ORIGINAL PAPER

Breastfeeding and Breast Cancer Risk: Our Experience and Mini-review of the Literature

Anastasia Bothou[1,2,3], Stefanos Zervoudis[4], Maria Iliadou[1], Panagiota Pappou[1], Georgios Iatrakis[1,4], Georgios Tsatsaris[3], Panagiotis Peitsidis[1,4], Aggeliki Gerende[3], Anna Chalkidou[3], Xanthi Anthoulaki[3], Nikolaos Nikolettos[3], Panagiotis Tsikouras[3]

[1]Department of Midwifery, University of West Attica (UniWA), Athens, Greece

[2]Neonatal Department, "Alexandra" General Hospital, Athens, Greece

[3]Department of Obstetrics and Gynecology, Democritus University of Thrace

[4]REA Hospital, Athens, Greece

Corresponding author:
Dr. A. Bothou, MSc, PhD. "Alexandra" General Hospital, Lourou 2-4, Athens, Greece, Zip code: 11528. E-mail: natashabothou@windowslive.com, Tel: +00306951030017. ORCID ID://http/ww.oric.org/0000-0000-0000-0000.

ABSTRACT

Background: According to data from World Health Organization, breast cancer constitutes the second most common diagnosed malignancy after lung cancer and the second leading cause of death among women in 2020, worldwide. The protective role of breastfeeding in the emergence of breast malignancy has been mentioned in several studies, indicating the important part it can have in the effort of reducing breast cancer's incidence. **Objective:** To investigate a possible association between breastfeeding and breast cancer risk in Greek women. **Methods:** Totally, 391 women participated in our case-control retrospective study. In the case group included 238 women with breast cancer, while in control group 153 women without breast cancer who were enrolled in two breast clinics in Greece. All women were examined clinically and with breast ultrasound, while those older than 40 years old also with bilateral digital mammography. **Results:** The x^2 (chi-square) test found a statistically significant reverse correlation between breast cancer and breastfeeding ≥12 months (cumulative) (p = 0.001). It was observed that the percentages of patients who breastfed ≥12 months were lower than those of healthy women. **Conclusion:** Breastfeeding and particularly the cumulative period of ≥12 months is related to the maximum of the protection from breast cancer.

Keywords: Breast cancer, Breastfeeding, Lactation, Breast Malignancy, Breast cancer risk factors.

1. BACKGROUND

According to data from World Health Organization, breast cancer constitutes the second most common diagnosed malignancy after lung cancer and the second leading cause of death among women in 2020, worldwide (1). Similarly, in Europe, including Greece, breast cancer was also in this period of time the second most frequent detected cancer after lung cancer and the second cause of mortality for women. Analytically, in Greece the incidence rate was 27.5% (1). Breast cancer mortality varied among countries and related to woman's age, however, little variation exists across Human Development Index (HDI) levels (67.0-88.4 per100,000) in women (2).

It has been discovered that genetic, environmental, reproductive and lifestyle-related factors are implicated to the development of this disease. Family history or breast cancer mutation of BRCA1 and/or BRCA2 genes, early age at menarche and late age at menopause, low number of full-term pregnancies, late age at first completed pregnancy, short cumulative breastfeeding duration, high endogenous amount of estrogen, increased BMI, complex benign breast diseases, high breast mammographic density and alcohol consumption are strongly related factors for breast cancer (3-7). Low physical activity and smoking are also related with increase breast cancer risk but in lower intensity. The protective role of breastfeeding in the emergence of breast malignancy has been mentioned in several studies, indicating the important part it can have in the effort

Cumulative breastfeeding months * CASE/CONTROL Crosstabulation

			CASE/CONTROL		Total
			Patients	Healthy	
Cumulative breastfeeding months		Count	35	13	48
		% within Breastfeeding	72.9%	27.1%	100.0%
		% within CASE/CONTROL	14.7%	8.5%	12.3%
		% of Total	9.0%	3.3%	12.3%
	<1 month	Count	44	12	56
		% within Breastfeeding	78.6%	21.4%	100.0%
		% within CASE/CONTROL	18.5%	7.8%	14.3%
		% of Total	11.3%	3.1%	14.3%
	1-3 months	Count	32	17	49
		% within Breastfeeding	65.3%	34.7%	100.0%
		% within CASE/CONTROL	13.4%	11.1%	12.5%
		% of Total	8.2%	4.3%	12.5%
	>3-6 months	Count	20	22	42
		% within Breastfeeding	47.6%	52.4%	100.0%
		% within CASE/CONTROL	8.4%	14.4%	10.7%
		% of Total	5.1%	5.6%	10.7%
	>6-9 months	Count	26	13	39
		% within Breastfeeding	66.7%	33.3%	100.0%
		% within CASE/CONTROL	10.9%	8.5%	10.0%
		% of Total	6.6%	3.3%	10.0%
	>9-11 months	Count	9	11	20
		% within Breastfeeding	45.0%	55.0%	100.0%
		% within CASE/CONTROL	3.8%	7.2%	5.1%
		% of Total	2.3%	2.8%	5.1%
	≥12-24 months	Count	22	40	62
		% within Breastfeeding	35.5%	64.5%	100.0%
		% within CASE/CONTROL	9.2%	26.1%	15.9%
		% of Total	5.6%	10.2%	15.9%
	>24-36 months	Count	8	17	25
		% within Breastfeeding	32.0%	0.8%	100.0%
		% within CASE/CONTROL	3.4%	11.1%	6.4%
		% of Total	2.1%	4.4%	6.4%
	>36 months	Count	2	3	5
		% within Breastfeeding	40.0%	60.0%	100.0%
		% within CASE/CONTROL	0.8%	2.0%	1.3%
		% of Total	0.5%	0.8%	1.3%
	Not at all	Count	40	5	45
		% within Breastfeeding	88.9%	11,1%	100.0%
		% within CASE/CONTROL	16.8%	3.3%	11.5%
		% of Total	7.7%	1.3%	11.5%
Total		Count	238	153	391
		% within Breastfeeding	60.9%	39.1%	100.0%
		% within CASE/CONTROL	100.0%	100.0%	100.0%
		% of Total	60.9%	39.1%	100.0%

Table 1. Cumulative breastfeeding months

of reducing breast cancer's incidence. The possible mechanisms of the protective effect of breastfeeding are unclear until now and more investigation is needed. Nevertheless, some theories have been proposed. During breastfeeding, the circulation hormones such Estradiol, Prolactin and Growth hormone is reduced and by this way the risk of breast malignancy decreased. Another biological explanation regarding the protection of breastfeeding concerns

the status of the epithelial cells of parous mammary gland which are more differentiated and less proliferative and by this way less prone to malignant mutation (8). Remarkably, type III lobules are developed only during pregnancy and type IV lobules which are fully mature appear under the influence of hormonal changes only during lactation (9). The protection of mammary cells against cancerous mutation is enhanced through breastfeeding which contributes to their final differentiation making them less susceptible to malignant transformation. Finally, the process of apoptosis that occur during breastfeeding removes from breast ductal tissue mammary cells with initial DNA mutation and therefore decreases the risk of breast cancer development (10). On the other hand, breastfeeding has also some challenges e.g. mastitis, abscess, chronic inflammation and possible due to the traumatic procedure of breast pumping etc. not very frequently (11), but the balance between breastfeeding or not, is clearly pro breastfeeding. Nevertheless, as it was mentioned above, more investigation should be conducted in order to clarify the protective role of breastfeeding.

2. OBJECTIVE

To investigate a possible association between breastfeeding and breast cancer risk in Greek women.

3. MATERIAL AND METHODS

This research is a case-control bicentric study. We collected the data of breast cancer patients who consulted in two breast clinics in Greece, between 2016 and 2019. The 391 participants included in the study were divided in two groups. More specifically, the case-group included 238 women (60.9%) with breast cancer confirmed after breast surgical procedure by the histopathological analysis. On the other hand, the control group included 153 healthy women (39.1%), who were examined with clinical examination, breast ultrasound and/or bilateral digital mammography without evidence for breast cancer. All the women of the two different groups were assessed in the same period of time, after a written informed consent.

The information regarding breastfeeding and the possible relationship with the presence or absence of breast cancer was analyzed using SPSS 20 software. Moreover, Chi-square test (x^2) was performed in order to calculate the p-value. A statistical significant result was considered if p-value was inferior to 0.05.

4. RESULTS

By calculating cumulatively the breastfeeding months of all participants, 48 out of 391 participants (12.3%) of the survey either did not have a pregnancy or did not breastfeed at all because they had not given birth to a living newborn. Of these, 5 (72.9%) were breast cancer patients and 13 (27.1%) were healthy. 56 (14.3%) of the 391 participants of this study breastfed for <1 month. Of these, 44 (78.6%) were breast cancer patients and 12 (21.4%) were healthy. 49 of the 391 (12.5%) participants breastfed for 1-3 months. Of these, 32 (65.3%) were breast cancer patients and 17 (34.7%) were healthy. 42 of the 391 (10.7%) participants breastfed for a period of >3-6 months. Of these, 20 (47.6%) were patients and 22 (52.4%) were healthy. 39 of the 391 (10%) partici-

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	63.797ª	8	.000
Likelihood Ratio	66.187	8	.000
N of Valid Cases	391		

a. 2 cells (11.1%) have expected count less than 5. The minimum expected count is 1.96.

Table 2. Breastfeeding correlation test ≥12 months (cumulatively) with the risk of breast cancer

pants breastfed for >6-9 months. Of these, 26 (66.7%) were breast cancer patients and 13 (33.3%) were healthy. 20 of the 391 (5.1%) participants breastfed for a period of >9-11 months. Of these, 9 (45%) were breast cancer patients and 11 (55%) were healthy. 62 of the 391 (15.9%) participants breastfed for a period of ≥12-24 months. Of these, 22 (35.5%) were patients and 40 (64.5%) were healthy. 25 of the 391 participants (6.4%) breastfed for a period of >24-36 months. Of these, 8 (32%) were breast cancer patients and 17 (68%) were healthy. 5 of the 391 (1.3%) participants breastfed for >36 months. Of these, 2 (40%) were breast cancer patients and 3 (60%) were healthy. Finally, 45 of the 391 participants (11.5%) did not breastfeed at all by personal choice. Of these, 40 (88.9%) were breast cancer patients and 5 (11.1%) were healthy.

Simply put, of the 238 breast cancer patients, 35 (14.7%) either had no pregnancy or did not breastfeed at all because they had not given birth, 44 (18.5%) breastfed for <1 month, 32 (13.4%) breastfed for 1-3 months, 20 (8.4%) breastfed for > 3-6 months, 26 (10.9%) breastfed for > 6-9 months, 9 (3.8%) breastfed for > 9-11 months, 22 (9.2%) breastfed for ≥12-24 months, 8 (3.4%) breastfed for > 24- 36 months, 2 (0.8%) breastfed for >36 months and 40 (16.8%) did not breastfeed at all by choice. In addition, of the 153 healthy participants in the study, 13 (8.5%) either had no pregnancy or did not breastfeed at all because they had not given birth to a live newborn, 12 (7.8%) breastfed for <1 month, 17 (11.1%) breastfed for 1-3 months, 22 (14.4%) breastfed for >3-6 months, 13 (8.5%) breastfed for >6-9 months, 11 (7.2%) breastfed for >9-11 months, 40 (26.1%) breastfed for ≥12-24 months, 17 (11.1%) breastfed for >24-36 months, 3 (2%) breastfed for> 36 months and 5 (3.3%) did not breastfeed at all by personal choice (Table 1).

The x^2 (chi-square) test found a statistically significant reverse correlation between breast cancer and a cumulative breastfeeding ≥12 months (p = 0.001) (Table 2). It was observed that the percentages of breast cancer patients who breastfed ≥12 months were lower than those of healthy women.

5. DISCUSSION

In our study, the association between longer cumulative breastfeeding and breast cancer's incidence reduction was proved. Particularly, we observed that participants referring breastfeeding's duration for one year or longer presented the lowest risk of breast cancer. Throughout the years the role of breastfeeding as a protective factor against breast cancer has been extensively investigated in several

studies and the number of them that relate breastfeeding with breast cancer prevention is constantly increasing. In a multi-population study consisted of 50.302 women with breast cancer and 96.973 control cases from 47 epidemiological studies in 30 countries it was found that the relative risk for breast cancer is reduced by 4.3% for every 12 months of cumulative breastfeeding, indicating that the duration of breastfeeding is linear linked to the percentage of breast malignancy's reduction (12). This conclusion seems to be in accord with our findings. The possible correlation between breast malignancy and breastfeeding was also discussed by Nagata et al in a systematic review focused on the Japanese Population (13). In overall, three cohort studies and five case-control ones were included. Only the majority of the case-control studies found an association, with the extended duration of breastfeeding presented to be a protective factor against breast cancer, a fact that totally corresponds with our results (13). A dose dependent relation between the cumulative period of breastfeeding and breast cancer risk was also observed in a meta-analysis of Chowdhury et al, with the greatest risk reduction being found in women breastfed for up to one year (8). Additionally, the protective effect of breastfeeding was proved in a supplementary study by Ma et al. (14). According to their results regarding the molecular type of breast cancer around 40% risk reduction against triple negative and Luminal A breast cancer type was revealed for women breastfed for 1 year or longer, whereas those breastfeed for 6 months or longer and belonging at a younger age group were protected by 82% (14). Tan et al investigate as well this correlation in a multi-cultural study of Asian population consisted of 7.663 women with different cultural and religious characteristics, covering that way a wide range of cultural settings (15). In consistence with our findings, a J-shaped association between cumulative breastfeeding duration and breast cancer incidence was observed. Particularly, a cumulative breastfeeding period of more than 12 months was associated with the highest percentage of breast cancer risk reduction, a fact that corresponds absolutely with our findings (15). A non-linear association between breastfeeding and risk of breast malignancy was also discovered in an analysis consisted of approximately 6.000 Hispanic women, which data came from four population-based studies (16). The results showed that the longer the cumulative breastfeeding period was, the more reduced the risk of breast cancer was for both pre-and postmenopausal women, with a cumulative period of 25 months of breastfeeding being correlated with 37 % decrease of the relative risk (16).

Breastfeeding as a modifiable factor seems to be of unique interest in the field of breast cancer prevention. Data from World Health Organization warn that only 40% of mothers follow the trend <<breastfeeding only>> for their infants at the first six months of their lives (17). National Survey comes to supplement the above statement revealing that the percentage of mothers that breastfeed their infants according to published and medical accepted recommendations be extremely low, estimated to 36%. The same study showed that only 38.5% of women in United States were informed about the breastfeeding's benefits. Interestingly, it was also observed that women had a greater likelihood of longer cumulative breastfeeding according to the recommendations from the Centers for Disease Control and Prevention (CDC) when they were informed about the protective effect that lactation offers against breast cancer (18). Among the benefits that breastfeeding could offer to the public health could be the decrease of breast cancer's incidence in some subpopulations such as black women. In this population, the risk of breast cancer is higher compared to white women regarding triple-negative and Hormonal Receptors Negative breast cancer (10). Although, breastfeeding is correlated with multiple benefits for both mother and infant, the target for extended period of breastfeeding is not yet well accomplished by the mothers.

6. CONCLUSION

Breastfeeding provides benefit to the infant and to the mother. Regarding breast cancer mostly studies as our proved that breastfeeding particularly more than 1 year has a protective effect. Thus, it is an urgent need for women all over the world to be informed about the benefits of breastfeeding as protector factor of breast cancer. Moreover, this positive effect has more evidence when breastfeeding is performed for cumulative period of ≥12 months, this duration seems to allow the maximum of the protection.

• REFERENCES

1. World Health Organization, Globocan, 2020.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May; 71(3): 209-249. doi: 10.3322/caac.21660.
3. Jerônimo AF, Freitas ÂG, Weller M. Risk factors of breast cancer and knowledge about the disease: an integrative revision of Latin American studies. Cien Saude Colet. 2017 Jan; 22 (1): 135-149. doi: 10.1590/1413-81232017221.09272015.
4. Schonfeld SJ, Pee D, Greenlee RT, Hartge P, Lacey JV Jr, Park Y, Schatzkin A, Visvanathan K, Pfeiffer RM. Ef- fect of changing breast cancer incidence rates on the calibration of the Gail model. J Clin Oncol. 2010, 28: 2411-2317.
5. Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, Schairer C, Mulvihill JJ. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst. 1989; 81: 1879-1886. doi: 10.1093/jnci/81.24.1879.
6. Brentnall AR, Cuzick J. Risk Models for Breast Cancer and Their Validation. Stat Sci. 2020 Mar 3; 35(1): 14-30. doi:

10.1214/19-STS729.

7. Iatrakis G, Daures JP, Geahchan N, Maudelonde T, Bothou A, Chraibi C, Omar O, Voiculescu S, Antoniou E, Youseff T, Tsikouras P, Galazios G, Chalazonitis A, Zervoudis S. Manosmed* University`s Risk factor calculator for female breast cancer: Preliminary data. Review of Clinical Pharmacology and Pharmacokinetics, International Edition. 2018; 32: 23-27.

8. Chowdhury R, Sinha B, Sankar MJ, Taneja S, Bhandari N, Rollins N, Bahl R., Martines J. Breastfeeding and maternal health outcomes: a systematic review and meta-analysis. Acta Paediatr. 2015 Dec; 104(467): 96-113. doi: 10.1111/apa.13102.

9. Russo J, Rivera R, Russo IH. Influence of age and parity on the development of the human breast. Breast Cancer Res Treat. 1992; 23: 211-218.

10. Anstey EH, Shoemaker ML, Barrera CM, O'Neil ME, Verma AB, Holman DM. Breastfeeding and Breast Cancer Risk Reduction: Implications for Black Mothers. Am J Prev Med. 2017 Sep; 53(3S1): S40-S46. doi: 10.1016/j.amepre.2017.04.024.

11. Bothou A, Iatrakis G, Zervoudis S, Tsatsaris G, Lykeridou K, Deuteraiou D, Galazios G, Nikolettos N, Tsikouras P. Breast milk suction pumping and a possible relation to breast cancer: A bicentric study. Review of Clinical Pharmacology and Pharmacokinetics, International Edition. 2020; 35: 5-8.

12. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. Lancet. 2002 Jul 20; 360(9328): 187-195. doi: 10.1016/S0140-6736(02)09454-0.

13. Nagata C, Mizoue T, Tanaka K, Tsuji I, Tamakoshi A, Wakai K, Matsuo K, Ito H, Sasazuki S, Inoue M, Tsugane S. Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan. Breastfeeding and breast cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. Jpn J Clin Oncol. 2012 Feb; 42(2): 124-130. doi: 10.1093/jjco/hyr182.

14. Ma H, Ursin G, Xu X, Lee E, Togawa K, Duan L, Lu Y, Malone KE, Marchbanks PA, McDonald JA, Simon MS, Folger SG, Sullivan-Halley J, Deapen DM, Press MF, Bernstein L. Reproductive factors and the risk of triple-negative breast cancer in white women and African-American women: a pooled analysis. Breast Cancer Res. 2017 Jan 13; 19(1): 6. doi: 10.1186/s13058-016-0799-9.

15. Tan MM, Ho WK, Yoon SY, Mariapun S, Hasan SN, Lee DS, Hassan T, Lee SY, Phuah SY, Sivanandan K, Ng PP, Rajaram N, Jaganathan M, Jamaris S, Islam T, Rahmat K, Fadzli F, Vijayananthan A, Rajadurai P, See MH, Thong MK, Mohd Taib NA, Yip CH, Teo SH. A case-control study of breast cancer risk factors in 7,663 women in Malaysia. PLoS One. 2018 Sep 14; 13(9): e0203469. doi: 10.1371/journal.pone.0203469.

16. Sangaramoorthy M, Hines LM, Torres-Mejía G, Phipps AI, Baumgartner KB, Wu AH, Koo J, Ingles SA, Slattery ML, John EM. A Pooled Analysis of Breastfeeding and Breast Cancer Risk by Hormone Receptor Status in Parous Hispanic Women. Epidemiology. 2019 May; 30(3): 449-457. doi: 10.1097/EDE.0000000000000981.

17. World Health Organization, Breastfeeding, 20 Feb 2018.

18. Hoyt-Austin A, Dove MS, Abrahão R, Kair LR, Schwarz EB. Awareness That Breastfeeding Reduces Breast Cancer Risk: 2015-2017 National Survey of Family Growth. Obstet Gynecol. 2020 Dec; 136(6): 1154-1156. doi: 10.1097/AOG.0000000000004162.