% of Total	60.9%	39.1%	100.0%

Table 2. Controlling the history of allergy and the risk of breast cancer.

Chi-Square Tests					
	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	11.626[a]	1	.001		
Continuity Correction[b]	10.653	1	.001		
Likelihood Ratio	12.671	1	.000		
Fisher's Exact Test				.001	.000
Linear-by-Linear Association	11.596	1	.001		
N of Valid Cases	391				
a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 22.70.					
b. Computed only for a 2x2 table					

Table 3. Degree of allergy.

	Slight allergy	Mild allergy	Severe allergy	Total
Breast cancer patients	32 (68.1%)	13 (27.7%)	2 (4.2%)	47
Healthy women	7 (63.6%)	3 (27.3%)	1 (9.1%)	11