Chapter 21
Exposure to Breast Milk in Infancy and Risk of Adult Breast Cancer: A Summary of the Evidence

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Key Points

- While there are many established short-term benefits of breastfeeding for infant nutrition and health, the potential long-term benefits regarding chronic disease and cancer morbidity in adulthood, including risk of breast cancer, are still unclear.
- In this chapter, we review the epidemiologic evidence regarding the association between being breastfed in infancy and risk of short-term and long-term health outcomes, focusing specifically on adult breast cancer.
- Few studies have investigated the relation between feeding practices in infancy and adult health. No overall association has been found for incidence of all cancers or any individual cancer type. The existing data on infant feeding practices in relation to breast cancer risk are not sufficient to confirm or refute any protective or harmful effect of having been breastfed on breast cancer risk, and additional studies are needed. Published studies have suffered from several methodological limitations including recall bias, misclassification of exposure, lack of control for confounding, small numbers, and limited variation in exposure.
- Until more definitive studies are conducted, health professionals should avoid informing their patients about a possible link between infant feeding and breast cancer while continuing to stress the many established benefits of breastfeeding for both infant and mother.

Key words Breast cancer • Lactation • Breastfeeding • Menopausal status • Risk factors

Abbreviations

RR Relative risk
CI Confidence interval
US United States

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_21,

Introduction

There has been considerable interest in the health-related benefits of breastfeeding for the infant. While there are many established short-term benefits of breastfeeding for infant nutrition and health [1], the potential long-term benefits regarding chronic disease and cancer morbidity in adulthood, including risk of breast cancer, are still unclear. In this chapter, we review the epidemiologic evidence regarding the association between being breastfed in infancy and risk of short-term and long-term health outcomes, focusing specifically on adult breast cancer. We also present the results of a meta-analysis of published studies on breastfeeding in infancy and risk of adult breast cancer, updating a 2005 meta-analysis on this topic [2]. Finally, we make recommendations for improving future epidemiologic studies that investigate the effects of exposure to breast milk in infancy on longer-term health.

Most pediatric and nutritional organizations in the US recommend exclusive breastfeeding[1] for the first 6 months of life, and breastfeeding with nutritionally adequate and complementary foods for at least 12 months [3]. The World Health Organization (WHO) recommends extending the latter time period for *up to 2 years of age or beyond* [4]. The prevalence of breastfeeding in the US is lower than in Western Europe and other nations. In the US, ~33–36% of infants are breastfeeding at 6 months of age, and 17–20% of infants are breastfeeding at 12 months of age whereas worldwide, 79% of infants are still breastfeeding at 12 months [3].

Most literature on the health effects of being breastfed in infancy pertain to short-term health effects and illnesses in childhood. In a 2007 review [1] of published literature regarding the effects of breastfeeding on child health outcomes, exposure to breast milk in infancy was associated with a reduced risk of acute otitis media, nonspecific gastroenteritis, necrotizing enterocolitis, respiratory tract infections, atopic dermatitis, early-onset asthma, childhood obesity, type 1 diabetes, childhood leukemia, and sudden infant death syndrome (SIDS) [1]. There was no conclusive evidence for an effect of breastfeeding on infant mortality or cognitive performance [1], and subsequent studies have continued to produce inconsistent results [5–13]. None of the studies explicitly examined the difference between “direct breastfeeding” (infant suckling at mother’s nipple) and “feeding of expressed breast milk.” Moreover, definitions of “exclusive breastfeeding” varied widely in the literature. Almost all studies were nonexperimental (observational), which are susceptible to confounding and several biases, and there was a wide range in data quality across the different studies [1]. In addition, publication bias could not be ruled out. In contrast to the findings from observational studies, a recent cluster-randomized trial in Belarus—the Promotion of Breastfeeding Intervention Trial (PROBIT)—showed a positive influence of prolonged and exclusive breastfeeding on childhood cognitive performance [14], but no effect on asthma and allergy [15] or childhood obesity [16], when infants were followed up until age 6.5 years. Furthermore, no differences were observed for child behaviors (e.g., conduct problems, hyperactivity, peer problems) or mothers’ satisfaction with interpersonal relationships, though mothers in the intervention group were more likely to breastfeed their next child [17].

The inconsistent results across observational and experimental data suggest that bias and residual confounding due to socioeconomic factors may explain some of the findings in previous observational studies. However, experimental data are not without their own limitations, including potential for bias due to nonadherence; confounding and chance variation (when samples are small); reduced generalizability (when confined to specific groups based on age, ethnicity, and geography); and inappropriate intervention (e.g., inaccurate or narrow range of exposure) [18]. Thus, differences between experimental and observational data do not necessarily reflect the limitations of observational studies [18].

Few studies have investigated the relation between feeding practices in infancy and adult health. Meta-analyses and systematic reviews of observational studies indicate that having been breastfed may reduce total cholesterol levels [19] and diastolic blood pressure [20], and lower risk of type 2

[1] WHO defines “exclusive breastfeeding” as no other food or drink, not even water, except breast milk (including expressed milk or milk from a wet nurse), but allows the infant to receive oral vitamins, minerals, and medicines.

diabetes [21] and obesity [22] in adulthood. No overall association has been found for incidence of all cancers or any individual cancer type [2]. However, with respect to infant feeding practices and risk of adult breast cancer, the results are less clear.

The characteristics of published studies assessing the association between exposure to breast milk in infancy and breast cancer are presented in Table 21.1 [2, 23–36]. Eleven of these studies—three cohort studies [2, 26, 28], seven case–control studies [25, 27, 30, 31, 33, 35, 36], and one cross-sectional study [32] were included in a meta-analysis of reports published before 2006 [2]. Penrose et al. [29] was omitted from meta-analysis because it compared odds of familial vs. sporadic breast cancer among exposed and unexposed women. The authors concluded that being breastfed in infancy was unrelated to overall risk of breast cancer and to risk among postmenopausal women, but was inversely associated with *premenopausal* breast cancer (RR = 0.88, 95% CI = 0.79–0.98) [2]. Most studies relied on the long-term recall or reporting of infant feeding practices among participants who were questioned *after* the diagnosis of breast cancer, introducing potential for recall bias. However, the three cohort studies, which used prospectively ascertained exposure information or used mothers' reports about breastfeeding to validate exposure data, found no evidence of an association overall or by menopausal status [2, 26, 28]. Since 2006, three additional case–control studies have been published on this topic [23, 24, 34]. Two of these newest studies supported an inverse association overall [23, 24]; one found a stronger inverse association among premenopausal women [24], and the other did not examine differences by menopausal status [23]. The third new study, based on a substantially larger number of cases, showed little evidence of an association overall or by menopausal status [34].

We updated the inverse-variance fixed-effect meta-analysis of published studies on infant feeding practices and risk of breast cancer (through August 2011) using the same search criteria as Martin et al., [2] and the "metan" command in STATA (Figs. 21.1, 21.2, and 21.3) [37]. The I^2 statistic was computed to estimate the degree of heterogeneity between studies that is not dependent on the number of studies, where an I^2 value of 0% indicates no between-study heterogeneity [37]. Consistent with Martin et al., [2] the updated meta-analysis showed a weak inverse association among all women (RR = 0.94, 95% CI: 0.89, 0.99) (Fig 21.1), an inverse association among premenopausal women (RR = 0.88, 95% CI: 0.78, 0.98) (Fig 21.2), and no association among postmenopausal women (RR = 0.98, 95% CI: 0.91, 1.05) (Fig 21.3). The I^2 tests indicated no statistically significant between-study heterogeneity in parameter estimates, albeit the studies among premenopausal women displayed a much higher degree of heterogeneity (premenopausal: $I^2 = 53.9\%$, $p = 0.07$; postmenopausal: $I^2 = 18.4\%$, $p = 0.30$). Thus, the published reports to date indicate a possible inverse association with premenopausal breast cancer, and no evidence of an association with postmenopausal breast cancer. However, given that the largest and most methodologically sound studies to date produced null results—a US prospective cohort study that used maternal reports to validate breastfeeding [28], a British prospective cohort study that also relied on maternal reports provided on average 7 years after birth [2], and a large case–control study of more than 3,700 cases [34]—it seems premature to conclude that having been breastfed reduces the risk of premenopausal breast cancer.

The exact mechanism(s) by which early life exposure to breast milk might influence adult breast cancer risk is unclear. Breast milk contains the optimal balance of fats, proteins, and carbohydrates for infant nutrition, as well as various immunologic and growth factors, providing benefits for child immunity, growth, and development [38]. However, breast milk also contains environmental toxicants (e.g., organochlorines and heavy metals) due to inadequately controlled pollution [38–41]. Initial interest in a viral etiology for human breast cancer was generated by animal studies showing that mammary tumors in certain strains of mice could be caused by a tumor virus transmitted via breast milk [42]. Early studies hypothesized that viral transmission through breastfeeding explained the elevated risk found in women whose mothers had developed breast cancer [25, 29, 32]. More recent reports of an inverse association between exposure to breast milk and breast cancer led to the hypothesis that anti-apoptotic milk proteins (e.g., α-lactalbumin) [43], progesterone and gonadotropin-releasing hormones [44], or reduced cytochrome P4501A activity may mediate the association [45]. Breast milk

Table 21.1 Characteristics of published epidemiologic studies of breastfeeding in infancy and risk of invasive breast cancer

Study design	Investigators	Enrollment date (case–control) or follow-up period (cohort)	Participants' birth year	No. cases	No. person-years (p-y) or controls	Method of exposure ascertainment	Coding of exposure	Estimated relative Risk (95% CI)[a]	Control variables
Cohort	Ekbom et al. [26]	1874–1954	1874–1954	458 <50 y: 212 ≥50 y: 246	1,197 <50 y: 600 ≥50 y: 597	Record-linkage. Hospital records completed by midwives/nurses on average 10 days after delivery	Exclusive or partly BF vs. no	*All women*: 1.03 (0.46, 2.27) ≤50 year: 0.96 (0.37, 2.49) ≥50 year: 1.23 (0.39, 3.85)	Maternal age at delivery, childhood socioeconomic status, duration of hospital stay, maternal age at menarche, parity, age at first birth, menopausal status
	Michels et al. [28]	1991–1997	1921–1964	Total: 1,073 Premeno: 413 Postmeno: 660	695,655 p-y	Self-report via questionnaire (validated using maternal reports: r = 0.74)	Ever vs. never; duration	*All women*: 1.05 (0.91, 1.21) Duration: <9 month: 0.95 (0.80, 1.14) ≥9 month: 1.19 (0.93, 1.53) *Premenopausal*: 0.97 (0.71, 1.20) Duration: <9 month: 0.85 (0.66, 1.10) ≥9 month: 0.88 (0.52, 1.49) *Postmenopausal*: 1.12 (0.92, 1.37) Duration: <9 month: 1.06 (0.83, 1.36) ≥9 month: 1.30 (0.98, 1.72)	Age, birth year, preterm birth, family history of BRCA, height, BMI at 18, weight change since 18, history of benign breast disease, age at first birth, energy intake, alcohol
	Martin et al., 2005	1948–2003	1918–1939	74 <50 year: 13 ≥50 year: 61	94,610[b]	Maternal report via questionnaire (average 7 years after birth)	Ever vs. never; duration	*All women*: 1.62 (0.89, 2.94) ≤50 year: 2.50 (0.55, >4.00)[c] ≥50 year: 1.50 (0.78, 2.85)[c]	Age, survey district, social class of father, per capita weekly household food expenditure in childhood, birth order

Case–control	Bucalossi et al. [25]	1928–1956	Early 1900s	2,969	836	Self-report or proxy report by relatives via interviews or questionnaires	Ever vs. never	1.09 (0.72, 1.64)	None
	Henderson et al. [35]	1971–1972	>1906	Total: 308 <40 year: 69	308 <40 year: 69	Self-report via in-person interview	Ever vs. never	*All women*: 1.27 (0.79, 2.05) ≤40 year: 1.18 (0.53, 2.63)	Date of birth, race, socioeconomic status
	Brinton et al., 1983	1973–1977	1919–1932 (median)	1,192	1,080	Self-report via in-person interview	Ever vs. never	0.86 (0.7, 1.1)	Age
	Freudenheim et al. [27]	1986–1991	1901–1951	Total: 528 Premeno: 229 Postmeno: 299	Total: 528 Premeno: 229 Postmeno: 299	Self-report via in-person interview	Ever vs. never	*All women*:0.74 (0.56, 0.99) *Premenopausal*: 0.76 (0.52, 1.12) *Postmenopausal*: 0.73 (0.47, 1.13)	Age, education, BMI, family history of BRCA, age at menarche, parity, age at first birth, menopausal status, history of being breast disease, duration breastfed own children, fat and carotenoid intake, height
	Weiss et al. [33]	1990–1992	1946–1972	<45 year: 508	<45 year: 471	Maternal report via questionnaire	Ever vs. never	≤45 year: 0.74 (0.6, 1.0)	Age, BMI, family history of BRCA, previous breast biopsy, alcohol, number of mammograms, age at menarche, age at first birth, parity
	Titus-Ernstoff et al. [31]	1992–1995	1911–1945	Total: 4,008 Premeno: 205 Postmeno: 3,803	Total: 4,291 Premeno: 220 Postmeno: 4,071	Self-report via telephone interview	Ever vs. never	*All women*: 0.93 (0.83, 1.04) *Premenopausal*: 0.65 (0.41, 1.04) *Postmenopausal*: 0.95 (0.85, 1.07)	Age, state, education, religion, family history of BRCA, BMI, age at menarche, parity, age at first birth, age at menopause

(continued)

Table 21.1 (continued)

Study design	Investigators	Enrollment date (case–control) or follow-up period (cohort)	Participants' birth year	No. cases	No. person-years (p-y) or controls	Method of exposure ascertainment	Coding of exposure	Estimated relative Risk (95% CI)[a]	Control variables
	Sanderson et al. [30]	1994–1996	>1944	<45 year: 506	<45 year: 433	Maternal report via questionnaire or telephone interview	Ever vs. never; duration	≤45 year: 1.0 (0.8, 1.3) Duration: <3 month: 1.0 (0.7, 1.4) 3–5 month: 1.1 (0.7, 1.6) ≥6 month: 1.0 (0.7, 1.5)	Age. birth year, BMI, family history of BRCA, menopausal status, age at menarche, parity, age at first birth, infertility, use of OCs, birth weight, maternal age, birth order, maternal smoking
	Barba et al. [24]	1996–2001	1916–1966	Total: 845 Premeno: 270 Postmeno: 575	Total: 1,537 Premeno: 543 Postmeno: 994	Self-report via in-person interview	Ever vs. never	*All women*:0.82 (0.68, 0.99)[d] *Premenopausal*: 0.56 (0.38, 0.83) *Postmenopausal*: 0.86 (0.67, 1.11)	Age, education, race, BMI, history of benign breast disease, family history of BRCA, lactation, age at menarche, parity, age at first birth, age at menopause
	Nichols et al. [23]	2002–2006	1933–1986	1,648	773	Self-report via telephone interview	Ever vs. never	*All women*: 0.83 (0.72, 0.96) *First-born women*: 0.97 (0.74, 1.29)	Age, age at menarche, age at first birth, parity, menopausal status, postmenopausal hormone use, family history of BRCA, height, weight at age 20, weight gain, mammography use

	Wise et al. [34]	1997–2001	1922–1976	Total: 3,779 Premeno: 1,760 Postmeno: 1,985	Total: 4,433 Premeno: 1,531 Postmeno: 2,395	Self-report via telephone interview	Ever vs. never; duration (19% of women only)	*All women*: 0.99 (0.90, 1.09) *Premenopausal*: 0.94 (0.80, 1.10) *Postmenopausal*: 1.01 (0.89, 1.15) *All women, duration*: <3 month: 0.90 (0.70, 1.15) 3–6 month.: 0.77 (0.58, 1.02) >6 month: 1.05 (0.74, 1.48)	Age, state, education, religion, family history of BRCA, BMI, age at menarche, parity, age at first birth, menopausal status, age at menopause
Cross-sectional	Tokuhata [32]	1950–1966	1910–1939 (median)	13	1,314	Interview or questionnaires to mothers' relatives	Ever vs. never	0.88 (0.20, 3.94)	None
Case-series	Penrose et al. [29]	Early 1900s	Late 1800s-early 1900s	79	360	Self-report via in-person interview	Ever vs. never familial vs. sporadic BRCA	2.22 (0.85, 5.77)	None

[a]Relative risk (odds ratio, risk ratio, or incidence rate ratio) and 95% confidence interval comparing any or exclusive breastfed vs. bottle-fed, or breastfeeding duration category relative to bottle-fed. *BF* breastfeeding

[b]Estimated based on data reported on total person-years (N = 185,458) and proportion of women in sample (51%)

[c]Based on Figures C and D (no exact estimates provided) [2]

[d]Crude estimate based on numbers of cases and controls provided in Table 2 of text [24]

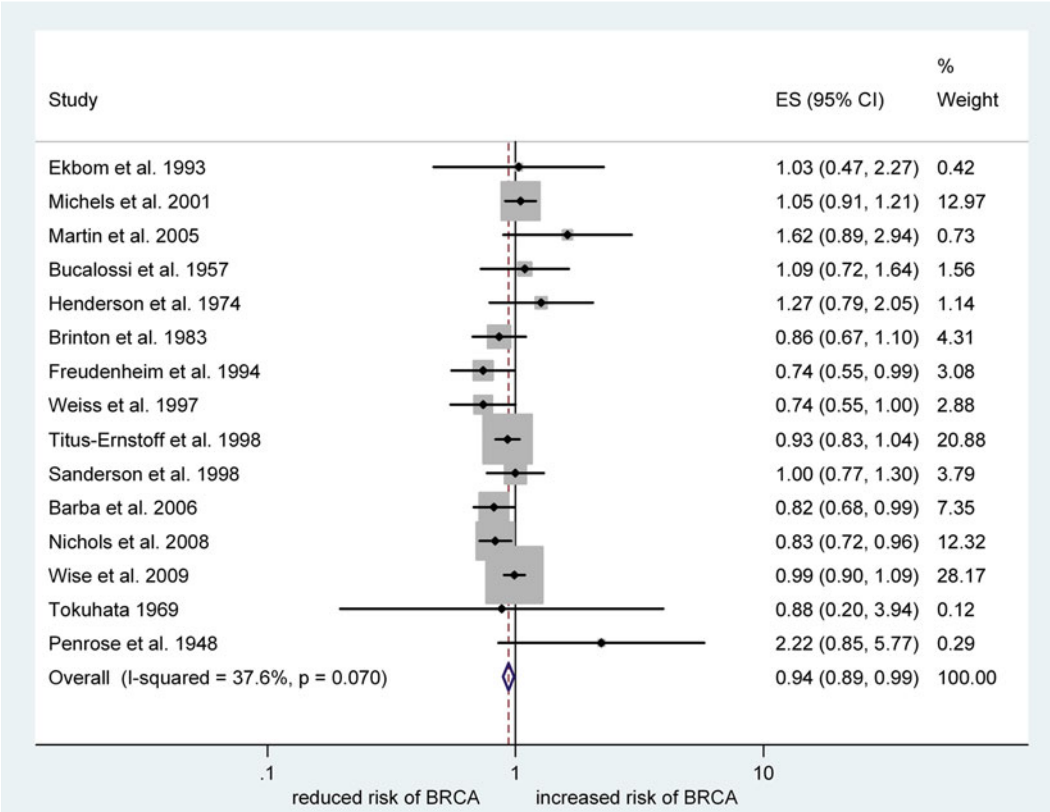

Fig. 21.1 Forest plot displaying an inverse-variance weight fixed-effect meta-analysis of studies on breastfeeding in infancy and risk of breast cancer: all women. Relative risks (ES) and 95% confidence intervals (CI) for breast cancer incidence, comparing women who were ever versus never breastfed in infancy. The study author and year of publication are indicated on the y-axis (ordered by type of study and year of publication). The box for each study is proportional to the inverse of the variance; horizontal lines show 95% CIs for each study-specific RR. The pooled estimate is shown at the bottom by a dashed vertical line (RR) and diamond (95% CI)

likely contains both chemo-protective and harmful agents, making it difficult to identify its direct influence on breast cancer risk.

In summary, the existing data are not sufficient to confirm or refute any protective or harmful effect of having been breastfed on breast cancer risk, and additional studies are needed. Published studies have suffered from several methodological limitations and future studies could be improved by using a prospective design (to avoid recall bias); collecting detailed exposure data on breastfeeding patterns (e.g., duration of breastfeeding, exclusivity of breastfeeding, and type of feeding: suckling vs. expressed milk); collecting data on a wide range of potential confounders including infant and parental characteristics; enrolling a large sample with sufficient numbers of premenopausal and postmenopausal cases; enumerating a study population with wide variation in the prevalence of breastfeeding; and conducting validation studies of breastfeeding reports using both participant and maternal data. For example, family studies of siblings with different breastfeeding histories would be particularly useful to adjust for confounding by social, environmental, and familial factors. Over a longer period of time, experimental studies that can rule out confounding such as PROBIT—albeit expensive to implement—could answer a broad range of questions about the long-term health benefits of breastfeeding [1]. In addition, the inclusion of new breastfeeding questions on the 2003 National Immunization Survey

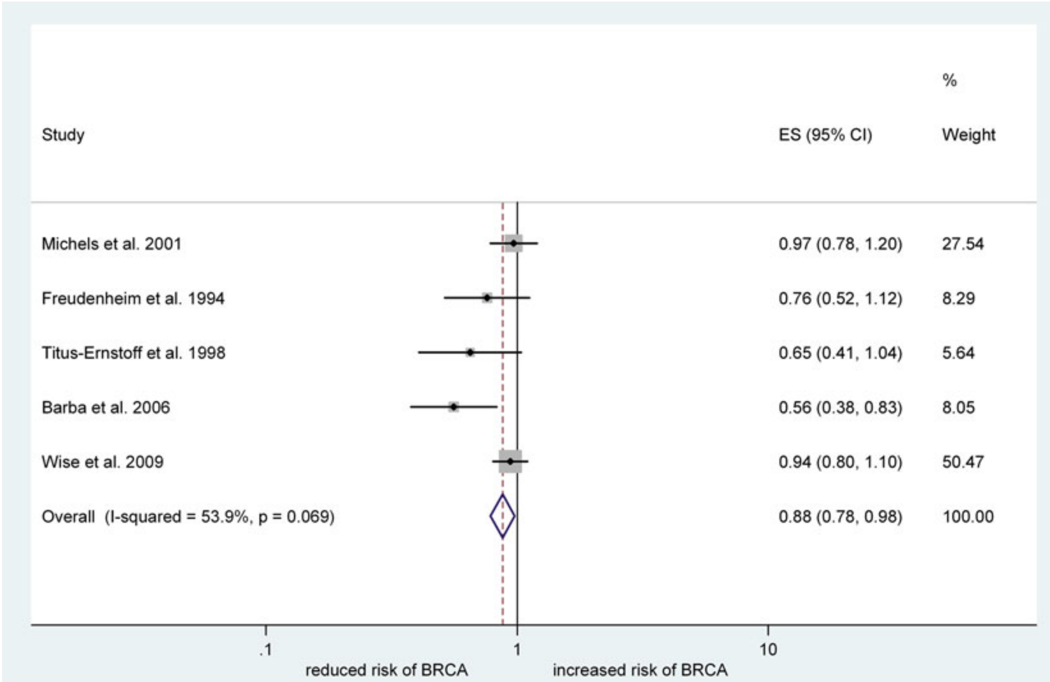

Fig. 21.2 Forest plot displaying an inverse-variance weight fixed-effect meta-analysis of studies on breastfeeding in infancy and risk of breast cancer: premenopausal women

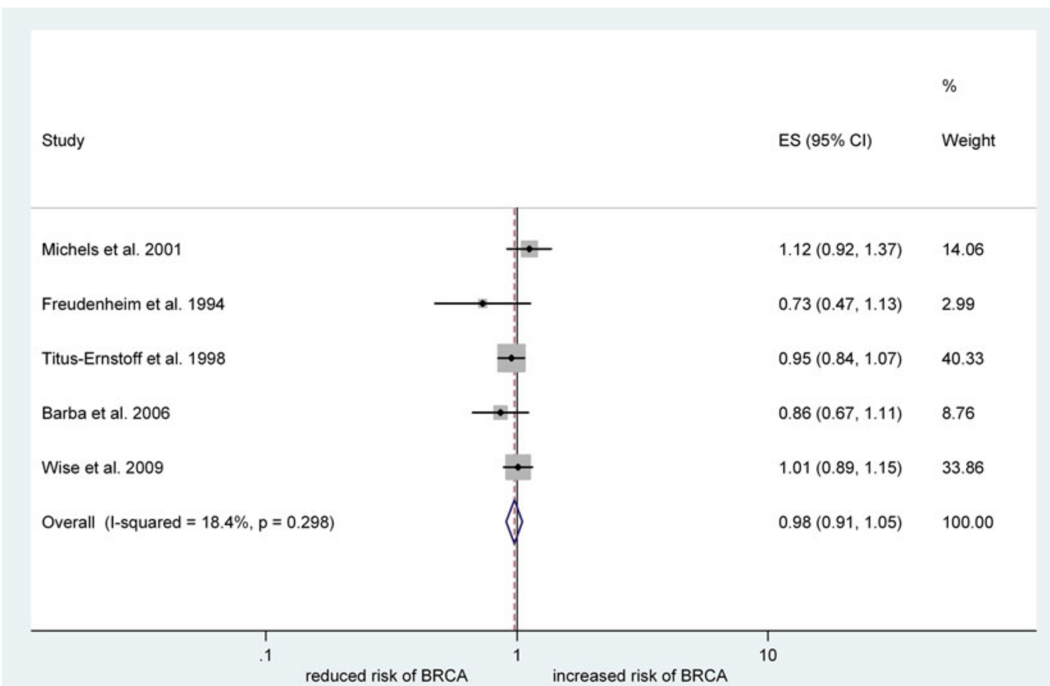

Fig. 21.3 Forest plot displaying an inverse-variance weight fixed-effect meta-analysis of studies on breastfeeding in infancy and risk of breast cancer: postmenopausal women

[46] (on initiation, duration, and exclusivity of breastfeeding) could provide useful data not only on breastfeeding trends, but also on the long-term health effects of being breastfed.

Health care professionals continue to play an important role in promoting breastfeeding by providing up-to-date information to pregnant and postpartum women, removing institutional barriers to breastfeeding, and advocating for policies that support breastfeeding as the norm for infant feeding [3]. Until more definitive studies are conducted, health professionals should avoid informing their patients about a possible link between infant feeding and breast cancer while continuing to stress the many established benefits of breastfeeding for both infant and mother.

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