

Breastfeeding and its Association with Breast Cancer: a Systematic Review of the Literature

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ABSTRACT

Objective: Breast cancer is a global public health issue. The disease can be diagnosed in both older and younger women, with the latter facing several dilemmas. Breastfeeding is of general concern to the scientific community as well as its connection with the prevention of breast cancer is being sought. The purpose of this review is to search for studies investigating the relationship between breast cancer and breastfeeding.

Material and methods: The articles included in the present paper were searched in PubMed and Scopus databases according to PRISMA guidelines for systematic reviews. This systematic review sought primary studies investigating the relationship between breastfeeding and breast cancer and that were published in English between 2017–2022.

Results: Seventeen articles that investigated the relationship of breast cancer with lactation duration, women's age, family history and lifestyle were included in the present review.

Conclusions: It was found that, in most studies, breastfeeding could be evaluated as a protective factor of the disease. From all studied articles, the need for the design of additional studies investigating the relationship between breastfeeding and breast cancer emerges.

Keywords: breast cancer, breastfeeding, pregnancy, prevention, protective factor.

INTRODUCTION

Breast cancer is considered the most commonly diagnosed cancer during pregnancy (1) as 10% of patients with the disease worldwide are under the age of 40. It is also the most common diagnosis among teenage and young adult girls aged 15 to 39 years. Specifically, it is estimated that approximately 0.2%–2.6% of all breast cancers occur during pregnancy and approximately 35%–55% of women under 45 years of age will

develop breast cancer within 5–10 years of pregnancy (2).

Breast cancer is a disease in which breast cells start to multiply uncontrollably. The majority of breast cancers start in the ducts or lobules and can spread outside the boundaries of the breasts through the blood vessels and lymph nodes.

There are several advantages to breastfeeding for both the mother and child (3-4). As for the mother, it has been observed that breastfeeding contributes to the more immediate loss of preg-

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nancy weight after childbirth and contributes to the faster return of the uterus to its normal size. Breastfeeding is also a protective factor for women's health as it has been shown to help reduce the risk of type 1 and 2 diabetes mellitus, dyslipidemia, breast cancer and ovarian cancer. Moreover, the infant has several benefits from breastfeeding as it provides all the necessary nutrients in the appropriate quantity and quality according to its stage of development, and helps to protect it from a variety of infections such as respiratory, gastrointestinal and ear infections and contributes to their future protection from the development of food allergies (5).

Breastfeeding is considered to be the best option for infant feeding as it contains the essential nutrients in the right proportion and quality. The World Health Organization (WHO) recommends exclusive breastfeeding for the first six months of an infant's life and its continuation until the second year of life, combined with the introduction of solid foods (6-7). Breastfeeding is a factor that may help reduce the risk of breast cancer, especially in cases where a woman has been breastfeeding for more than one year (8), but there is less benefit for those who manage to breastfeed for a shorter period (9). Breastfeeding has also been associated with an improved prognosis for the disease and a reduction in relapses. However, there are also studies in which the protective effect of breastfeeding is not proven (10). □

MATERIAL AND METHOD

This systematic review aims to investigate the relationship between breastfeeding and the development of breast cancer.

In the present study we used PRISMA methodology for systematic reviews, in which scientific studies related to the topic of the study are compared with each other. The following steps were carried out for data collection and analysis: 1) search for literature sources on the internet; 2) selection of studies that met the inclusion and exclusion criteria; and 3) analysis, comparison and presentation of the results of the studies.

Articles published between 2017 and 2022 were searched in two databases, PubMed and Scopus. PubMed searches were conducted from 15 February 2023 to 17 February 2023 and Scopus searches between 17 February 2023 and 26

February 2023. The query used to search the relevant articles included ("Breast neoplasms*" [tw] OR "breast cancer" [tw]) AND ("breastfeeding" [tw] OR lactation [tw] OR "breastfeeding duration") [tw] OR ("exclusive breastfeeding" [tw] OR "breastfed" [tw] OR breastfed [tw]) AND (prevention [tw] OR "limiting factor" [tw] OR "protective factor") for PubMed and ("Breast neoplasms*" OR "breast cancer") AND ("breastfeeding" OR "lactation" OR "breastfeeding duration") OR ("exclusive breastfeeding" OR "breastfed") AND (prevention OR "limiting factor" OR "protective factor") for Scopus.

Sixty-one of the 186 papers found in both databases were available in PubMed and the remaining 126 in Scopus. Following processing, duplicate articles accounted for 41 of the deleted articles, leaving 145 items awaiting additional title and abstract verification. Following this review, 104 items were eliminated, leaving a total of 41, of which three were full-text but unavailable. Inclusion and exclusion criteria were used for the remaining 38 articles. The analysis contained a total of 17 published papers that satisfied the inclusion criteria (Figure 1, Table 1).

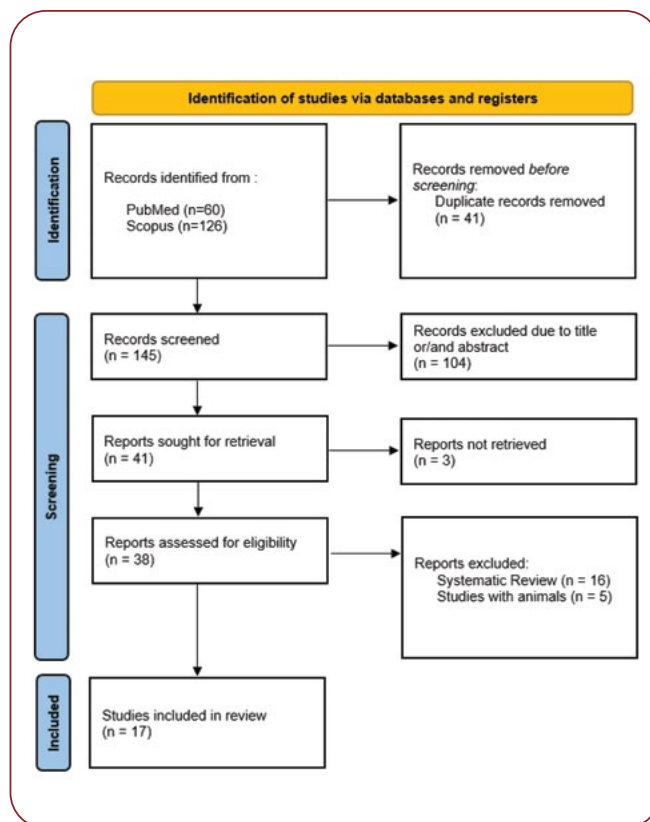


FIGURE 1. Flow chart of the systematic review according to PRISMA 2020

TABLE 1. Overview of included studies

	Authors (year)	Study population	Type of study	Tools-intervention	Results
Short Breastfeeding Duration is Associated with Premature Onset of Female Breast Cancer	Fernández-Aparicio A, <i>et al</i> (2022)	Women aged 19-91 years with diagnosed and treated BC at the University Hospital of Granada, Spain	Retrospective study	Article title	Women who breastfed for >3 months and had a family history of BC were diagnosed with the disease at age <60. In contrast, those with no family history of BC were diagnosed at about 70 years of age. Maternal lactation appears to have a possible protective effect on BC.
Association of risk factors and breast cancer among women treated at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia: a case-control study	Hassen F, <i>et al</i> (2022)	Female patients aged 40-60 years who were treated for BC and women without BC from Ethiopia	Case-control study	Participants were interviewed by experienced and trained nurses. Physical examination of the breast was performed by oncology residents to select appropriate controls.	There was no statistically significant association between BC and age at menopause, oral contraceptive use, duration of breastfeeding and age at last delivery.
Reproductive risk factors associated with breast cancer in young women by molecular subtype	Ruddy KJ, <i>et al</i> (2022)	Women recently diagnosed with BC in Minnesota	Retrospective study	The study examined a subset of Mayo Clinic Breast Disease Registry (MCBDR) enrollees diagnosed between 2015–2020 who were aged <55 at the time of BC diagnosis and not known to be intact based on previous MCBDR survey responses.	The only variable that significantly differed by subtype was a history of seeking care for breast or nipple pain that interfered with breastfeeding, which was more common in patients with TNBC.
Promote Community Engagement in Participatory Research for Improving Breast Cancer Prevention: The P.I.N.K. Study Framework	Franchini M, <i>et al</i> (2022)	Women who have been examined in P.I.N.K. diagnostic centres in Italy	Cross sectional study	The P.I.N.K. study collects data using questionnaires to investigate women's risk factors, family history and lifestyle to create a comprehensive set of information that will allow the definition of personalized risk profiles. Questionnaire data are linked to a database that stores standardized clinical data collected by radiologists.	Current findings suggest that pregnancy, breastfeeding, salt restriction, and oral contraception use could have different effects on cancer risk, based on a woman's overall risk profile.
Comparison of clinical features and the impact of reproductive factors on by age at diagnosis young and elderly breast cancer patients in the middle Anatolian region of Turkey	Eren SK, <i>et al</i> (2022)	Women in Turkey diagnosed with BC at the General Surgery Clinic of Kayseri City Training and Research Hospital	Retrospective study	Data were collected retrospectively between October 2015–March 2021, including 77 young BC patients (≤ 40 years) and 107 elderly ones (>65 years) out of a total of 567 patients.	The total duration of breastfeeding, the number of biological children and the first age of term pregnancy were statistically significantly different between groups.
Impact of Birth Cohorts in Breast Cancer risk Among South Korean Women	Yeo JH, Kim MT (2021)	South Korean women aged ≥30 who had at least one full-term pregnancy	Cross sectional study	Data collection from personal interviews using a questionnaire	The effect of reproductive risk factors on BC incidence may be much weaker than the effect of socioeconomic factors.
A methylation signature at the CpG island promoter of estrogen receptor beta (ER-β) in breasts of women may be an early footprint of lack of breastfeeding and nulliparity	Daraei A, <i>et al</i> (2021)	Women from Tehran who have not had BC	Clinical study	Demographic and reproductive data, medical history, family background of cancers were collected by postoperative questionnaire. Genomic DNA of all breast tissues was extracted using High Pure PCR Template Preparation Kit.	These results may provide key clues for uncovering the epigenetic mechanism by which lack of breastfeeding influences the risk factor for breast cancer, as well as for introducing possible new early screening and prevention strategies.
Clinical and pathological features and risk factors for primary breast cancer patients	Lei YY, <i>et al</i> (2021)	BC patients aged 26-95 years old in China	Retrospective case-control study	149 patients with primary BC diagnosed and treated from January 2013 to March 2020 were included as a case group and 165 patients with benign breast tumours diagnosed and treated from January 2019 to March 2020 were included as a control group.	Age, age at menarche, age at first birth, and history of benign breast surgery were statistically different in the two groups (p<0.05). The risk of BC in people with late childbearing was higher than that of people with early childbearing (1.086-fold).

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Breast cancer risk factors in relation to molecular subtypes in breast cancer patients from Kenya	Sayed S, <i>et al</i> (2021)	Women suffering from breast cancer in Kenya	Case-control study	Risk factor data were collected at the time of diagnosis through questionnaire. Logistic regression models were used to determine associations between BC risk factors and molecular tumor subtypes adjusted for clinical characteristics and risk factors. All information came from simultaneous national surveys or was obtained directly for a period of time close to the period in which the study was conducted.	Overall, the cumulative or average duration of breastfeeding did not significantly differ between subtypes. There is an inverse relationship between BC rate and illiteracy rate ($\beta=2808.3$), breastfeeding duration ($\beta=3354.1$), adherence to traditional dietary patterns/fibre ($\beta=30467$) and adherence to snacking dietary pattern ($\beta=43612$). Breastfeeding has a protective role in the development of BC and also a lower number of cases with menopausal status was observed at age ≤ 45 years. Breastfeeding was observed to have no protective effect in women with a positive family history.
Dietary patterns and breast cancer in Colombia: an ecological study	Herrán OF, <i>et al</i> (2020)	Women aged 18-64 years from Colombia	Ecological study		
Prospective breast cancer risk factors prediction in Saudi women	Babiker S, <i>et al</i> (2020)	Women diagnosed with BC at King Abd Alla Medical Center (KAMC), Mecca, Saudi Arabia	Case-control study	Records of BC patients attended at KAMC during January–December 2017 were selected. Collected data included sociodemographic and reproductive factors and body mass index.	Breastfeeding has a protective role in the development of BC and also a lower number of cases with menopausal status was observed at age ≤ 45 years.
A retrospective study on breast cancer presentation, risk factors, and protective factors in patients with a positive family history of breast cancer	Liaw YY, <i>et al</i> (2020)	Women aged over 18 with BC diagnosed between January 2007–December 2016 in Malaysia	Retrospective study	Study subjects were divided into two groups: BC patients with at least one relative with BC and BC patients with no family history. Data collection by questionnaire	Breastfeeding was observed to have no protective effect in women with a positive family history.
Healthy lifestyle and breast cancer risk: a case-control study in Morocco	Khalis M, <i>et al</i> (2019)	Women from Fez region of Morocco who were diagnosed and women who were diagnosed with BC from February 2016 to August 2017	Case-control study	Use of a questionnaire for data collection	Compared to the control group, BC cases consumed more red and processed meat and cheese but less white meat, fish, vegetables and fruit, and were less physically active and had lower breastfeeding levels for at least 24 months. After adjusting for possible confounding factors, a higher score on healthy lifestyle was associated with a lower risk of BC.
Synergistic Effect Between Full-Term Pregnancy/Breastfeeding and Familial Susceptibility On Breast Cancer Risk	Lin H, <i>et al</i> (2019)	Women diagnosed with BC between January 2012 and January 2016 in two centers from China	Case-control study	Data were extracted from structured electronic medical record systems for patients.	Breastfeeding and full-term pregnancy showed a protective effect (OR 0.675, 95% CI 0.560-0.814 and OR 0.631, 95% CI 0.503-0.789, respectively), while a family history of malignancy was associated with a higher risk of BC (OR 1.251, 95% CI 1.005-1.557).
Parity, breastfeeding and breast cancer risk by hormone receptor status and molecular phenotype: results from the Nurses' Health Studies	Fortner RT, <i>et al</i> (2019)	Nurses aged 30-55 from Boston hospital (USA)	Prospective study	Parity, breastfeeding and BC risk by hormone receptor [estrogen receptor (ER) and progesterone receptor (PR)] and molecular subtypes were investigated in the Nurses' Health Study (NHS, 1976-2012) and NHSII (1989-2013).	Breastfeeding was associated only with a reduced risk of BC (HR = 0.83 [0.75-0.92]), and not with ER+ disease (HR = 0.99 [0.94-1.04]), compared with women who never breastfed and unbreastfed women. Results were similar, regardless of breastfeeding duration (e.g. ≥ 12 months <i>versus</i> never, ER-HR = 0.83 [0.73-0.94], $P_{trend} = 0.05$, ER+ HR = 1.02 [0.96-1.09], $P_{trend} = 0.22$).
Breastfeeding: a reproductive factor able to reduce the risk of luminal B breast cancer in premenopausal white women	Giudici F, <i>et al</i> (2017)	White premenopausal women living for at least 10 years in Trieste	Case-control study	Patients received a histopathologically confirmed first diagnosis of primary BC between 2006–2013. The control group comprised women who spontaneously participated in BC prevention campaigns between 2009–2014.	Women who breastfed for up to 12 months had a lower risk of developing BC (estimated OR 0.41, 95% CI 0.24-0.70, $P=0.0009$). Those who had breastfed for more than 12 months had an increased risk of breast cancer (OR 2.32, 95% CI 1.26-4.34, $P=0.007$).
Risk factors and protective factors associated with breast cancer	López TM, <i>et al</i> (2017)	Women diagnosed with BC who attended the Breast Pathology, Gynecology Service of the University Hospital of Caracas, Venezuela, between January 2013 and December 2015	Retrospective study	Use of a questionnaire for data collection	There was no statistically significant association, indicating that the initial stage of BC diagnosis was independent of breastfeeding (X ² 24.24 < X ² 5.9). Finally, this study did not consider breastfeeding as a protective factor for the development of BC.

Selection and exclusion criteria

The selected articles met the following criteria: a) researchers who conducted the study aimed to demonstrate whether there was an association between breast cancer and breastfeeding; b) did not study another disease at the same time; c) did not involve animal studies but only human studies; d) the study sample had to comprise women who have given birth at least once; and e) study results were published between 2017–2022.

The excluded articles did not control for a link between breast cancer and breastfeeding or only studied women's knowledge and attitudes about whether they considered breastfeeding to be a protective factor for breast cancer, or did not provide results on the association between breastfeeding and breast cancer. Also, articles that explored the effects of breast cancer on women who wanted to breastfeed or the effects of treatments on breastfeeding and studies that showed a possible link with other diseases or cancers were rejected. Finally, neither grey literature nor systematic reviews and meta-analyses were accepted.

Study limitations and advantages

The main advantage of this systematic review was that it studied the relationship between breastfeeding and breast cancer, and focused on articles published within five years making it up to date.

The disadvantages of the present systematic review comprise the possible failure to find relevant articles due to the choice of keywords used by authors and the exclusion of some relevant articles due to language restrictions as those that had been published in any language other than English were all rejected. Another drawback is that the reviewed articles did not study the same target population nor did they use the same intervention techniques to find the association between breastfeeding and breast cancer. □

RESULTS

After a careful investigation of the reported studies, it was observed that breastfeeding in the majority of the studies showed a protective effect on the occurrence of breast cancer. Furthermore, the studies seemed to highlight the need for further research related to the evalua-

tion of breastfeeding as a factor influencing the occurrence of breast cancer.

In the study by Fernández-Aparicio *et al* (2022), women who breastfed for more than three months and had a family history of breast cancer were diagnosed at age <60 years. In contrast, those without a family history of breast cancer were diagnosed at about 70 years of age. The differences between the two groups were statistically significant ($p=0.025$). Regarding the duration of the mother's lactation period, no statistically significant differences ($p=0.17$) in mean age at diagnosis were found. However, there were statistically significant differences in family history of cancer ($p=0.05$). In other words, women with a family history of breast cancer were diagnosed at a mean age of 55 years. Thus, maternal lactation appears to have a potential protective effect on breast cancer (11).

In the research conducted by Sayed *et al* (2021), the study population was characterized by advanced age at menarche (≥ 13 years, 92%), young age at first pregnancy (< 25 years, 70%), having three or more children (68%), high prevalence of breastfeeding (95%) and long duration of breastfeeding ($\geq$ one year per child, 80%). However, overall, cumulative or average duration of breastfeeding did not differ significantly between subtypes (12).

The study by Herráin *et al* (2020) showed an inverse relationship between breast cancer rate and illiteracy rate ($\beta=-2808.3$), duration of breastfeeding ($\beta=-3354.1$), adherence to traditional dietary patterns/fibre ($\beta=-30467$) and adherence to snacking dietary pattern ($\beta=-43612$) (13).

The study by Lei *et al* (2021) showed that the number of births, number of miscarriages, lactation time, family history of malignant tumours and history of gynaecological diseases were not statistically significant between the two groups ($p\geq 0.05$), while subjects' age, age at menarche, age at first birth and history of benign breast surgery were statistically different between the two groups ($p<0.05$). The risk of breast cancer was higher in women with late childbearing than in those with early childbearing (1.086 times). Finally, it appeared that the number of births, miscarriage times, lactation time, gynecological diseases and family history of breast or other malignant tumors were not associated with breast cancer risk (14).

The study by Hassen *et al* (2022) showed that there was no statistically significant association between breast cancer and age at menopause, oral contraceptive use, duration of breastfeeding and age at last delivery. However, the association between breast cancer and family history of first-degree relatives decreased after the gradual application of multiple logistic regression models (15). In the study by Ryddy *et al* (2022), the only variable that differed significantly by subtype was a history of seeking care for breast or nipple pain that interfered with breastfeeding, which was more common in patients with triple-negative breast cancer (TNBC). The study was limited to a small sample size making it unrepresentative of the general population of the country (16).

The study carried out by Franchini *et al* in 2022 showed that preventive programmes focusing on increasing physical activity should be widely promoted, especially among older women. In addition, current findings suggest that pregnancy, breastfeeding, salt restriction and oral contraception use could have different effects on cancer risk based on a woman's overall risk profile (17).

According to the study conducted by Babiker *et al* in 2020, women in the age range of 41 to 50 had a higher risk of developing breast cancer. Married women with a BMI >30, fewer children, no breastfeeding and pregnancy at age ≥ 30 also had an increased risk of breast cancer, although there was a higher incidence of the disease in subjects with a family history and menopausal status in their 46- to 50-year-old age groups. Additionally, the study demonstrated that breastfeeding prevented breast cancer from developing (18).

According to the study carried out by Eren *et al* in 2022, there were statistically significant differences between the groups in terms of the first age of a term pregnancy, number of biological offspring and total amount of time spent on breastfeeding. A single binary logistic regression analysis in both young and elderly patients revealed that the age of menarche had a statistically significant risk effect when the influence of reproductive risk variables was examined according to age ($p < 0.05$). The age at menarche and the number of children were the two variables found to be the most important factors determining the risk, based on the results of multiple binary logistic regression analysis (19).

The study by Fortner *et al* (2019) showed that 93% of NHS participants and 67% of NHSII participants were pregnant at the start of the study. The majority of subjects reported ever breastfeeding. Breastfeeding was associated only with a reduced risk of breast cancer, and not with ER+ disease, compared with women who never breastfed and unlactated women. Results were similar regardless of the duration of breastfeeding. The association between childbearing and ER+ tumors did not differ according to breastfeeding history. Associations between breastfeeding and breast cancer risk were similar regardless of breastfeeding duration (20).

According to the study conducted by Giudici *et al* in 2017, women who breastfed for up to a year had a reduced risk of breast cancer. The risk of breast cancer was not substantially correlated with other reproductive variables. More intriguingly, breastfeeding was the only reproductive component that was statistically significant in multivariate analysis (21). Breastfeeding for up to 12 months had a strong protective impact against Luminal B breast tumors (21). The study by Daraei *et al* (2021) showed that there was a significant difference in ESR2 0 N exon methylation between breastfeeding duration subgroups in study participants ($p=0.04$). Through detailed pairwise comparisons of breastfeeding duration, it was observed that women without breastfeeding had high ESR2 0 N exon methylation compared to the breastfeeding >24 months subgroup ($p=0.023$). However, Spearman correlation coefficient analysis showed that reduced duration of breastfeeding in women was significantly associated with a high level of ESR2 0 N exon methylation ($r=-0.208$, $p=0.022$). Interestingly, infertile women were found to have an increased level of ER- β 0 N exon methylation than those who had conceived ($p=0.036$). In addition, high ER- β 0 N exon methylation in the breasts of non-breastfeeding women compared to the breastfeeding subgroup was observed ($p=0.048$). Similarly, the non-breastfeeding subgroup showed high 0 N exon methylation compared to women breastfeeding >24 months ($p=0.023$) (22). In the study conducted by Yeo and Kim (2021), it was shown that both the early age of menarche ($p=0.001$) and short duration of breastfeeding ($p=0.017$) were associated with an increased risk of breast cancer. The effect of reproductive risk factors on breast cancer incidence may be

much weaker than the impact of socioeconomic factors (23). In the study carried out by Liaw *et al* (2020), breastfeeding was observed to have no protective effect on women with a positive family history (24), while Lin *et al* (2019) found that breastfeeding and full-term pregnancy exerted a protective effect, and a family history of malignancy was associated with a higher risk of breast cancer (25).

The study by Lopez *et al* (2017) did not find a statistically significant correlation, indicating that breastfeeding was not associated with early detection of breast cancer. Finally, as a preventative factor against the development of breast cancer, nursing was not considered in this study (26). The study by Khalis *et al* (2019) showed that, compared to the control group, women with breast cancer consumed more red and processed meat and cheese and less white meat, fish, vegetables and fruit and were less physically active and had lower levels of breastfeeding for at least 24 months. After adjusting for potential confounders, a higher healthy lifestyle score was associated with a lower risk of breast cancer (27). ■

DISCUSSION

Since 6% of breast cancers occur in women under 40, breast cancer is the most common malignancy among women of reproductive age (28). Nine out of ten women have survived the condition for at least five years after their original diagnosis, and around half of those who have survived have thought about getting pregnant thanks to early detection and the choice of effective treatments. There is limited data on the experiences of women who breastfed after surviving breast cancer (29). For example, an Italian study (2010) on breast cancer patients who had completed their pregnancy after having managed the disease showed that two of the 20 study participants had a recurrence of the tumour, one in the breastfeeding group and one in the non-breastfeeding group, and the authors concluded that breastfeeding had no negative effect on the outcome of the disease (30). The same conclusion was reached in a study conducted in 2018 in various European countries (31). However, women who choose to breastfeed after breast cancer treatment face a range of physical, psychological and social challenges. Physical challenges include secondary health problems that

may arise especially in cases where there is no possibility of using both breasts. Psychological challenges include fear of failure to provide appropriate care for the child, fear of recurrence of the disease, reduced confidence in their bodily functions. When social challenges are concerned, women have to deal with prejudices among relatives, friends and even health professionals. The Obstetric and Gynaecological Society of Canada has issued guidelines for the management of women who give birth after breast cancer. Those guidelines state that there is no proven risk of an increase in the chances of breast cancer recurrence due to breastfeeding in women and therefore, female patients who are cured of the disease should be encouraged to breastfeed their children (28).

It has been shown that, even after breast conservation surgery and radiotherapy, the affected breast was unable to follow the processes necessary for lactogenesis. However, women should be informed that the unilateral breast can produce a sufficient amount of milk for the infant and further support should be given by health professionals to prevent nipple injuries or obstruction of the milk ducts that could lead to mastitis (32) and also to prevent milk ducts from becoming blocked (28).

In the studies conducted by Eren SK *et al* (2022) (19), Lopez MT *et al* (2017) (26), Liaw YY *et al* (2020) (24) and Babiker S *et al* (2020) (18), breastfeeding was found to have no protective effect on breast cancer incidence, but in those carried out by Lin H *et al* (2019) (20) and Fortner RT *et al* (2019) (25), breastfeeding was evaluated as a protective factor. In the study by Fortner RT *et al* (2019), breastfeeding was linked to a lower risk of breast cancer with negative hormone receptors. Additionally, women who had given birth to three or more children and breastfed had a significantly lower risk of breast cancer with luminal A than did childless women (25). In a study by Lin H *et al* (2019), full-term pregnancy and breastfeeding were regarded as preventive variables because breastfeeding seemed to lower the incidence of breast cancer by almost 32% (20). The study by Ruddy KJ *et al* (2022) indicated that women with a low birth index were more likely to develop TNBC, and this finding has led to the evaluation of terminal pregnancy as a protective factor (16). The same study showed that women who developed TNBC were

more likely not to seek medical help for breast or nipple pain that prevented them from breastfeeding. Furthermore, the study by Lopez MT *et al* (2017) found no statistically significant association between breastfeeding and the initial stages of breast cancer diagnosis, so breastfeeding was not considered a protective factor for the disease (26).

In the study by Eren SK *et al* (2022), the use of multiple binary logistic regression analyses showed that there was an effect of breastfeeding on the age at diagnosis of breast cancer (19); the only reproductive factors that appeared to have a statistically significant association with breast cancer age included age at menarche and the number of children the women had given birth to. Moreover, a study by Khalis M *et al* (2019) showed that women who developed breast cancer were more likely to have had their first full-term pregnancy at an older age (27).

In two of the three studies examining the effect of breastfeeding on breast cancer in women with a positive history, breastfeeding did not appear to be a protective factor. More specifically, the study by Fernandez-Aparicio A *et al* (2022) concluded that the effect of family history was stronger than the protective effect of breastfeeding, as women with a family history of breast cancer with a breastfeeding duration of more than three months had an average age of diagnosis of 55 years, while those with no family history and a breastfeeding duration of more than three months had an average age of diagnosis of about 70 years (11). However, in the study by Lin H *et al* (2019) there appeared to be a synergistic effect of breastfeeding and family history on breast cancer risk, with participants who did not breastfeed and had a positive family history having a higher risk of breast cancer (OR: 2.630, 95%) (25). Comparing women who had a positive history and breastfed with those with a positive history who had not breastfed, the risk was 1.6 times greater in the latter and three times greater in women who did not have children and had a positive history (20).

Lei YY *et al* (2021) (14) and Sayed S *et al* (2021) (12) found no correlation between the length of lactation and the risk of breast cancer. Also, Ruddy KJ *et al* (2022) (16) did not find any correlation. More specifically, in the study by Sayed S *et al* (2021) estrogen receptor (ER) negative patients were more likely to have a longer

cumulative duration of breastfeeding; however, with the addition of another factor (the number of children) it was shown that breastfeeding was driven by the number of children (12). Moreover, patients diagnosed with luminal B breast cancer who had four or more children had a shorter cumulative breastfeeding duration than those with luminal A breast cancer. Nevertheless, the study found that the total amount of breastfeeding time did not significantly differ among subtypes. While women who breastfed > 12 months appeared to have a lower risk of developing the disease with a significant protective effect for luminal B subtype (21), Yeo *et al*'s study (2021) concluded that short breastfeeding duration was associated with an increased risk of breast cancer (23). Fernandez-Aparicio A *et al* (2022) came to the conclusion that maternal lactation appeared to have a possible protective effect on breast cancer (11). Finally, the study by Daraei A *et al* (2021) analyzed the effect of reproductive factors on the methylation levels of the CpG promoter of ESR2, which played an important role in stopping the expression of the ER- β gene, which has anti-cancer activity, in the early stages of breast cancer development. The study showed that women who had never breastfed had higher rates of methylation; also, the short duration of breastfeeding appeared to be associated with an increased risk of developing breast cancer as it led to higher methylation levels in the ESR2 promoter (22).

The studies by Herrain OF *et al* (2020) (13) and Yeo *et al* (2021) (23) studied socioeconomic factors in relation to breast cancer and breastfeeding. In the first study there appeared to be an inverse proportional relationship between breastfeeding and illiteracy, *i.e.*, low levels of education, while in the second study, socioeconomic factors seemed to exert a weaker effect on breast cancer incidence than reproductive factors. Regarding the eating habits of women diagnosed with the disease, the study by Khalis M *et al* (2019) (27) and Hassen F *et al* (2022) (15) seemed to create a profile of women who were more likely to develop the disease. More specifically, the profile of those women included a high intake of milk, red meat, cheese, processed meat and solid oils combined with low consumption of white meat, fruits, and vegetables, a breastfeeding duration of less than 24 months and low physical activity. Finally, the study by Franchini M

et al (2022) (17) also showed that lifestyle, especially concerning non-modifiable factors, played an important role in the development of breast cancer.

Furthermore, Babiker S (2020) (18) and Giudici F et al (2017) (21) underlined that further studies were needed to investigate the effect of breastfeeding on breast cancer prevention and to determine the ideal duration of breastfeeding that would positively affect women. □

CONCLUSIONS

Breastfeeding has been thoroughly studied as a protective factor against breast cancer throughout the years, and the number of studies linking the practice to the prevention of breast

cancer is steadily rising. From all reviewed articles, the need for the design of additional studies investigating the relationship between breastfeeding and breast cancer emerges.

Pregnancy appears to reduce the incidence of breast cancer through molecular pathways related to RNA processing and cellular differentiation. These mechanisms may also affect the development or maintenance of breast cancer stem cells.

Therefore, there is a pressing need for women all over the world to be aware of the advantages of breastfeeding as a breast cancer prevention strategy. □

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