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Mastitis and Risk of Breast Cancer: a Case Control-Retrospective Study and Mini-Review

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ABSTRACT

Objective: *To investigate a possible association between mastitis and breast cancer risk in a cohort of Greek women.*

Material and methods: *A series of 343 women who visited two breast clinics in Greece and delivered live neonates were studied in our case-control retrospective study. The case group comprised women with breast cancer and the control group women without breast cancer. All participants were subjected to a clinical examination with breast ultrasound and those aged over 40 years underwent digital bilateral mammography.*

Results: *The X2 (chi-square) test was the statistical tool used by us. We noted a statistically significant relationship between mastitis and risk for breast cancer (p=0.04). Moreover, the relative risk for breast cancer among patients with mastitis was RR: 2.069.*

Conclusion: *Our study showed a relation between mastitis and breast cancer. Mastitis could be a potential risk factor. Further studies with larger number of patients are mandatory in order to confirm this possible relationship.*

Keywords: breast cancer, mastitis, breastfeeding, breast malignancy, breast cancer risk factors.

INTRODUCTION

Globally, breast cancer is the most frequent reported malignancy in women and the predominant cause of death (1). Many factors are known to be implicated, including mutation of breast cancer associated genes, increasing age, prenatal factors, family history of breast cancer, early menarche, delayed menopause, low parity, older age at first full-term pregnancy, hormone replacement therapy, high breast density, obesity, lack of exercise, alcohol consumption and tobacco use (2-4).

Oncogenesis and its correlation with inflammation was first discussed by Rudolf Virchow,

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impelled by the presence of leukocytes in malignant tissues. It is known that persistence of inflammation induces damage to cellular DNA, lipids and proteins through reactive oxygen and nitrogen species, and leads to tumorigenesis (5). Considering the above statement, mastitis as an inflammatory condition could affect women not only during breastfeeding, but also in any period of their life and could be a potential risk factor of breast cancer.

Lactational or puerperal mastitis referred to breast infection developed during breastfeeding (6). The milk stasis due to inadequate drainage of milk often as a result of oversupply, clogged duct, long interval period between breastfeeding or a sudden weaning in combination with the bacteria diffusion could contribute to the development of lactational mastitis (7). Bacteria involvement through fissures in the nipple area is increased in the maternal milk because this nutrient environment leads to their rapid colonization (8).

Except from the mother's skin, bacteria could be present in the mouth and nose of the infant during breastfeeding (7). The predominant bacteria found, is *Staphylococcus aureus*. Though, methicillin-resistant *S. aureus* has been the last years found to be the most causative factor implicated in the development of the infection. Other bacteria like *Streptococcus*, *Enterobacter* are involved in mastitis to a lesser extent.

Lactational mastitis represents the most common type of breast infection during postpartum and according to data affects 1% to 10% of breastfeeding women, its prevalence reaches 33% of the women during lactating period (8), with an increased risk during the first three weeks after delivery (7). Usually, a swollen, red, warm and painful area of the breast makes the clinical diagnosis and, if the infection is not treated, decreased milk flow, fever, myalgia, chills and flu-like symptoms could occur (9) (Figure 1).

Non-lactation mastitis affects not-breastfeeding women, with periductal mastitis, duct ectasia, plasma cell mastitis, idiopathic granulomatous and rarely, tuberculous mastitis (10). Periductal mastitis and plasma cell mastitis globally affect 5%-9% of non-menopausal women and their occurrence is strongly related to smoking (Figure 2). Clinically, in periductal mastitis, nipple discharge is the first symptom and can lead to abscess formation. Frequently, breast fistula can also be a complication (9). On the contrary, granulomatous

FIGURE 1. Lactional mastitis

FIGURE 2. Periductal mastitis

FIGURE 3. Peau d'orange

mastitis is a very uncommon inflammatory condition, uncrowded etiology may be autoimmune or developed within five years after weaning (7). Clinically nipple retraction, mass-like lesion, abscesses, skin ulceration, skin texture of an orange rind (*peau d'orange*) are the major findings (11) (Figure 3).

Tuberculous mastitis, comprising a key breast infection, accounts for about 0.025–0.1% of all treated breast conditions in the Western world, whereas in India the highest incidence prevalence approaches 3.6% of all breast diseases. Women during the second and third decade of their lives are more likely to be patients whose cases have been also recorded in breastfeeding women (12). Often, a painful breast lump is a common clinical symptom. Axillary node enlarged, fistula formation, and skin disorders are to be seen as well (11). Our study aimed to investigate the association between mastitis and breast cancer and therefore, this underlying correlation. ❑

MATERIAL AND METHODS

We conducted a case-control retrospective study using data of patients who visited two breast clinics in Greece and delivered live neo-

nates. The case-group comprised 203 women with histologically confirmed breast cancer history and the control group 140 women without history of breast cancer who underwent clinical examination, breast ultrasound and/or bilateral digital mammography. Both groups were examined in the same period of time between 2017 and 2020. All patients were asked to sign a written informed consent. The data was analyzed with SPSS 20 statistical package software. Chi-square test (X2) was used for statistical analysis and p-value < 0.05 was considered statistically significant. ❑

RESULTS

Of all 343 study participants, 36 (10.5%) developed mastitis. Of these, 27 (75%) were breast cancer survivors, who developed mastitis before breast and cancer development, and nine (25%) had no breast cancer. Of the total number of participants, 307 (89.5%) delivered live newborns and did not develop mastitis; of these, 176 (57.3%) subjects had breast cancer and the remaining 131 (42.7%) had not (Table 1).

In other words, out of the 203 breast cancer survivors who had given birth to live newborns before the onset of the present disease, 27 (13.3%) developed mastitis, while 176 (86.7%) did not. In addition, of all 140 patients without breast cancer who had given birth to live newborns, nine (6.4%) developed mastitis, while 131 (93.6%) did not.

Moreover, it is interesting to note that some of the associated risk factors for breast cancer were also studied, particularly including 1) family history of breast cancer; 2) personal history of complex breast diseases; 3) breast mammography density; 4) age at the first pregnancy; and 5) miscellaneous minor factors such as age of menarche, age of menopause, alcohol drinking, hormonal treatment, etc. In the group of patients with history of mastitis and later breast cancer, the associated factors of breast cancer were not statistically different from those seen in the group of patients without history of both mastitis and cancer. Actually, the parameter "history of mastitis" was more frequently present in patients with breast cancer that in those without breast cancer (p=0.04), underlying that "history of mastitis" could be considered an independent breast cancer risk factor, as it is proposed in many studies in the literature.

TABLE 1. Percentages of patients who developed mastitis

Mastitis * CASE/CONTROL					
			CASE/CONTROL		Total
			Patients – cancer survivors	Patients without breast cancer	
Mastitis	No	Count	176	131	307
		% within mastitis	57.3%	42.7%	100.0%
		% within case/control	86.7%	93.6%	89.5%
		% of total	51.3%	38.2%	89.5%
	Yes	Count	27	9	36
		% within mastitis	75.0%	25.0%	100.0%
		% within case/control	13.3%	6.4%	10.5%
		% of total	7.9%	2.6%	10.5%
Total		Count	203	140	343
		% within mastitis	59.2%	40.8%	100.0%
		% within case/control	100.0%	100.0%	100.0%
		% of total	59.2%	40.8%	100.0%

TABLE 2. Association of mastitis with the occurrence of breast cancer

Chi-square tests					
	Value	df	Asymp. sig. (2-sided)	Exact sig. (2-sided)	Exact sig. (1-sided)
Pearson chi-square	4.165[a]	1	.041		
Continuity correction[b]	3.466	1	.063		
Likelihood ratio	4.401	1	.036		
Fisher's exact test				.049	.029
Linear-by-linear association	4.153	1	.042		
N of valid cases	343				
a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 14.69.					
b. Computed only for a 2x2 table					

TABLE 3. Relative risk of mastitis and breast cancer

Risk estimate			
	Value	95% confidence interval	
		Lower	Upper
Odds ratio for case/control (Breast cancer survivors/No breast cancer patients)	.448	.204	.984
For cohort mastitis = No	.927	.865	.993
For cohort mastitis = Yes	2.07	1.004	4.263
N of valid cases	343		

Association of mastitis with the occurrence of breast cancer

Of the 343 women who breastfed, 27 (7.9%) developed mastitis and breast cancer. The control X2 (chi-square) test showed a significant correlation (p = 0.04) (Table 2). Moreover, women with

mastitis had a relative risk for developing breast cancer of 2.07 [O.R. 2.07, C.I (1.004-4.263)] (Table 3). ❑

DISCUSSION

In our population-based study, a significant correlation between mastitis and breast cancer risk was found. During the last decade, many studies that have been carried out in an effort to find the possible role of inflammation in the neoplastic procedure. Chen *et al* conducted a population based study, including 8 634 females, of which 734 had been diagnosed with mastitis. Their results were consistent with our findings, showing the higher risk for developing breast cancer among women with mastitis (13).

In addition, Chang *et al* examined the incidence of breast malignancy among women with non-lactational mastitis. In their study, they enrolled 3,091 patients with non-lactational mastitis and 12,364 without mastitis. According to their results, non-lactational mastitis seems to be a risk factor for breast cancer. It is clearly mentioned that non-lactation mastitis constitutes a risk factor for patients belonging to either of the following three subgroups: women aged 40-49 years, women with lower socioeconomic status and women who receive hormonal replacement treatment (14).

The correlation between inflammation and carcinogenesis was supported by many studies. Inflammatory biomarkers, including C-reactive protein (CRP) and leukocyte counts, were examined as possible risk factor of tumorigenesis in a population-based cohort study. During this investigation, there was a positive association between inflammatory factors and cancer (15). High sensitivity CRP protein, white blood cell (WBC) count, abnormal levels of C-X3-C motif chemokine ligand 1, platelet-derived growth factor subunit B homodimer, interleukin 10, C-C motif chemokine ligand (CCL) 21, and CCL 11 were also linked to an increased risk of prostate cancer, thus supporting the role of inflammation not only in breast cancer but also in other types of cancer (16-17).

Also, Bhatelia *et al* indicated inflammation as a breast cancer risk factor. In their scientific report, they found that bacteria, viruses, fungi and endogenous molecules released by an injury or from dead cells in the body contributed to activation of inflammation pathways, proving that chronic inflammatory conditions facilitated the process of tumorigenesis and metastasis (18). In the case of mastitis, the long exposure to this pathogen associated patterns and specifically to the associated bacteria is the key component that links mastitis with the increased risk of breast cancer (14, 19).

We describe below a case that enhances the role of inflammation in the etiology of breast malignancy. A 34-years old woman was examined for a recurrent clinical feature of right breast swelling and abscess. Biopsies were performed and the histological result pointed to chronic granulomatous mastitis. During the follow-up period, a metastatic orbital tumor was detected. A core biopsy of the right breast followed, indicating the presence of invasive ductal carcinoma. The fact that chronic granulomatous mastitis was the primary breast disease in this patient before the development of the breast malignancy suggests that breast cancer could arise from sites of a chronic inflammatory condition (20).

In 2013, Limaiem *et al* presented another case of a rare diagnosis of a coexistence of granulomatous mastitis and ductal carcinoma in a 77-year-old patient. In their concluding remarks, they also proposed the theory that mastitis could be a possible cause of breast malignancy (21).

A slight overall association between mastitis and breast cancer was noted in a large cohort study conducted by Lambe *et al*, in which 106 (approximately 1.2%) women of the total number of 8 411 female participants with clinical features of mastitis had been diagnosed with breast cancer (19).

In summary, the majority of published reports showed that inflammation and, by extension, mastitis could be linked to the risk of breast cancer. ❑

CONCLUSION

Our study associated mastitis with a future risk of breast cancer. Crucially, the immediate access to health providers together with preventative measures makes mastitis a modifiable risk factor in contrast to other non-modifiable risk factors for breast cancer such as gene mutation and aging. Future studies should clarify the possible role of inflammation as a co-factor in the mutation progress of ductal cells and carcinogenesis. ❑

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