

# Breastfeeding and risk of breast cancer: a meta-analysis of published studies

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**Evidence in favour of an association of breastfeeding with a breast cancer risk reduction remains limited and inconsistent. To evaluate the relation between breastfeeding and breast cancer, a meta-analysis based on a review of the literature was carried out, using as variables ever/never breastfeeding and duration of breastfeeding. Menopausal status at the time of diagnosis of breast cancer was considered to be a potential effect modifier. Only case-control studies could be included in the final analysis. A slight but significant decreased risk of breast cancer was observed in ever breastfeeding, compared with never breastfeeding parous women, using both the fixed and random-effect models. This decrease was more pronounced in non-menopausal women at the time of diagnosis of breast cancer and in long-term breastfeeding women. Hence, breastfeeding appeared to be a protective factor but was of small magnitude compared with other known risk factors for breast cancer. Whether this result should imply a modification in the attitude of both health care providers and women towards breastfeeding, which represents one of the few identified protective factors which is under the control of the mother, and is thus (theoretically) modifiable, remains questionable.**

*Key words:* breastfeeding/breast cancer/meta-analysis/epidemiological methods

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## Introduction

Breast cancer represents the most frequent localization of cancer in women from Westernized countries (Harris *et al.*, 1992; Black *et al.*, 1997; Parkin *et al.*, 1999), with a steadily increasing incidence in diagnosis and relative stability in mortality over the years (Kelsey *et al.*, 1993; Parkin, 1998). This stimulated a large number of studies which aimed at identifying both genetic and environmental risk factors and to quantify the magnitude of their effects (Kelsey *et al.*, 1993). Different degrees of evidence have emerged, suggesting a link between lactation and breast cancer. The first, yet weak,

evidence comes from the ecological relationship between the observed trend in breast cancer incidence and the decline of breastfeeding in women from Westernized countries, compared with their mothers and with women from other parts of the world (Anonymous, 1993; Parkin, 1998; Tulldahl *et al.*, 1999). A second (indirect) line of evidence comes from the old observation of the relationship between breastfeeding duration and the delayed return of ovulation during the postpartum period, which has been documented by both clinical observations and physiological studies (Howie *et al.*, 1982; Gray *et al.*, 1990; Kurz *et al.*, 1991), suggesting an impairment of ovarian secretions. In turn, suppression of ovarian function has been shown to be associated with a reduced risk of breast cancer, compared with normally cycling women (Kelsey *et al.*, 1993). Furthermore, both in-vivo and in-vitro studies have demonstrated the role of exposure to prolactin and oestrogens of mammary epithelial cells on their normal differentiation (Russo *et al.*, 1982; Henderson *et al.*, 1985; Key *et al.*, 1988; Dickson, 1996). In addition, lactation has been suggested to play a role in the elimination of some mammary carcinogens (Dewailly *et al.*, 1994).

However, epidemiological evidence on this issue remains controversial, some studies reporting that breastfeeding did not modify breast cancer risk (MacMahon *et al.*, 1970, 1982; Brinton *et al.*, 1983, 1995; Brignone *et al.*, 1987; Kvale and Heuch, 1987; Rosero-Bixby *et al.*, 1987; Siskind *et al.*, 1989; London *et al.*,

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1990; Thomas *et al.*, 1993; Rao *et al.*, 1994; Katsouyanni *et al.*, 1996; Michels *et al.*, 1996; Negri *et al.*, 1996; Enger *et al.*, 1997; Freudenheim *et al.*, 1997; McCredie *et al.*, 1998), while other studies suggested either a decreased risk in women who had ever breastfed (Ross and Yu, 1994; Romieu *et al.*, 1996; Wu *et al.*, 1996), or a decreased risk only in some specific subgroups of women according to different criteria, e.g. duration of breastfeeding (Layde *et al.*, 1989) or menopausal status (McTiernan and Thomas, 1986; Yang *et al.*, 1993; Newcomb *et al.*, 1994; Enger *et al.*, 1998).

The aim of the present study was to carry out a meta-analysis of the relationship between breastfeeding and breast cancer, based on the epidemiological literature published in peer-reviewed journals.

## Methodological details

### Formulation of the questions

The primary question was: does breastfeeding modify the risk of breast cancer? This raised the subsidiary question of the magnitude of the effect in relation to the duration of breastfeeding. In addition, as menopausal status at the time of breast cancer diagnosis is a classical characteristic which is considered in individual therapeutic decisions, and which has been frequently taken into account in previous epidemiological studies on breast cancer and breastfeeding, we considered whether this factor was a potential effect modifier.

### Criteria for considering studies for this review

For obvious reasons, our study was based on epidemiological studies only. We included all case-control studies, as well as all cohort studies addressing risk factors for breast cancer, which incorporated the history of breastfeeding as a specific variable, and which were published between 1980 and 1998.

### Search strategy for identification of studies

The National Library of Medicine 'Medline' database and the Excerpta Medica database 'Embase' were systematically searched for the period 1980–1998, using the following exploded MeSH key words: 'breast neoplasms' or 'mammary neoplasms' intersected with 'breastfeeding' or 'lactation' or 'prolonged lactation'. Bibliographies from potentially relevant studies were subsequently hand-searched for further studies. As we wished to limit our analysis to published studies, no attempt was made to identify unpublished studies.

### Criteria of inclusion

A study was included in the analysis provided: (i) it was published between 1980 and 1998; (ii) it presented primary (original) data; (iii) it was published either in English or French; (iv) the type of the study was either a case-control, or a prospective cohort study; (v) data on breastfeeding exposure were reported and used in the analysis; (vi) breast cancer was the event of interest; and (vii) the specific odds-ratios (OR) measuring the breastfeeding and breast cancer association were given or could be derived. The OR was used as the risk measure in the original studies, as it is classically used in case-control studies.

### Criteria of exclusion

As the aim of the study was to compare women who had breastfed with women who had not breastfed, parous women represented the reference category. Therefore, studies were discarded in which data from parous women who had not breastfed could not be separated from nulliparous women.

### Statistical analysis

The combined OR was obtained using both the fixed effect model (Greenland, 1987) and the random effect model (DerSimonian and Laird, 1986). In the fixed effect model, it is assumed that the effect is the same in all pooled studies and that the variations observed between studies correspond only to random measurement errors. Under this rationale, only results for which the homogeneity hypothesis cannot be rejected deserve to be reported. Cochran's test (Cochran, 1954) is a classical tool used for detecting lack of homogeneity and helps in individualizing studies or group of studies, which are the source of this heterogeneity and which should be more closely inspected.

On the contrary, the random effect model acknowledges the fact that the variations observed between studies correspond to a combination of a specific true effect (which differs between studies), and measurement errors. The only possible hypothesis is then to assume that the true effects associated with each study are independent realizations of an unknown latent random variable corresponding to this true effect. The latter variable is characterized by a probability density function, which is entirely determined by its mean and its variance under an assumption of Gaussian distribution.

More recently, it has been suggested that in addition to Cochran's test for detecting a lack of homogeneity (and which is of limited power), discrepancies between estimates of the pooled effect using the fixed and the random effect models could help in detecting heterogeneity (Normand, 1999). In addition, although pooled mean estimates using both models remain usually rather close, confidence intervals based on the random effect model are generally wider, leading to more conservative decisions, giving additional justification for using the random effect model, at least when the assumption of homogeneity is not valid.

Each model was fitted using both crude and adjusted data extracted from publications. The adjustment generally concerned several covariates related to the genital life. However, it was not usually based on the same covariates in all the studies. Therefore, the pooling of the ORs was carried out using, for each study, the OR adjusted on the maximum number of covariates as reflected in the publication. In the analysis of the relationship between the OR of breast cancer and breastfeeding duration, a classical test for trend assuming a linear relationship was performed (Breslow and Day, 1980), in addition to the graphical inspection. However, as the data suggested a non-linear threshold effect (rather than a linear trend) for a longer duration of breastfeeding, the three different categories of breastfeeding duration were coded using two dummy variables, the latter being subsequently used as regression variables in a multivariate regression model of the individual ORs (Kleinbaum *et al.*, 1988).

### Graphical representation

In addition to the classical graphical representation of the results of a meta-analysis (Parmar *et al.*, 1996), we used the radial representation as proposed by Galbraith, in order to highlight some of the disparities between studies (Galbraith, 1988). Briefly, each study  $i$  ( $i=1\dots n$ ) is represented in a  $(x, z)$  scatterplot by a couple  $(x_i, z_i)$ . On the  $x$  axis, the value  $x_i$  is defined as the inverse of the standard error (SE), whereas on the  $z$  axis, the value  $z_i$  corresponds to the standardized effect expressed in  $z$ -score, i.e.  $OR_i$  divided by its estimated SE. Points with larger  $x$  values, i.e. smaller SE, correspond to more precise (and hence more informative), studies. The estimated OR for each study corresponds to the slope of the line starting from the origin of the axis and passing through the point  $(x_i, z_i)$  and can be visualized on a specific circular scale. This representation is particularly useful in the analysis of homogeneity between studies (Galbraith, 1988).

All calculations and graphical representations were carried out using Excel (Microsoft Co, Seattle, WA, USA) and Matlab (MatWorks Inc.) softwares. Additional checks were carried out using the dedicated software packages, EASYMA (Cucherat *et al.*, 1997) and RMETA (<http://www.ci.tuwien.ac.at/R>).

### Quantification of the interaction between breastfeeding and menopausal status

For each case-control study, the interaction between these two factors on the OR of breast cancer can be quantitatively defined by the interaction term:

$$\frac{OR_{BF-M}}{OR_M \cdot OR_{BF}}$$

where  $OR_{BF-M}$  is the OR of breast cancer in non-menopausal breastfeeding mothers,  $OR_M$  the OR of breast cancer in non-menopausal women and  $OR_{BF}$  the OR of breast cancer in breastfeeding mothers; never-breastfeeding menopausal mothers were the reference category. As data concerning menopausal status were not always available in controls, the interaction term, together with its estimated variance, were derived using a case-only approach (Begg and Zhang, 1994; Piegorsch *et al.*, 1994). Then, the different terms were pooled using the classical methods described previously.

### Summary of selected studies

In all, 40 studies were identified concerning the relationship between breastfeeding and breast cancer: 37 were case-control studies (MacMahon *et al.*, 1982; Brinton *et al.*, 1983, 1995; Duffy *et al.*, 1983; Lubin *et al.*, 1983; Byers *et al.*, 1985; Chiedozi, 1985; McTiernan and Thomas, 1986; Brignone *et al.*, 1987; Rosero-Bixby *et al.*, 1987; Layde *et al.*, 1989; Siskind *et al.*, 1989; Adami *et al.*, 1990; Rojas *et al.*, 1990; Parades and Lopez, 1991; Haring *et al.*, 1992; Reuter and Baker, 1992; Yoo *et al.*, 1992; Hardy *et al.*, 1993; Mayberry and Stoddard, 1993; Thomas *et al.*, 1993; Yang *et al.*, 1993; United Kingdom National Case-Control Study Group, 1993; Newcomb *et al.*, 1994; Rao *et al.*, 1994; Ross and Yu, 1994; Katsouyanni *et al.*, 1996; Lai *et al.*, 1996; Negri *et al.*, 1996; Ramon *et al.*, 1996; Romieu *et al.*, 1996; Wu *et al.*, 1996; Enger *et al.*, 1997, 1998; Freudenheim *et al.*, 1997; Gilliland

**Table I.** Literature search on 'breastfeeding (BF) and risk of breast cancer'; list of discarded case-control studies according to inclusion/exclusion criteria

Inclusion/ exclusion criteria	Reference	Year of publication	Country
Neither English nor French language	Haring <i>et al.</i>	1992	The Netherlands
	Hardy <i>et al.</i>	1993	Brazil
	Parades <i>et al.</i>	1991	Mexico
	Rojas <i>et al.</i>	1990	Spain
Incomplete information on BF variables	Lai <i>et al.</i>	1996	Taiwan
	Mayberry <i>et al.</i>	1993	USA
	Reuter <i>et al.</i>	1992	USA
	Yoo <i>et al.</i>	1992	Japan
	Byers <i>et al.</i>	1985	USA
	Cheidozi <i>et al.</i>	1985	Nigeria
	Ramon <i>et al.</i>	1996	Spain
Never BF parous women indistinguishable from nulliparous women	UK NCCSG	1993	UK
	Adami <i>et al.</i>	1990	Sweden, Norway
	Duffy <i>et al.</i>	1983	Scotland

**Table II.** List of 23 case-control studies fulfilling inclusion/exclusion criteria

First author	Publication year	Study site	Cases (% BF)	Controls (% BF)	Age range (years)	OR (CI 95%)
MacMahon	1982	Estonia	226 (89.4)	482 (92.3)	>30	0.70 (0.37–1.33)
Lubin	1983	Canada	499 (66.7)	747 (75.0)	30–80	0.67 (0.50–0.90)
Brinton	1983	USA	1139 (61.0)	1056 (64.3)	45–54	0.87 (0.71–1.07)
McTiernan	1986	USA	268 (60.4)	285 (68.4)	20–54	0.71 (0.47–1.07)
Brignone	1987	Sicilia	645 (78.0)	741 (75.8)		1.13 (0.84–1.52)
Rosero	1987	Costa Rica	142 (85.9)	741 (88.9)	25–58	0.76 (0.41–1.42)
Siskind	1989	Australia	390 (90.3)	944 (91.6)	<75	0.85 (0.52–1.37)
Layde	1989	USA	3830 (48.9)	3931 (53.6)		0.83 (0.75–0.92)
Thomas	1993	Multicentre	2336 (88.4)	14900 (89.7)	<75	0.87 (0.74–1.02)
Yang	1993	Canada	856 (60.5)	877 (63.2)	20–55	0.89 (0.71–1.13)
Rao	1994	India	596 (97.1)	664 (98.3)	<70	0.57 (0.23–1.43)
Newcomb	1994	USA	5434 (56.3)	7563 (54.8)	<75	1.06 (0.98–1.16)
Ross	1994	China	1456 (88.4)	1456 (92.2)		0.64 (0.48–0.86)
Brinton	1995	New Jersey Georgia	1110 (61.0)	1034 (64.1)	<45 <54	0.87 (0.71–1.08)
Romieu	1996	Mexico	301 (88.0)	963 (94.0)	<75/ <80 <sup>a</sup>	0.47 (0.28–0.79)
Wu	1996	USA	401 (43.1)	674 (54.9)	20–55	0.62 (0.46–0.84)
Katsouyanni	1996	Greece	656 (87.5)	1164 (91.0)	56/54 <sup>b</sup>	0.69 (0.48–1.00)
Negri	1996	Italy	2139 (77.3)	2174 (77.0)	23–74	1.02 (0.86–1.20)
Freudenheim	1997	USA	620 (46.6)	693 (52.5)	40–85	0.79 (0.61–1.02)
Enger	1997	USA	452 (58.0)	452 (60.2)	< 40	0.91 (0.67–1.25)
Enger	1998	USA	974 (48.3)	973 (55.5)	55–64	0.75 (0.60–0.92)
Gilliland	1998	Mexico	610 (60.8)	740 (62.8)	30–74	0.88 (0.67–1.14)
McCredie	1998	New Zealand	791 (77.4)	1656 (79.6)	25–54	0.87 (0.68–1.11)

Identified data and odds ratio (OR) of breast cancer (BC) in relation to ever *versus* never breastfeeding (BF). Control = never breastfeeding parous women; OR = unadjusted odds ratio. Studies are identified with the name of the first author and year of publication. Full references are given in the bibliography section.

<sup>a</sup>Maximum age value in cases/controls respectively; <sup>b</sup>median age in cases/controls respectively.

*et al.*, 1998; McCredie *et al.*, 1998) and three were cohort studies (Kvale and Heuch, 1987; London *et al.*, 1990; Michels *et al.*, 1996).

Among the 37 case-control studies, 10 did not satisfy the inclusion criteria: four studies were excluded as they were published in languages other than English or French; six studies were also discarded due to insufficient information regarding the breastfeeding variables.

Among the 27 remaining studies, four were discarded as data concerning parous women which never breastfed, could not be separated from data concerning nulliparous women. Studies excluded from the analysis are summarized in Table I.

Finally, 23 among the 35 case-control studies were used. Details of these 23 studies are presented in Table II. It should be mentioned that a previous study (Ross and Yu, 1994) was already

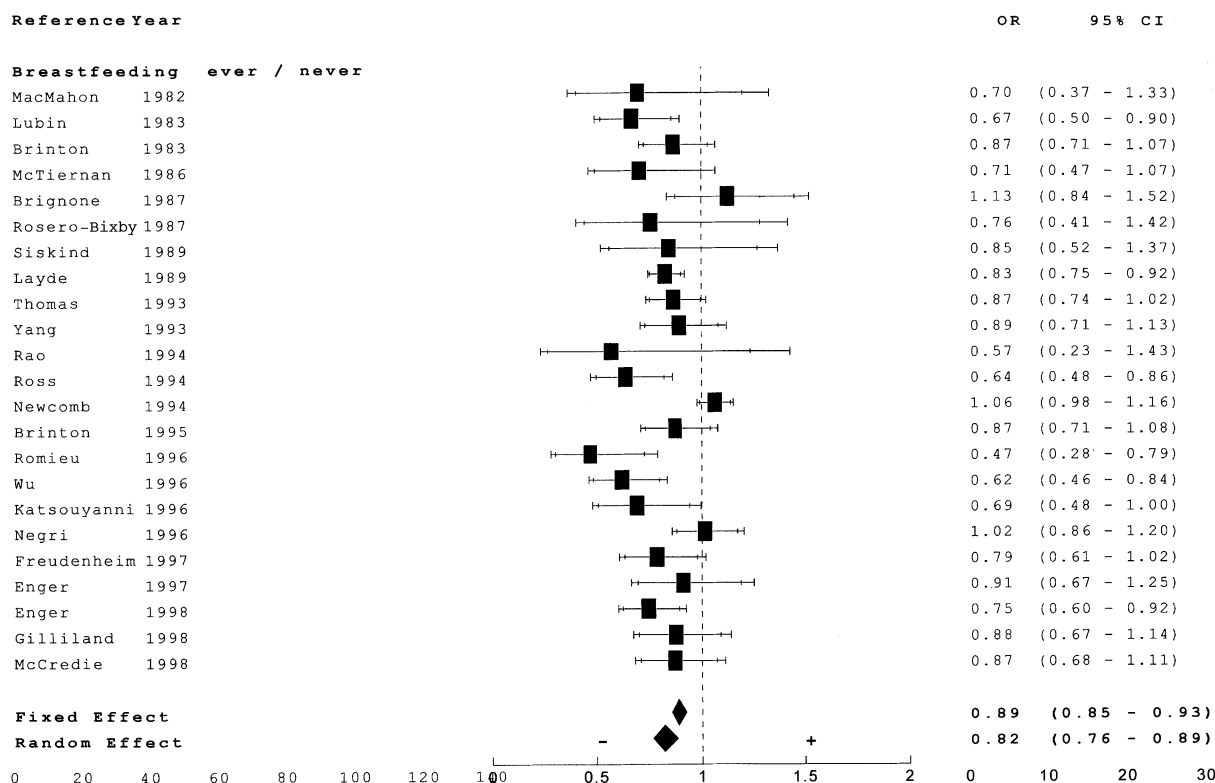
a summary statistics of the raw data of four different studies carried out in four Chinese large cities (Wang *et al.*, 1985; Tao *et al.*, 1988; Yuan *et al.*, 1988; Wang *et al.*, 1992), but individual data from these four studies could be derived and were used in the present study. Details of adjusting factors in the selected studies are given in Table III.

The remaining three studies were cohort studies (Kvale and Heuch, 1987; London *et al.*, 1990; Michels *et al.*, 1996); among them, two were clearly related to the same population, with no possibility of pooling the results (London *et al.*, 1990; Michels *et al.*, 1996). In the third one, data on breastfeeding could not be directly derived (Kvale and Heuch, 1987). Therefore, the three studies were not included in the meta-analysis, and only the 23 case-control studies participated in the subsequent analysis.

**Table III.** Studies with available adjusted odds ratios (ORs) and their corresponding adjusting factors

First author and year	OR (CI 95%)	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R
Lublin, 1983	0.60 (0.50–0.80)	1	1	1															
Brinton, 1983	0.94 (0.80–1.10)		1																
Siskind, 1989	0.85 (0.55–1.30)	1	1		1	1	1	1											
Rao, 1994	2.02 (0.80–4.90)	1							1										
Newcomb, 1994	0.97 (0.90–1.05)		1	1		1	1	1		1	1	1							
Brinton, 1995	0.87 (0.70–1.00)		1	1	1								1						
Romieu, 1996	0.54 (0.33–0.89)	1	1	1		1	1				1			1					
Wu, 1996	0.74 (0.56–0.98)	1			1				1										
Katsouyanni, 1996	0.93 (0.67–1.27)	1		1	1	1				1	1	1							
Negri, 1996	1.17 (1.00–1.30)	1	1	1			1	1	1	1	1	1		1				1	
Enger, 1997	0.93 (0.69–1.26)		1	1	1	1	1						1			1	1		
Enger, 1998	0.79 (0.66–0.96)	1	1	1		1	1			1		1		1		1		1	1

Studies with adjusted odds ratios and the corresponding adjusting factors. A = age at diagnosis, B = age at first full term pregnancy, C = parity, D = site of birth or ethnicity, E = age at menarche, F = familial history of breast cancer, G = personal history of benign breast disease, H = site of residence, I = age at menopause, J = status of menopause, K = Body mass index, L = use of oral contraceptives, M = social category, N = marital status, O = alcohol use, P = physical exercise, Q = educational level, R = use of hormone replacement therapy. Adjusting factors for each study are indicated by 1.



**Figure 1.** Individual and pooled odds ratios (OR) of breast cancer for ever/never breastfeeding. The estimated OR for each study corresponds to the centre of the filled rectangle. The height is proportional to the corresponding information, i.e. the inverse of the variance. The line corresponds to the confidence interval (CI): the outer ticks represent the 99% CI limits; the inner ticks represent the 95% CI limits. The vertical dotted line corresponds to the absence of difference between cases and controls regarding the odds of breast cancer. Pooled effects, using both fixed and random effect models, are represented by the corresponding centre of the filled diamonds. The length of the corresponding horizontal axis of the diamonds marks the 95% CI limits, whereas the height increases with the total information. Studies are identified with the name of the first author and year of publication. Full references are given in the bibliography section.

**Table IV.** Summary of the main results of the meta-analysis.

	Fixed Effect		Random Effect		Fixed Effect		Random Effect	
	OR	95% CI	OR	95% CI	OR <sub>a</sub>	95% CI	OR <sub>a</sub>	95% CI
Breastfeeding (ever/never)	0.89	0.86–0.92	0.82	0.76–0.89	0.88	0.84–0.92	0.84	0.74–0.96
Status at the time of either BC diagnosis or interview (ever/ never BF)								
Non-menopausal	0.83	0.77–0.90	0.81	0.72–0.91	0.77	0.72–0.84	0.76	0.66–0.87
Menopausal	1.01	0.95–1.08	0.84	0.69–1.03	0.92	0.85–0.98	0.83	0.68–1.01
Duration of breastfeeding (months)								
0 (reference)	1.00		1.00					
0–6	1.02	0.96–1.09	1.00	0.85–1.17	–			
6–12	0.97	0.89–1.05	0.97	0.85–1.10	–			
12+	0.75	0.71–0.81	0.72	0.65–0.83	–			

Summary of the estimates of the pooled odds ratio (OR) of breast cancer for ever- versus never-breastfeeding (BF), according to menopausal status at the time of the diagnosis of breast cancer (BC) and according to duration of breastfeeding, respectively. OR<sub>a</sub>=pooled OR using adjusted ORs; CI=confidence interval.

## Assessment of the methodological quality

### Origin of the women

Cases were recruited in hospitals in nine studies (MacMahon *et al.*, 1982; Brinton *et al.*, 1983; Brignone *et al.*, 1987; Siskind *et al.*, 1989; Thomas *et al.*, 1993; Rao *et al.*, 1994; Katsouyanni *et al.*, 1996; Negri *et al.*, 1996; Romieu *et al.*, 1996), and in registries in 14 studies (Lubin *et al.*, 1983; McTiernan and Thomas, 1986; Rosero-Bixby *et al.*, 1987; Layde *et al.*, 1989; Yang *et al.*, 1993; Newcomb *et al.*, 1994; Ross and Yu, 1994; Brinton *et al.*, 1995; Wu *et al.*, 1996; Enger *et al.*, 1997; Freudenheim *et al.*, 1997; Enger *et al.*, 1998; Gilliland *et al.*, 1998; McCredie *et al.*, 1998). All controls associated with hospital-based cases were hospital-based controls, with two exceptions (Siskind *et al.*, 1989; Romieu *et al.*, 1996). In the registry-based studies, controls were selected from the corresponding communities. In one study (Katsouyanni *et al.*, 1996), hospital cases were associated with both hospital and community-based controls.

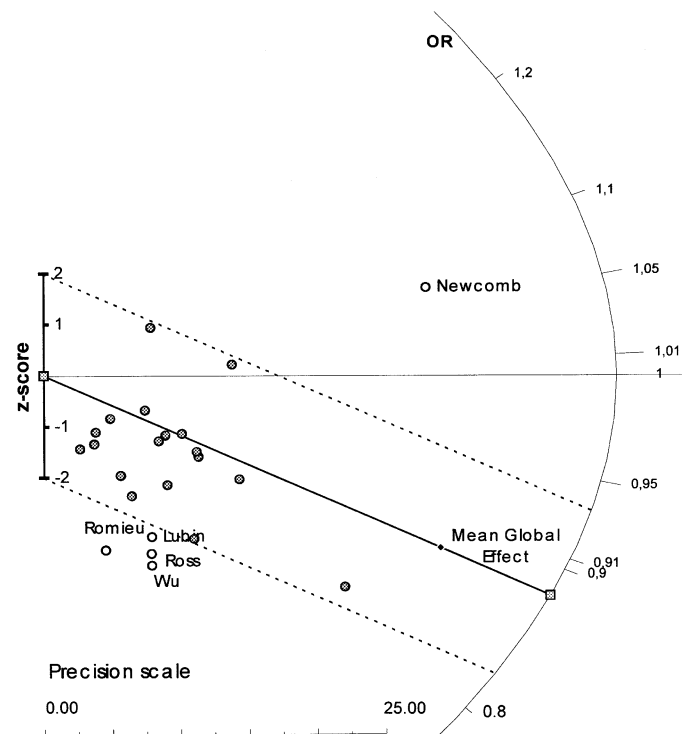
Reasons for non-participation were reported in 10 studies (Brinton *et al.*, 1983; Lubin *et al.*, 1983; Siskind *et al.*, 1989; Yang *et al.*, 1993; Newcomb *et al.*, 1994; Brinton *et al.*, 1995; Enger *et al.*, 1997, 1998; Gilliland *et al.*, 1998; McCredie *et al.*, 1998).

### Assessment of breast cancer diagnosis

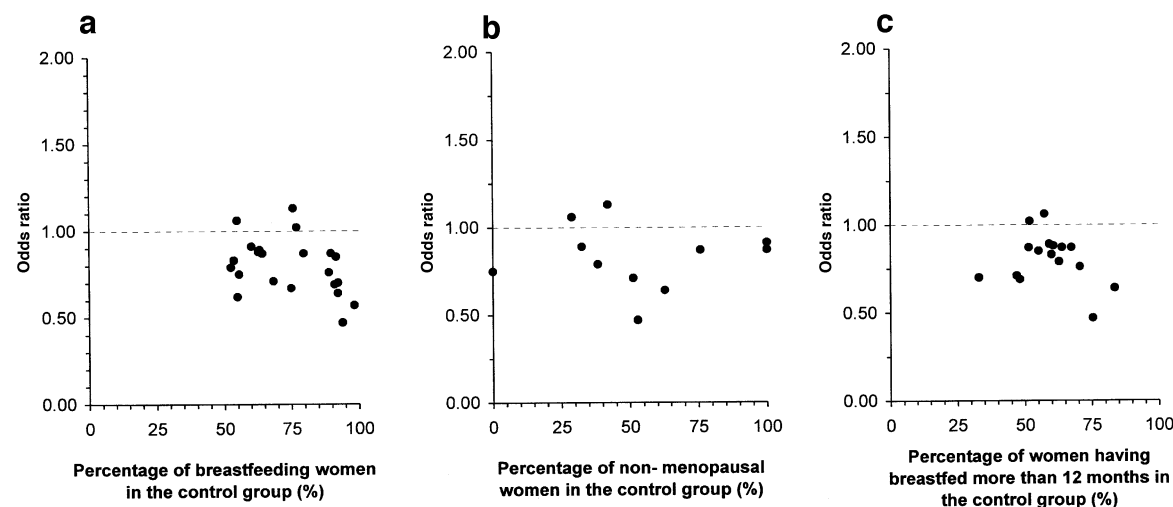
Histological confirmation of breast cancer cases was obtained in all studies but one, in which no precision was given regarding the histology (Rao *et al.*, 1994).

### Data collection

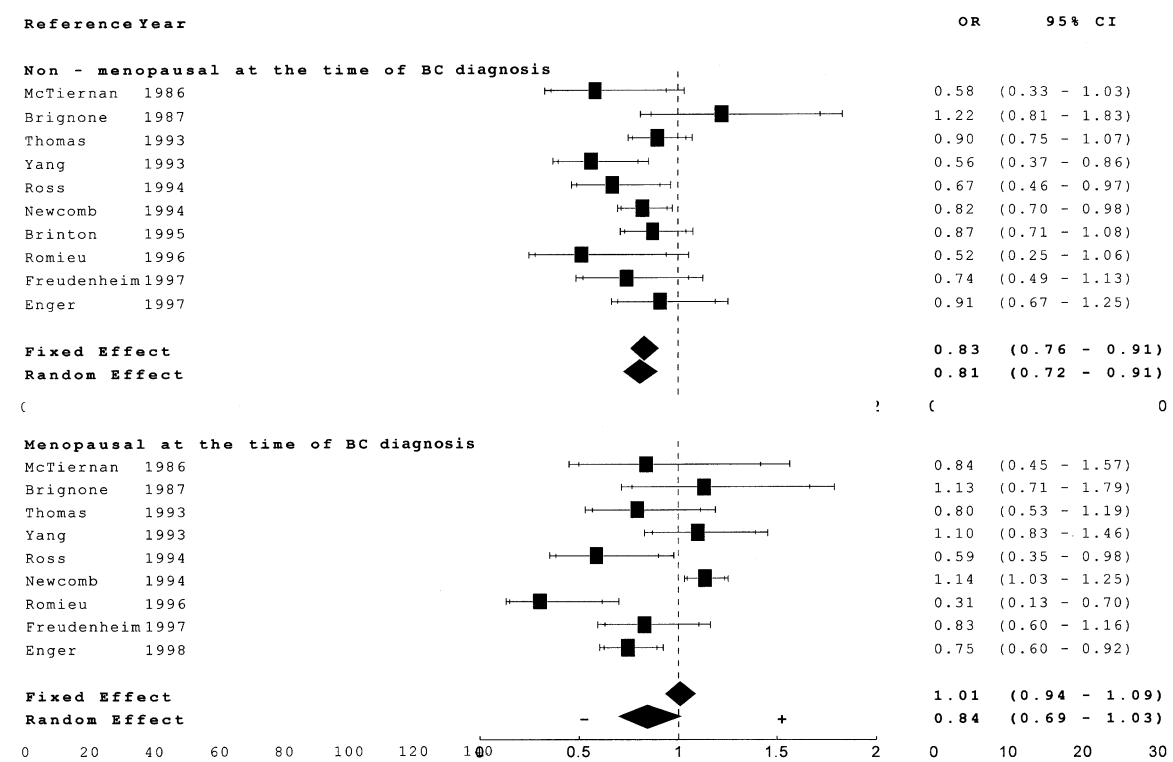
Standardized questionnaires were used in all studies. A self-administered questionnaire was used in one study (Yang *et al.*, 1993). Phone interviews were performed in three studies (Newcomb *et al.*, 1994; Enger *et al.*, 1998; McCredie *et al.*, 1998). In two studies, cases were interviewed in hospital and



**Figure 2.** Radial plot for ever/never breastfeeding. *x* axis=precision scale proportional to the inverse of the SE for each study. *y* axis=normalized effect *z* defined by odds ratio (OR) divided by its estimated SE. For each study, represented by a filled circle, the corresponding OR value can be read on the circular scale, by drawing a line from the origin of the axes, passing through the point. The dotted lines correspond to the 95% CI on both sides of the mean regression line, passing through the point corresponding to the pooled effect, represented by a filled square, which crosses the circular scale at the estimated pooled OR. Points outside these lines indicate studies differing from the others. These studies are identified with the names of the first author.



**Figure 3.** (a) Plot of the odds ratio (ORs) of breast cancer according to the proportion of breastfeeding women in the control groups. (b) Plot of the ORs of breast cancer according to the proportion of menopausal women in each study in the control groups. (c) Plot of the ORs of breast cancer according to the proportion of women having breastfed for >12 months in the control groups.



**Figure 4.** Individual and pooled odds ratios (OR) of breast cancer (BC) according to menopausal status.

controls at home (Lubin *et al.*, 1983; Romieu *et al.*, 1996). In the remaining studies, the participants were interviewed by trained interviewers, in the same location for both cases and controls. This location was the participant's home in 11 studies (Brinton *et al.*, 1983; McTiernan and Thomas, 1986; Rosero-Bixby *et al.*, 1987; Layde *et al.*, 1989; Siskind *et al.*, 1989; Ross and Yu, 1994; Brinton *et al.*, 1995; Wu *et al.*, 1996; Enger *et al.*, 1997;

Freudenheim *et al.*, 1997; Gilliland *et al.*, 1998) and the hospital in six studies (MacMahon *et al.*, 1982; Brignone *et al.*, 1987; Thomas *et al.*, 1993; Rao *et al.*, 1994; Katsouyanni *et al.*, 1996; Negri *et al.*, 1996). In three studies, the interview had been performed at the time of the mammography, before the diagnosis of cancer had been ascertained (Brinton *et al.*, 1983; Brignone *et al.*, 1987; Rao *et al.*, 1994). No quality score was used.

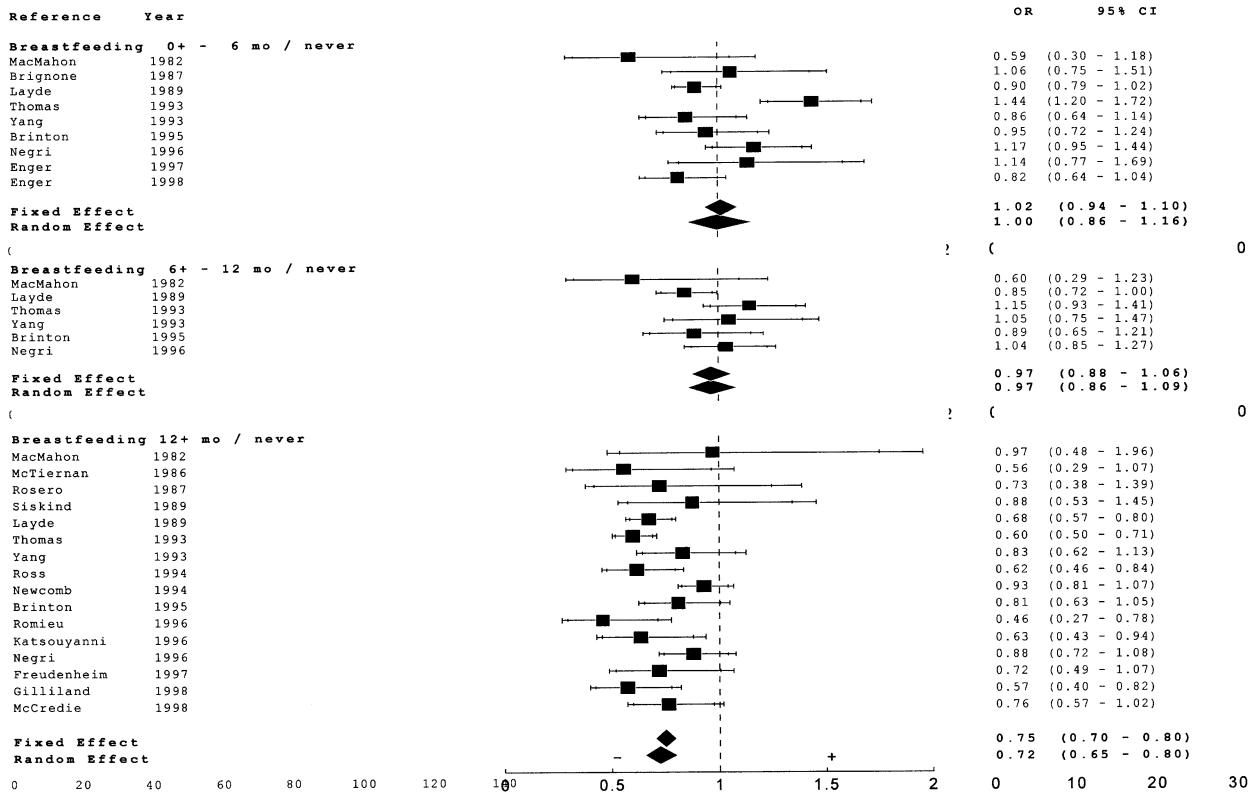


Figure 5. Individual and pooled odds ratios (OR) of breast cancer (BC) according to duration of breast feeding.

## Quantitative summaries

### Question 1: Breast cancer risk in ever- versus never-breastfeeding women

All the 23 studies were eligible. The data set is detailed in Tables II and III. Results are presented in Figure 1 and summarized in Table IV. The pooled OR for breast cancer risk according to breastfeeding practice was 0.90 [95% confidence interval (CI); 0.86–0.94] using the fixed effect model. Using the random effect model, the pooled OR was 0.84 (95% CI 0.78–0.91). These results suggest a slight, but significant, protective effect of ever-breastfeeding versus never- for breast cancer. These results were not modified by using adjusted ORs. However, Cochran's Q statistic for testing homogeneity was 74.43 [degrees of freedom (df)=21], and the homogeneity hypothesis was rejected. Potential sources of heterogeneity were investigated. Figure 2 displays the radial plot of the 23 studies, suggesting that five studies (Lubin *et al.*, 1983; Ross and Yu, 1988; Newcomb *et al.*, 1994; Romieu *et al.*, 1996; Wu *et al.*, 1996) differed from the others. A new analysis was performed, after having discarded these five studies. The new pooled ORs, restricted to the 18 remaining studies, were 0.86 (95% CI 0.82–0.90) using the fixed effect model and 0.86 (95% CI 0.82–0.91) using the random effect model respectively. Hence, the general conclusion of a slight but significant protective effect of breastfeeding was not modified on this now homogeneous pool of studies. No evident common features could be isolated regarding the main characteristics of these five studies.

Another classical potential source of heterogeneity between the ORs is the discrepancy in the proportion of exposed controls among studies. Therefore, the different ORs were plotted against the corresponding proportion of breastfeeding control women. No specific trend could be detected (Figure 3a).

### Question 2: Breast cancer risk according to menopausal status at the time of the diagnosis in ever- versus never-breastfeeding mothers

Data on menopausal status were not available in 11 studies (MacMahon *et al.*, 1982; Brinton *et al.*, 1983; Lubin *et al.*, 1983; Rosero-Bixby *et al.*, 1987; Layde *et al.*, 1989; Siskind *et al.*, 1989; Rao *et al.*, 1994; Negri *et al.*, 1996; Wu *et al.*, 1996; Gilliland *et al.*, 1998; McCredie *et al.*, 1998). One study did not provide the raw data, but only adjusted ORs for premenopausal and menopausal women (Katsouyanni *et al.*, 1996). One study concerned only post-menopausal women at the time of the diagnosis (Enger *et al.*, 1998). Two studies concerned only premenopausal women at the time of the diagnosis of breast cancer (Brinton *et al.*, 1995; Enger *et al.*, 1997). The eight remaining studies gave information separately both on non-menopausal and menopausal women. A summary of data concerning respectively non-menopausal (10 studies) and menopausal women (nine studies) and their corresponding pooled ORs is given in Figure 4 and Table III. A significant decrease of the pooled OR of breast cancer for non-menopausal women at the time of the diagnosis was found. No significant decrease of the OR could be shown for menopausal women.



When testing for homogeneity between studies, and adopting adjusted 0.05 type I error, according to the Bonferroni rule, the hypothesis was rejected in menopausal women (Cochran's  $Q$  42.7), while it was not rejected in the group of non-menopausal women (Cochran's  $Q$  18.4).

A quantitative estimation of the interaction between breastfeeding and menopausal status was obtained by pooling the individual interaction terms for each study, as estimated using the case-only approach referred to earlier. The pooled interaction term, based on eight studies, was 0.69 (95% CI 0.63–0.76). It suggested that the OR of breast cancer in non-menopausal breastfeeding mothers was less than the simple product of the OR associated with the menopausal status and the one associated with breastfeeding respectively, thus emphasizing the importance of the menopausal status as an effect modifier. This observation raised the hypothesis that a discrepancy between the proportions of menopausal women between studies may have contributed to the observed heterogeneity when addressing question 1. However, the plot of the ORs according to the proportion of menopausal women in the control group for each study did not show any specific trend (Figure 3b).

### **Question 3: Breast cancer risk according to breastfeeding duration**

Data on total duration of breastfeeding were not available in four studies (Brinton *et al.*, 1983; Lubin *et al.*, 1983; Rao *et al.*, 1994; Wu *et al.*, 1996). Among the 19 remaining studies, the duration of breastfeeding was not given precisely, and was usually grouped by categories differing between studies. Nevertheless, breastfeeding duration could be divided in four categories: (i) no breastfeeding; (ii) breastfeeding for 1–6 months; (iii) breastfeeding for 7–12 months; (iv) breastfeeding for >12 months. For each category, the pooled OR was calculated with no breastfeeding as the reference category. There were nine studies in category 2, six studies in category 3 and 16 studies in category 4. The corresponding summaries are shown in Figure 5 and Table III. A significant decrease of the pooled OR of breast cancer risk was observed only in women who breastfed for at least 12 months, compared with women who had never breastfed. When comparing the pooled ORs for the three categories of duration of breastfeeding, it suggested a trend towards a decreasing risk of breast cancer with increasing duration of breastfeeding ( $\chi^2$  for trend  $P < 0.0005$ ). However, when testing for a threshold effect, there was a significant difference only between the OR corresponding to a breastfeeding duration of >12 months and the ORs corresponding to breastfeeding duration categories of 1–6 months ( $P < 0.0002$ ) and 7–12 months ( $P < 0.003$ ) respectively.

Differences in duration of exposure to breastfeeding might represent yet another important difference between studies, explaining part of the heterogeneity observed when addressing question 1. Figure 3c shows the plot of the ORs in relation to the proportion of women having breastfed for >12 months in the control group for each study. It suggests a minor trend towards lower OR of breast cancer in studies with a larger proportion of women having breastfed for >12 months, which may explain part of the heterogeneity.

To summarize, the present study suggests a slight but significant reduction of breast cancer risk in women who had

ever breastfed. This decreased risk appeared to be duration-related as mothers having breastfed for >12 months were at lower risk than women having breastfed for a shorter duration. This effect was essentially present in women who were not menopausal at the time of breast cancer diagnosis.

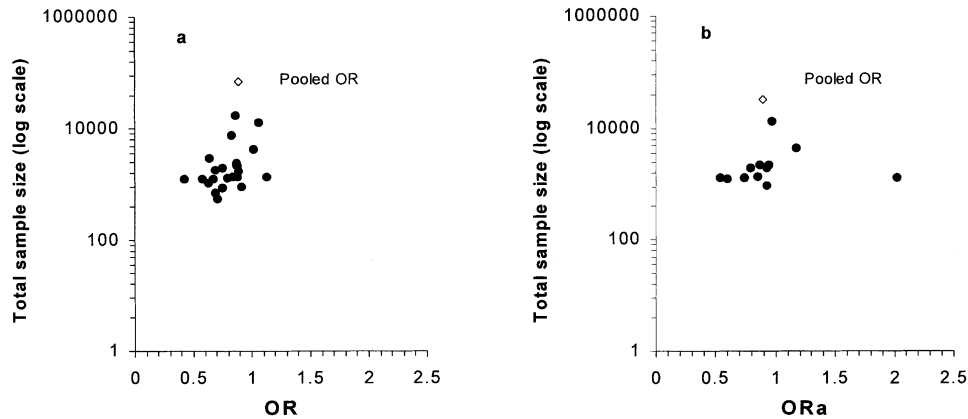
### **Sources of bias**

Several sources of biases might have influenced these results and need to be discussed. As the pooled studies were case-control studies, the results are highly dependent on a recall bias. It has been argued that women with a diagnosis of breast cancer tend to scrutinize their past medical history more intensively than the controls (Paganini-Hill and Ross, 1982). This phenomenon seems to be greater when covariates commonly known to be associated with the disease are investigated. A past history of breastfeeding does not seem to be obviously associated with breast cancer risk and, therefore, the recall bias should not to be too high, at least for ever- versus never-breastfeeding, as pregnancy and related events represent important events in a woman's life. If it can be reasonably assumed that women recalled accurately the fact of having breastfed or not in these studies, the exact duration of breastfeeding appeared to be recorded less precisely and was more linked to social clues or medical attitudes, with a large variability between generations, countries and social classes. However, broad duration categories seem to represent an accurate, though incomplete, mirror of actual breastfeeding duration.

Another important source of bias when discussing the results of any meta-analysis is the publication bias, as there is a general tendency in the medical literature to publish only studies showing a significant effect, whereas studies showing negative effects are more likely to be neither submitted nor accepted for publication (Easterbrook *et al.*, 1991). As we worked only on published studies, we cannot rule out the possibility of unpublished studies with no observed effect of breastfeeding on breast cancer risk. However, selecting only published results in this particular domain warranted us against poorly designed studies. Different methods have been proposed to assess the magnitude of the publication bias (Normand, 1999). As small studies more often tend to be non-significant, the funnel plot consists in plotting, for each study, the estimate of the effect versus the sample size. This plot has been shown to be skewed and asymmetrical in the presence of publication bias (Egger *et al.*, 1997). Figure 6a and b displays the funnel plots corresponding to the data set for both the raw and adjusted ORs. No clear asymmetry or heterogeneous density of reported small sized studies could be observed.

### **Power of the meta-analysis**

In a randomized trial, the sample size is usually determined by taking into account the assumed control event rate for the disease or outcome of interest, the treatment or intervention expected, effect size, and type 1 and type 2 error rates. The same approach has been proposed to determine an optimal information size (OIS) for a meta-analysis (Pogue and Yusuf, 1997). In the present situation, considering that the cumulative risk for breast cancer was ~0.07 (Hill *et al.*, 1994) and taking into account the range of published values of the OR of breast cancer in breastfeeding



**Figure 6.** Funnel plot. (a) x axis=OR and (b) x axis=adjusted OR of breast cancer (BC) for each study. y axis=total size of the study. The open diamond corresponds to the pooled OR. In case of publication bias towards unreported non-significant small sized studies, the repartition of the dots corresponding to the studies appears heterogeneous, with irregular dot density on the bottom part of the plot, leading to an asymmetric, non-homogeneous graph.

women (Kelsey *et al.*, 1993; Black *et al.*, 1997), assuming an OR mean value=0.89, the OIS associated with a type 1 error=0.01 and a 90% power was 71 000 patients, using the classical sample size formula based on the normal approximation of the difference between two independent proportions, assuming equal sample size to exposed and control groups. The present meta-analysis totalled 70 777 women, with a ratio of 1.7 control per case, which represents a figure close to the above calculated OIS, in the global analysis. However, it should be noted that the sizes corresponding to these different subgroup analyses did not reach this level and were more limited in power.

### Inferring a causal relationship

The main concern is the biological and clinical significance of a statistically significant pooled OR and the possibility of inferring a causal relationship between breastfeeding and the observed slight decrease in breast cancer risk. It is clearly a crucial question, as the level of evidence attached to a result of a meta-analysis of case-control studies is essentially based on the increase of power, but does not alleviate all the potential sources of biases associated with case-control studies, with the additional problem of heterogeneity between studies. Although no definitive answer can be expected, it might be useful to discuss the estimated results in light of causality criteria (Bradford Hill, 1965), the usefulness and limits of which have been extensively commented upon in the literature (Rothman and Greenland, 1998).

### Strength of the association

This criterion is generally considered to be an important determinant of a causal relationship. The purpose of the present meta-analysis was to pool all the available data to gain power in appraising this criterion. Confidence in a strong association is generally higher than in a weak association, although this is not absolute. The present analysis suggests only a statistically significant weak association between breastfeeding and breast cancer. However, breast cancer is the paradigm of a multifactorial frequent chronic disease and a large OR value was not anticipated, considering the usual OR values associated with well established risk factors, whether they are protective or not.

### Consistency of the association

The consistency of the observed association with reference to other studies is the next issue to address. Consistency of the present meta-analysis with other published meta-analyses does not seem to be a relevant point at least for two reasons: (i) no meta-analysis has been so far published on this issue; and (ii) in any case, consistency between the results of two meta-analyses on the same topic would not be very conclusive as a large subset, if not all, of the studies of the two meta-analyses should be identical, thus leading to non-independent results.

Similarly, consistency of the results of the meta-analysis with the results from the individual pooled studies is more or less expected and cannot be used in favour of consistency. However, it can be noted that the pooled result remained on the same side as the majority of studies and was not due to a single or a few large studies.

Three cohort studies were retrieved in the literature search (Kvale and Heuch, 1987; London *et al.*, 1990; Michels *et al.*, 1996). Following recommendations by several authors (Rothman and Greenland, 1998; Normand, 1999), they were not initially pooled with the case-control studies, as their types and hence the level of evidence attached to them were different. None of them reached a statistically significant result in favour of a protective effect. Two of them concerned the same population observed at two different times and, hence, were not independent. It was impossible, by reading the publications, to isolate the women common to both studies. Therefore, only the most recent one (Michels *et al.*, 1996) was retained for comparison with the other cohort study and the case-control studies. Concerning another study (Kvale *et al.*, 1987), only the proportions of breastfeeding mothers among the breast cancer cases and the total population was given and some proportional assumption had to be made to reconstruct data in the control group.

The corresponding estimated ORs were tentatively pooled together with the OR of the individual case-control studies. The resulting pooled ORs were 0.90 [95% CI 0.87–0.97] using the fixed model and 0.84 [95% CI 0.79–0.91] using the random model respectively; both figures being very close to the values obtained using only the case-control studies. In summary, it appears that the results of these two cohort studies are consistent with the global result of the meta-analysis.

Since the completion of this meta-analysis, two additional case-control studies have been published, the results of which are consistent with the previous results: in the study by Coogan *et al.* (1999), data concerning lactation and breast cancer risk in black and coloured South African women, used to breastfeed in a high proportion (83 of cases versus 85% of controls ever breastfed) with a rather high proportion of long-term breastfeeding mothers >3 years. ORs of breast cancer ranged from 1.0 for a breastfeeding duration of <12 months to 0.8 for longer breastfeeding durations. None of them were significantly different from unity. In the population-based study by Furberg *et al.* (1999), concerning 751 parous cases versus 742 parous controls of African-American and Caucasian women residents of North Carolina, results suggest that any lactation, regardless of duration or timing, is associated with a slight reduction in the risk of breast cancer among younger (OR: 0.8; 95% CI 0.5–1.1) and older parous women (OR: 0.7 95% CI 0.5–0.9).

### **Specificity of the association**

Rothman *et al.* (1998) do not confer a great interest in specificity, which they judge 'useless and misleading because of the very common multiplicity of causal relationships between an exposure and its effects'. Nevertheless, when restricting the analysis to the eight studies, for which adjusted ORs on potential confounding variables were available, a significant protective effect of the same magnitude persisted. Among them, parity is an important potential confounder, which needs to be discussed more specifically. Adjustment on this factor could not be carried out using all the studies, as the appropriate information was not always present in the published tables. However, when the analysis was restricted to the eight studies in which data on parity was available, the pooled ORs were 0.83 (95% CI 0.84–0.92) and 0.88 (95% CI 0.70–0.98) for the fixed and random model respectively and did not change the side and magnitude of the effect

### **Temporality**

Temporality can be considered as fulfilled, since breastfeeding usually occurred before the diagnosis of breast cancer in all the studies considered. However, it does not completely rule out the possibility that the emerging cancerous clone preceded breastfeeding, although it appears unlikely.

### **Biological gradient and duration effect**

As the presence of a dose–effect or duration relationship represents an important argument in favour of causality, it was investigated more specifically. Only one of the published studies so far reported data suggesting an effect of duration of breastfeeding on breast cancer risk (Layde *et al.*, 1989). Unfortunately, published data did not use the same cut-off limits for breastfeeding durations, which appeared very difficult to ascertain as the durations were collected retrospectively. Nevertheless, bearing in mind this important limitation, some of the data could be classified according to four categories of breastfeeding duration. Using a classical regression of the ORs according to breastfeeding duration, a significant trend could be observed. However, additional analyses of data were more in favour of a significant threshold effect after 12 months of breastfeeding rather than a linear duration effect.

### **Biological plausibility**

The biological plausibility of an effect of breastfeeding on breast cancer occurrence can be discussed in light of the following experimental or epidemiological results. In animal experiments, Russo *et al.* (1982) have shown that the susceptibility of the carcinogen depended upon the proliferation rate of breast epithelial cells and was inversely related to the degree of differentiation of these cells. It is well known that pregnancy and delivery induce hormonal modifications, which contribute to the complete differentiation of epithelial cells, but this protective effect appears to be enhanced by breastfeeding. Post-lactational glandular involution and apoptosis contribute to a decrease in the proliferation rate and to enhance the cellular differentiation. It can be speculated that a reduction of the exposed pool of epithelial cells could decrease the probability of malignant transformation, thus slowing the delay of emergence of a transformed clone. A prolonged period of lactation is generally associated with a longer period of lactational amenorrhoea and ovulation disorders, and thus, through a lower exposure to menstrual cycles, to a relative reduction of total oestrogen exposure, which has been related to proliferative and carcinogenic effects (Key and Pike, 1988).

The potential role of menopause needs to be addressed, as the protective association was essentially present in women who were not menopausal at the time of breast cancer diagnosis. Menopause marks the end of the production by the ovaries of the reproductive hormones and the observation of a changing rate in the cumulative incidence of breast cancer at the time of menopause leads to the concept of a cancer depending upon hormonal status (Pike *et al.*, 1983). As the incidence of diagnosed breast cancers is higher after the age of 50, it can be speculated that, if the potential effect of breastfeeding on the risk of breast cancer is only a delaying effect, a minor change in the number of breast cancers prevented before menopause will profoundly affect the relative incidence of breast cancers, whereas the corresponding additional breast cancers detected in menopausal women will change only marginally and more heterogeneously than the incidence of breast cancer in menopausal women. Furthermore, in age-matched women, the risk of breast cancer is lower in menopausal women, compared with non-menopausal ones. Therefore, the protective effect of menopause could mask the weak protective effect of breastfeeding. Finally, it can be speculated that the effect of breastfeeding in women could decrease with time. No studies analysed the delay from the end of breastfeeding to the diagnosis of breast cancer. It should be also noted that the recall bias in case-control studies is usually less important for more recent events, contributing to a larger heterogeneity of the effect of breastfeeding in menopausal, compared with non-menopausal, women.

### **Coherence of the association**

The criterion of coherence cannot be invalidated since there is no apparent conflict between the results reported and the natural history of the disease. However, this absence of conflict does not bring any new information about a hypothetical causal relationship, as indeed discussing this criterion leads to very similar

arguments as the ones developed concerning biological plausibility.

### Experimental evidence

Experimental evidence in the meaning given by Hill (1965) of interventional studies clearly does not exist presently. Epidemiological studies are only observational and not experimentally designed. Reasons are both ethical and pragmatic, which correspond to a common situation in the study of similar issues in the aetiology of breast cancer.

### Analogy with other causal relationship

Finally, we could not find any analogy to support the arguments in favour of a causal relationship. In summary, out of the nine criteria, coherence, experimental evidence and analogy did not appear adapted to the addressed issue. The six remaining criteria appeared to be rather verified, bringing some additional weight in favour of a net, but small, benefit of breastfeeding regarding breast cancer risk.

This reasoning should not be viewed as an indisputable mean of establishing a causal relationship, but taking together with the quantitative results of the meta-analysis, it provided at least an objective appraisal of a controversial question, on explicit and objective basis.

### Conclusions

With the limitations commonly associated with a meta-analysis of published case-control studies, the present study does suggest a slight but significant protective effect of breastfeeding on the risk of breast cancer in non-menopausal women. Compared with well-established risk factors, e.g. familial history of breast cancer, age at first full-term pregnancy and parity, or personal history of benign breast disease with cellular hyperplasia and atypia, breastfeeding, which is theoretically dependent on a woman's attitude and behaviour and which *per se* can be modified by appropriate education, appeared to confer a protective effect against breast cancer, though of small magnitude. The main reasons for advocating breastfeeding remain obviously related to the child's health (Leroy *et al.*, 1995; Reimer, 1996; Rogan, 1996) and mother-child interaction. Whether the small epidemiological benefit of long-term breastfeeding, if confirmed, should be taken into account in designing a breast cancer prevention information programme, remains a matter of debate about the possibility of modifying the attitude towards breastfeeding, which is highly dependent on complex socio-cultural clues.

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