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Chapter 5

Breastfeeding and Reduced Risk of Breast Cancer in Women: A Review of Scientific Evidence

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Additional information is available at the end of the chapter

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Abstract

Recent research shows that women who breastfed their children are at considerably less risk of developing breast cancer. Nonetheless, the results of other studies show that this greater protection only applies to pre-menopausal women. Based on the above results, there is still a certain controversy as to whether breastfeeding protects women against breast cancer. The main objective of this chapter is to provide a review of the scientific evidence regarding the relationship between breast cancer and certain aspects of pregnancy as breastfeeding period. For this purpose, it was conducted a systematic review in four databases (Web of Science, MEDLINE, Scopus and CINAHL), using the MeSH terms (Breast Feeding, Primary Prevention, Breast Neoplasms). The available scientific evidence justifies that breastfeeding for periods of over 6 months results in statistically significant reductions in the risk of developing breast cancer, the most common gynecological tumor in young women. However, it remains to be studied further whether the observed risk reduction applies to women with inherited susceptibility to develop breast cancer.

Keywords: breastfeeding, breast, cancer, prevention, women

1. Introduction

Breast cancer is the most common gynecological tumor in women [1, 2]. Actually, the highest breast cancer incidence appears in high-income regions: population of North America, in population of Western Europe, Australia and New Zealand [3]. In fact, in developed countries, breast cancer is the leading cause of cancer death in women of 35–64 years of age. Each year, about 22% of new cancer cases diagnosed in women are breast cancer [4]. However, 17–36% of all breast cancers occur in women under the age of 40 [5].

The rapid increase in the incidence of breast cancer is a new social challenge as a result of a large number of risk factors, among them genetic causes and altered socio-economical conditions

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such as occupational exposure, rotating shift work and environmental factors (increased atmospheric pollution, sedentary lifestyle, and inadequate nutritional habits combined with an unbalanced diet). Other risk factors to be considered are lower age at menarche (below 10 years), late maternal age at first full-term pregnancy (over the age 30–40 years), and short periods of breastfeeding [6].

In the last years, different breast cancer prevention studies have been carried out internationally. Their main objective was to evaluate how a woman's chance of developing breast cancer was affected by breastfeeding as well as by pregnancy and childbirth. The results of these studies provide evidence about the influence of hormonal and reproductive factors in the development of breast cancer [7–9].

2. Methodology

A systematic review literature was conducted between March and April 2017; articles were collected from four databases (Web of Science, MEDLINE, Scopus and CINAHL), as well as from references in published research and reviews. The search strategy for potentially eligible studies included the following MeSH terms and combinations: Breast Feeding and Primary Prevention and Breast Neoplasms. The reference lists of included studies were also searched for additional eligible studies. Article inclusion criteria were as follows: (1) original studies and articles reporting on human females, (2) written in English and published in peer-reviewed journals, and (3) studies conducted in developed countries (Organization for Economic Co-operation and Development countries as defined by the World Bank). The following exclusion criteria were used: (1) studies using qualitative methodology, and (2) studies where analytic methods were not clearly reported. Titles and abstracts of retrieved studies were screened to assess whether inclusion criteria were met. Full texts were assessed when the abstract was found insufficient to make conclusions about inclusion. A total of 48 scientific articles were found, 41 in Web of Science, 2 in MEDLINE, 3 in Scopus, and 2 in CINAHL. Out of potentially relevant citations retrieved from electronic databases and searches of reference lists, finally, 34 articles were selected for this review (**Table 1**).

Authors	Title	Year	Design	Conclusions
Pathak DR, Osuch JR, He J.	Breast carcinoma etiology: current knowledge and new insights into the effects of reproductive and hormonal risk factors in black and white populations.	2000	Literature review	To promote public health in diverse populations, and to provide further insight into breast carcinoma etiology, research needs to focus on multicultural differences and similarities in the relation of hormonal risk factors and breast carcinoma.
González-Jiménez E, García PA, Aguilar MJ, Padilla CA, Álvarez J.	Breastfeeding and the prevention of breast cancer: a retrospective review of clinical histories.	2014	Retrospective study of the clinical histories	Breastfeeding for over six months not only provides children with numerous health benefits, but also protects mothers from breast cancer

Authors	Title	Year	Design	Conclusions
				when the mothers are nonsmokers.
Clemon M, Goss P.	Estrogen and the risk of breast cancer.	2001	Literature review	Although a relation between exposure to estrogen and the risk of breast cancer has been identified in specific groups of women, we cannot accurately predict the risk in an individual woman. Clinical markers of exposure to estrogen, such as serum estrogen concentrations, breast density on mammography, and bone mineral density, may prove to be useful tools for assessing a woman's risk of breast cancer.
Chlebowski RT, Hendrix SL, Langer RD, Stefanick ML, Gass M, Lane D, et al.	Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial.	2003	Randomized clinical trial	Relatively short-term combined estrogen plus progestin use may stimulate breast cancer growth and hinder breast cancer diagnosis.
Vyas U.	Risk of breast Cancer due to hyperprolactinemia caused by antipsychotics (Neuroleptics).	2012	Literature review	Some reports suggest that neuroleptics and other dopamine antagonists increase the risk of breast cancer due to hyperprolactinemia. There are other reports which suggest that they may decrease the risk of cancer especially rectum, colon and prostate.
Halbreich U, Kinon BJ, Gilmore JA, Kahn LS.	Elevated prolactin levels in patients with schizophrenia: mechanisms and related adverse effects.	2003	Literature review	Elevated prolactin levels may play important roles, both direct and indirect, in various pathologic states, including breast cancer.
Levine RS, Dolin P.	Pregnancy and breast cancer: a possible explanation for the negative association.	1992	Literature review	Larger studies are needed to demonstrate the preventive effect of pregnancy against the development of breast cancer.
Albrektsen G, Heuch I, Kvåle G.	Multiple births, sex of children and subsequent breast-cancer risk for the mothers: a prospective study in Norway.	1995	Prospective study	There was a slightly lower risk of breast cancer among women ever having had a multiple birth than among women with singletons only.
Håkansson A, Zhivotovsky B, Orrenius S, Sabharwal H, Svanborg C.	Apoptosis induced by a human milk protein	1995	Experimental study	A component of milk in a particular physical state–multimeric alpha-lact-albumin–is a potent Ca(2+)-elevating and apoptosis-inducing agent with broad, yet selective, cytotoxic activity.

Authors	Title	Year	Design	Conclusions
Bernstein L.	Epidemiology of endocrine-related risk factors for breast cancer.	2002	Literature review	The main risk factors for breast cancer identified by observing patterns of risk among various population groups are age, race/ethnicity, reproductive factors (menarche, menopause, and pregnancy and lactation history), and obesity.
González-Jiménez E, Garcia-Lopez PA, Schmidt-Rio-Valle J, Valenza C.	Influence of nutritional status, hormones serum levels, and family history on breast cancer development	2012	Retrospective study of the clinical histories	Extreme serum levels of estrogen, progesterone and prolactin appear to be related to the early development of breast cancer, which in turn is influenced by the existence of a family history of cancer among those women with normal or average hormone levels.
Løland BF, Baerug AB, Nylander G.	Human milk, immune responses and health effects	2007	Literature review	Human milk may confer long-term benefits such as lower risk of certain malignancies. A reduced incidence of breast cancer is best documented.
Aguilar Cordero MJ, González Jiménez E, Alvarez Ferre J, Padilla Lopez CA, Mur Villar N, Garcia Lopez PA, et al.	Breast feeding: an effective method to prevent breast cancer	2010	Retrospective study of the clinical histories	Breastfeeding for periods of longer than six months, not only provides children with many health benefits, but may also protect the mother from serious diseases, such as breast cancer.
Lee SY, Kim MT, Kim SW, Song MS, et al.	Effect of lifetime lactation on breast cancer risk: a Korean women's cohort study.	2003	Prospective study	This prospective study of a large Korean cohort provides strong empirical evidence that lactation decreases the risk of breast cancer among premenopausal women.
Chang-Claude J, Eby N, Kiechle M, Bastert G, et al.	Breastfeeding and breast cancer risk by age 50 among women in Germany.	2000	Case–control study	The reduction in risk associated with duration of breastfeeding was not primarily due to breastfeeding the firstborn and more evident in women who were older (> 25 years) when they first breastfed and among women who experienced a recent full-term pregnancy.
Dumitrescu RG, Cotarla I.	Understanding breast cancer risk–where do we stand in 2005?	2005	Literature review	Risk factors that modulate the development of breast cancer are: age, geographic location (country of origin) and socioeconomic status, reproductive events, exogenous hormones, lifestyle risk factors (alcohol, diet, obesity and

Authors	Title	Year	Design	Conclusions
				physical activity), familial history of breast cancer, mammographic density, history of benign breast disease, ionizing radiation, bone density, height, IGF-1 and prolactin levels, chemopreventive agents. Additionally, we summarized breast cancer risk associated with the following genetic factors: breast cancer susceptibility high-penetrance genes (BRCA1, BRCA2, p53, PTEN, ATM, NBS1 or LKB1) and low-penetrance genes such as cytochrome P450 genes (CYP1A1, CYP2D6, CYP19), glutathione S-transferase family (GSTM1, GSTP1), alcohol and one-carbon metabolism genes (ADH1C and MTHFR), DNA repair genes (XRCC1, XRCC3, ERCC4/XPF) and genes encoding cell signaling molecules (PR, ER, TNFα or HSP70).
Freudenheim JL, Marshall JR, Vena JE, Moysich KB, et al.	Lactation history and breast cancer risk	1997	Case–control study	Breast cancer risk was very weakly associated with long duration of lactation among premenopausal women. Among postmenopausal women, the protective effect of lactation was restricted to women with first lactation before age 25 years.
Stuver SO, Hsieh CC, Bertone E, Trichopoulos D.	The association between lactation and breast cancer in an international case–control study: a re–analysis by menopausal status	1997	Case–control study	This study did not suggest a protective effect of lactation among the pre-menopausal women. Although the 95% confidence intervals around the estimates generated do not exclude the possibility of a reduced risk of breast cancer associated with breast-feeding, no consistent dose–response with increasing total duration was evident.
Lipworth L, Bailey LR, Trichopoulos D.	History of breast-feeding in relation to breast cancer risk: a review of the epidemiologic literature	2000	Literature review	The evidence with respect to "ever" breast-feeding remains inconclusive, with results indicating either no association or a rather weak protective effect against breast cancer. It

Authors	Title	Year	Design	Conclusions
				appears that the protective effect, if any, of long-term breast-feeding is stronger among, or confined to, premenopausal women.
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 50,302 women with breast cancer and 96,973 women without the disease.	2002	Systematic review and Meta-analysis	The longer women breast feed the more they are protected against breast cancer. The lack of or short lifetime duration of breastfeeding typical of women in developed countries makes a major contribution to the high incidence of breast cancer in these countries.
Chowdhury R, Sinha B, Sankar MJ, Taneja S, et al.	Breastfeeding and maternal health outcomes: a systematic review and meta-analysis.	2015	Systematic review and Meta-analysis	Breastfeeding is protective against breast and ovarian carcinoma, and exclusive breastfeeding and predominant breastfeeding increase the duration of lactational amenorrhoea.
Islam T, Matsuo K, Ito H, Hosono S, et al.	Reproductive and hormonal risk factors for luminal, HER2-overexpressing, and triple negative breast cancer in Japanese women.	2012	Case–control study	Reproductive events in adolescence have differential impact on the risk of breast cancer molecular subtypes in Japanese.
Lipworth L, Bailey LR, Trichopoulos D.	History of breast-feeding in relation to breast cancer risk: a review of the epidemiologic literature.	2000	Literature review	The evidence with respect to "ever" breast-feeding remains inconclusive, with results indicating either no association or a rather weak protective effect against breast cancer.
Yoo KY, Tajima K, Kuroishi T, Hirose K, et al.	Independent protective effect of lactation against breast cancer: a case control study in Japan.	1992	Case–control study	Lactation has an independent protective effect against breast cancer in Japanese women.
Wang QS, Ross RK, Yu MC, Ning JP, et al.	A case–control study of breast cancer in Tianjin, China.	1992	Case–control study	The results strongly suggest that both parity and lactation independently contribute to breast cancer risk.
Michels KB, Willett WC, Rosner BA, Manson JE, et al.	Prospective assessment of breastfeeding and breast cancer incidence among 89,887 women	1996	Prospective study	The results suggest that there is no important overall association between breast-feeding and the occurrence of breast cancer.
Zheng T, Duan L, Liu Y, Zhang B, et al.	Lactation reduces breast cancer risk in Shandong Province, China.	2000	Case–control study	These results suggest that prolonged lactation reduces breast cancer risk.
Hajian-Tilaki KO, Kaveh-Ahangar T.	Reproductive factors associated with breast cancer risk in northern Iran	2011	Case–control study	The duration of breast feeding was inversely associated with breast cancer risk. Nulliparity,

Authors	Title	Year	Design	Conclusions
				late age at first birth and abortion were the most important reproductive factors associated with breast cancer risk.
Awatef M, Olfa G, Imed H, Kacem M, et al.	Breastfeeding reduces breast cancer risk: a case–control study in Tunisia	2010	Case–control study	The results support an inverse association between breastfeeding and breast cancer risk.
Nagata C, Mizoue T, Tanaka K, Tsuji I, et al.	Breastfeeding and breast cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population.	2012	Systematic review	The results suggest that breastfeeding possibly decreases the risk of breast cancer among Japanese women
Galukande M, Wabinga H, Mirembe F, Karamagi C, et al.	Breast cancer risk factors among Ugandan women at a tertiary hospital: A case–control study.	2016	Case–control study	Breastfeeding seems to be associated with reduced odds of breast cancer.

Table 1. Summary table of selected studies.

3. Pregnancy

Early pregnancy has a protective effect against breast cancer [10]. Some of the mechanisms explaining the protective effect of pregnancy have been explored in animal models of breast cancer. Both early age (less than 20 years versus more than 30 years) at first full-term pregnancy and higher parity decrease breast cancer risk to half of the risk of nulliparous women [10]. Although the mechanisms are not entirely elucidated, pregnancy has been hypothesized to reduce the risk of breast cancer primarily through two mechanisms: firstly estrogen-induced mitosis may be suppressed by estriol, the main estrogen produced during pregnancy. Secondly, estrogen-induced mitosis may be suppressed by the hormone prolactin, whose levels are increased during pregnancy [11]. Then, high levels of estriol may protect women against the development of breast cancer [12, 13]. However, there is somewhat less agreement concerning the role of prolactin in the disease. Different studies show a relationship between hyperprolactinemia and an increased risk of breast cancer in women [14, 15]. The mechanisms potentially involved are: increased synthesis and expression of prolactin receptors in malignant breast tissue and a prolactin-induced increase in DNA synthesis in breast cancer cell *in vivo* [14]. Secondly, and according to Levine and Dolin [16], pregnancy reduces the risk of breast cancer because of the excretion of lipophilic carcinogens by the mother through the fetal fat and vernix caseosa. Other studies have yielded conflicting results. According to Alberktsen et al. [17] in their study with 802,457 Norwegian women (20–56 years old), an increase in the diagnosis of breast cancer after full-term pregnancy was observed, particularly between 3 and 4 years after the delivery. Hakansson et al. [18] and, more recently, Rough et al. [19] reported that human milk causes the

vitro apoptosis or the programmed cell death of several varieties of cancer cells. On the other hand, the decrease of breast cancer risk due to prolonged lactation may be explained in part by the reduction of total number of ovulatory menstrual cycles and consequently cumulative ovarian hormone exposure [20]. Despite the scientific evidence available, there is an important controversy about the effect of hormones on the development of breast cancer. This is a complex task when we consider the complex etiopathogenic nature of breast tumors. Consequently, further studies are necessary in order to analyze this relationship [21].

4. Breast milk

Breastfeeding is still another research focus. An increasing number of studies have indicated that breastfeeding offers protection against breast cancer [22, 23]. In the long term, the protection offered by breastfeeding is greater for premenopausal women, but also persists for postmenopausal women even after 50 years since the first lactation [24]. These protective effects of breastfeeding appear to be stronger the longer a woman breastfeeds her first child, as well as cumulative, such that increased lifetime duration of lactation over multiple children confers greater protection against breast cancer [25]. From a biological perspective, there are various explanations why breastfeeding seems to prevent breast cancer and why it appears to significantly benefit female health. One mechanism may involve a markedly reduced susceptibility of the fully differentiated mammary gland to carcinogens due to, at least in part, a decrease in proliferative activity of parous epithelium [26]. Other important changes are estrogen reduction and elimination through mammary fluid and the excretion of carcinogenic agents through the breast tissue during the breastfeeding process [27–29].

According to a study carried out by Cancer Research UK, the short duration of breastfeeding typical of women in developed countries makes a major contribution to the high incidence of breast cancer in these countries. The results obtained showed that the relative risk of breast cancer decreased by 7.0% for each birth in addition to a decrease of 4.3% for every 12 months of breastfeeding [30]. Despite such studies, many researchers are still skeptical as to the protection against breast cancer potentially afforded by breastfeeding. They claim that the data obtained until now are both insufficient and in many cases, inconsistent. Therefore, the influence of each birth should be considered when the relationship between breastfeeding and breast cancer is studied. Likewise, the reported breastfeeding duration is not very trusty, with values generally rounded to multiples of 6 or 12 months, particularly among women who had breastfed for long periods of time [31].

Nevertheless, a slightly lower rate of breast cancer was observed in women who breastfed their children for periods of over 12 months [32]. Of the women who had given birth, those who were cancer-free were more likely to have breastfed than those who subsequently developed breast cancer (79% as compared to 71%) [33]. However, a history of ever breast-feeding may be too crude an indicator, and it may be more important to demonstrate a dose–response association with increasing duration of breast-feeding in making causal inferences [34]. These results suggest an inverse relationship between breastfeeding duration and risk of developing breast cancer.

The decrease of relative risk´ rate of developing breast cancer associated with breastfeeding did not change significantly for women in developed and developing countries, and did not change according to the age and ethnicity [31]. Other studies have analyzed breast cancer risk factors, including breastfeeding duration, in Asian and African populations. The results obtained about breastfeeding duration and risk of developing breast cancer between these populations are limited [35, 36].

Additionally Michels et al. [37], in the Nurse's Health Study, in a retrospective review of breastfeeding duration in nearly 90,000 women, reported that, in comparison to never breastfeeding, the RR was 0.86 for fewer than 3 months of breastfeeding, 0.95 for 7–11 months, 0.86 for 12–23 months, and 1.11 for 24 months or longer. These results show the importance of the breastfeeding duration in reducing the risk of breast cancer.

Moreover, Zheng et al. [38], in the period 1997–1999 in Shandong, China, studied breast cancer risk in 404 women and in a control group. Their results show that for those women who breastfed their children for more than 24 months, the odds ratio was 0.46 (95% CI, 0.27–0.78) when compared with those women who breastfed their child for 1–6 months. These data suggest that prolonged lactation reduces breast cancer risk. Similar results were found by Hajian-Tilaki et al. [39], in their study with 100 women diagnosed of breast cancer and 200 controls. The authors conclude that duration of breast feeding was inversely associated with breast cancer risk. In another case–control study in Tunisia between 2006 and 2009, involving 400 breast cancer cases and 400 controls, the authors likewise observed an inverse association between breastfeeding duration and breast cancer risk [40].

Other review study developed by Nagata et al. [41], in which they identified three cohort studies and five case–control studies show similar results as described above. There was no significant association between the risk of breast cancer and breastfeeding according cohort studies analyzed. Nevertheless, in most case–control studies observed a statistically significant reduction in risk for women who ever had breastfed or for women with longer breastfeeding duration. These results again suggest that breastfeeding decreases the risk of breast cancer among Japanese women.

Despite the extensive scientific evidence available, there is still controversy about the effect of breastfeeding on the prevention of breast cancer. Consequently, more studies in different parts of the world are needed to analyze this relationship [42].

5. Conclusions

Breastfeeding for periods of over 6 months results in statistically significant reductions in the risk of developing breast cancer, the most common gynecological tumor in young women. However, it remains to be studied further whether the observed risk reduction applies to women with inherited susceptibility to develop breast cancer. Further studies must be conducted to focus on populations in which breastfeeding was common for relatively long durations, and should attempt to collect information on the errors in the reporting of lifetime duration of breastfeeding and other forms of complementary feeding. Meanwhile, this

potential beneficial effect of breastfeeding for the mother should lead health professionals to encourage prolonged breastfeeding in their clinical practice.

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