Articles

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

*Collaborative Group on Hormonal Factors in Breast Cancer**

Summary

Background Although childbearing is known to protect against breast cancer, whether or not breastfeeding contributes to this protective effect is unclear.

Methods Individual data from 47 epidemiological studies in 30 countries that included information on breastfeeding patterns and other aspects of childbearing were collected, checked, and analysed centrally, for 50 302 women with invasive breast cancer and 96 973 controls. Estimates of the relative risk for breast cancer associated with breastfeeding in parous women were obtained after stratification by fine divisions of age, parity, and women's ages when their first child was born, as well as by study and menopausal status.

Findings Women with breast cancer had, on average, fewer births than did controls (2·2 *vs* 2·6). Furthermore, fewer parous women with cancer than parous controls had ever breastfed (71% *vs* 79%), and their average lifetime duration of breastfeeding was shorter (9·8 *vs* 15·6 months). The relative risk of breast cancer decreased by 4·3% (95% CI 2·9–5·8; p<0·0001) for every 12 months of breastfeeding in addition to a decrease of 7·0% (5·0–9·0; p<0·0001) for each birth. The size of the decline in the relative risk of breast cancer associated with breastfeeding did not differ significantly for women in developed and developing countries, and did not vary significantly by age, menopausal status, ethnic origin, the number of births a woman had, her age when her first child was born, or any of nine other personal characteristics examined. It is estimated that the cumulative incidence of breast cancer in developed countries would be reduced by more than half, from 6·3 to 2·7 per 100 women by age 70, if women had the average number of births and lifetime duration of breastfeeding that had been prevalent in developing countries until recently. Breastfeeding could account for almost two-thirds of this estimated reduction in breast cancer incidence.

Interpretation 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.

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Introduction

Although childbearing is known to protect against breast cancer, what contribution breastfeeding has on this protective effect, if any, has been difficult to determine. Breastfeeding is closely related to many other aspects of childbearing—for example, women breastfeed only after they have had a child, and the earlier they commence childbearing, the more children they have and the longer their lifetime duration of breastfeeding. No single study has been large enough to reliably characterise the relative contributions of such closely related factors in breast cancer. This study combines data from 47 epidemiological studies conducted in 30 countries, to examine the relation between breastfeeding and breast cancer, taking careful account of the effects of other related aspects of childbearing.

Methods

Contributing studies and collection of data

The Collaborative Group on Hormonal Factors in Breast Cancer has brought together worldwide data from epidemiological studies of women with breast cancer to describe the relation between breast cancer and various reproductive, hormonal, and other factors.[1–4] Case control and cohort studies were eligible for the collaboration if they had data for at least 100 women with incident invasive breast cancer and had recorded information on each woman with respect to reproductive factors and use of hormonal preparations. For data from cohort studies, a nested case control design was used, in which four randomly selected controls per case were matched for age at diagnosis and, where appropriate, broad geographical region. The methods of identifying studies and of data collection, checking, and correction, have been described elsewhere.[1–4]

Data were collated and analysed on individual women centrally so that analyses could be done with as similar definitions across studies as possible. Details sought from principal investigators of each participating study included data collected regarding each woman's total number of pregnancies, her age at each pregnancy, and the outcome of each pregnancy. A woman's parity was defined as the total number of births, be they livebirths or stillbirths. In some studies, details of past births did not include stillbirths, and for those studies a woman's parity was taken to be the total number of livebirths. Information was sought on the total number of children each woman had breastfed, her total (lifetime) duration of breastfeeding, and whether or not each individual live-born child had been breastfed, and, if so, for how long. Included in these analyses are data from 45 published[5–49] and two unpublished studies (Cancer Research UK, unpublished data) that contributed data on lifetime duration of breastfeeding, all but eight[6–8,20,23,33,44,47] of which also provided information on the number of children breastfed.

Study (country)[reference]	Number cases/controls	Mean parity cases/controls	Total months of breastfeeding (mean in parous women) cases/controls	% reduction in relative risk of breast cancer per 12 months breastfeeding and 99% CI (SE)
Cohort Studies				
RERF (Japan)[27]	328/1347	2·1/2·6	19·0/21·2	–0·4 (7·5)
Guernsey (UK)[39]	43/167	2·0/2·1	4·7/ 6·4	3·6 (52·0)
Tulinius (Iceland)[49]	1097/10271	3·0/3·5	9·7/11·3	7·0 (4·1)
Shanghai textile workers (China)[35]	1893/7572	2·2/2·6	16·8/19·0	5·0 (2·2)
Million Women Study (UK)[45]	824/3220	1·8/1·9	6·2/ 6·1	–2·9 (7·7)
All cohort studies	**4185/22577**	**2·2/2·7**	**13·0/13·8**	**4·6 (1·8)**
Case-control, population controls				
CASH (USA)[13]	4422/4635	2·5/2·8	4·1/ 5·4	11·7 (3·0)
Bernstein (USA)[37]	675/676	1·3/1·3	6·3/ 7·4	22·1 (8·4)
Bain/Siskind (Australia)[15]	474/964	2·5/2·7	14·4/15·4	–11·9 (6·8)
Rohan (Australia)[11]	451/451	2·3/2·4	9·5/ 9·9	0·9 (10·3)
Ewertz (Denmark)[10]	1498/1361	2·1/2·3	10·0/10·2	–6·1 (5·4)
Lee (Costa Rica)[14]	171/824	3·7/4·2	23·3/28·4	2·4 (6·1)
Meirik/Lund (Sweden/Norway)[8]	422/527	1·8/1·9	8·7/10·1	7·3 (10·2)
Long Island (USA)[19]	1170/1178	2·3/2·6	2·0/ 2·9	17·1 (10·4)
Yu/Yuan/Wang (China)[12,21]	834/834	2·3/2·9	30·2/41·1	10·4 (3·1)
Paul/Skegg (New Zealand)[17]	890/1862	2·6/2·6	8·6/ 9·8	10·8 (4·8)
Ross/Paganini-Hill (USA)[40]	1055/1092	2·3/2·8	4·1/ 5·7	4·5 (6·7)
Daling (USA)[30]	747/961	1·6/1·5	8·3/ 9·1	8·4 (6·1)
UK studies (UK)[16]*	1871/1871	1·9/2·0	4·9/ 5·2	11·5 (5·4)
4 State Study (USA)[28]	6820/9424	2·6/2·7	4·3/ 4·6	0·6 (2·3)
Rookus/van Leeuwen (Netherlands)[29]	915/915	1·8/2·0	3·8/ 4·4	16·9 (11·3)
Sanjose (Spain)[36]	325/341	1·9/2·0	12·8/14·3	–3·6 (8·0)
Yang/Gallagher (Canada)[22]	1015/1022	2·2/2·4	7·7/ 8·4	–1·7 (6·8)
Stanford/Habel (USA)[35]	448/492	2·7/2·9	5·3/ 5·1	–1·8 (10·2)
WISH (USA)[31]	1866/2009	1·7/1·9	7·6/ 8·8	5·4 (4·1)
Magnusson (Sweden)[44]	2664/2394	1·8/2·0	10·2/11·6	4·6 (4·2)
McCredie/Hopper (Australia)[41,43]	1581/1021	1·8/1·8	10·6/11·9	12·0 (4·7)
Chang-Claude (Germany)[46]	652/1273	1·4/1·6	4·4/ 5·7	11·0 (10·0)
Shu/Zheng (China)[48]	1448/1548	1·5/1·5	11·9/12·7	11·3 (4·9)
All case-control, population controls	**32414/37675**	**2·2/2·4**	**7·3/ 8·6**	**5·8 (1·0)**
Case-control, hospital controls				
Morabia (USA)[25]	451/682	2·3/2·8	8·3/ 9·9	–15·3 (9·5)
Vessey (UK)[5,9]	2344/2354	2·1/2·3	6·0/ 5·8	–12·8 (5·6)
Modan (Israel)[7]	722/1458	2·3/2·7	17·7/22·7	0·6 (4·8)
Kalache (Brazil)[24]	566/796	4·3/5·2	25·0/29·6	5·6 (3·4)
Le (France)[6]	264/264	1·7/1·8	1·9/ 2·7	–2·8 (27·5)
WHO (developing)[26]†	1594/15067	2·8/3·1	33·0/38·1	2·2 (1·6)
WHO (developed)[26]‡	1485/3937	2·4/2·4	8·7/ 9·8	4·8 (3·5)
Clavel (France)[18]	495/896	1·9/2·2	4·0/ 4·7	10·5 (10·5)
Lee (Singapore)[20]	200/420	2·9/3·6	13·0/20·4	–10·6 (6·8)
Katsouyanni (Greece)[33]	793/1548	1·8/1·8	12·6/14·5	10·7 (3·8)
Marubini (Italy)[23]	214/215	2·0/2·5	7·4/10·4	7·6 (16·9)
Franceschi (Italy)[32]	2412/2417	1·8/2·0	8·0/ 9·1	3·2 (5·7)
Hamajima (Japan)[42]	1483/5925	1·9/2·0	19·6/20·2	0·6 (2·3)
Gajalakshmi (India)[47]	529/529	3·1/3·8	51·4/66·2	9·4 (3·5)
Levi (Switzerland)[34]	151/213	1·6/1·5	3·6/ 4·3	24·8 (30·2)
All case-control, hospital controls	**13703/36721**	**2·3/2·7**	**14·6/24·2**	**2·5 (1·0)**
All studies	**50302/96973**	**2·2/2·6**	**9·8/15·6**	**4·3 (0·8)**

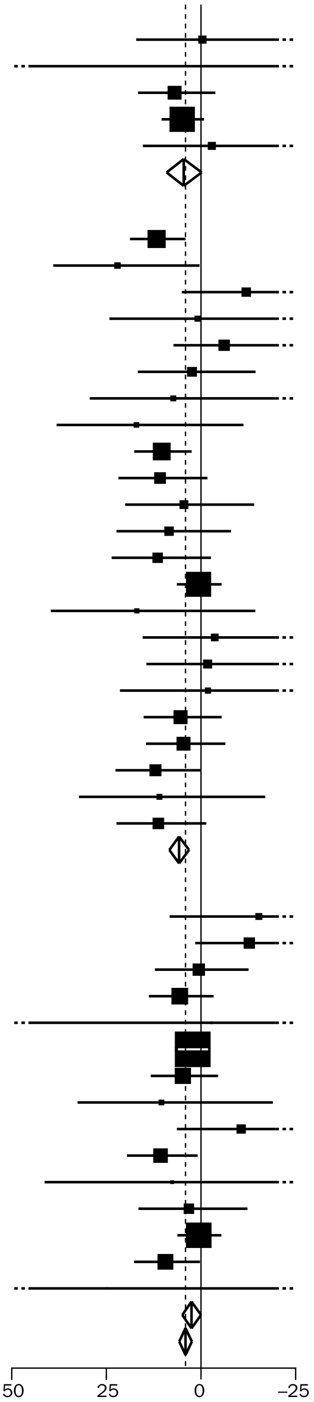


Figure 1: **Details and results from studies that contributed data on breastfeeding and breast cancer**
*Results of two unpublished studies are also cited here. †Ten developing countries. ‡Three developed countries.

Statistical analysis and presentation of results
The statistical methods used are similar to those used in previous reports.[1–3] In this study, data from different studies are combined by means of the Mantel-Haenszel stratification technique, the stratum-specific quantities calculated being the standard observed minus expected (O–E) numbers of women with breast cancer, together with their variances and covariances.[50] Use of these simple stratified O–E values in preference to more complex mathematical models sacrifices some statistical power but has the advantage of avoiding assumptions about the precise forms of any relations in the data. The stratified O–E values, together with their variances and covariances, yield both statistical descriptions (odds ratios, subsequently referred to as relative risks) and statistical tests (p values). When only two groups are compared, relative risk estimates are obtained from O–E values by the one-step method,[50] as are their standard errors (SE) and

	All parous women	Lifetime duration of breastfeeding (months)					
		Never	⩽6	7–18	19–30	31–54	⩾55
Women with breast cancer							
Number (%)	41 582 (100%)	12 214 (29·4%)	12 614 (30·3%)	10 369 (24·9%)	3362 (8·1%)	1996 (4·8%)	1027 (2·4%)
Parity	2·61	2·42	2·32	2·49	3·13	3·85	5·64
Number of children breastfed	1·47	0	1·53	2·19	2·90	3·63	5·37
Age at first birth (years)	24·5	24·7	24·7	24·9	24·2	23·1	21·1
Controls							
Number (%)	80 506 (100%)	16 900 (21·0%)	22 513 (28·0%)	21 109 (26·2%)	8241 (10·2%)	6279 (7·8%)	5464 (6·8%)
Parity	3·01	2·51	2·46	2·72	3·36	4·10	6·16
Number of children breastfed	2·11	0	1·76	2·41	3·12	3·82	5·81
Age at first birth (years)	23·6	24·2	24·1	24·1	23·3	22·2	20·4

Data are means unless otherwise indicated. *Excludes 7992 nulliparous cases, 13 379 nulliparous controls, and 3816 women with missing values.

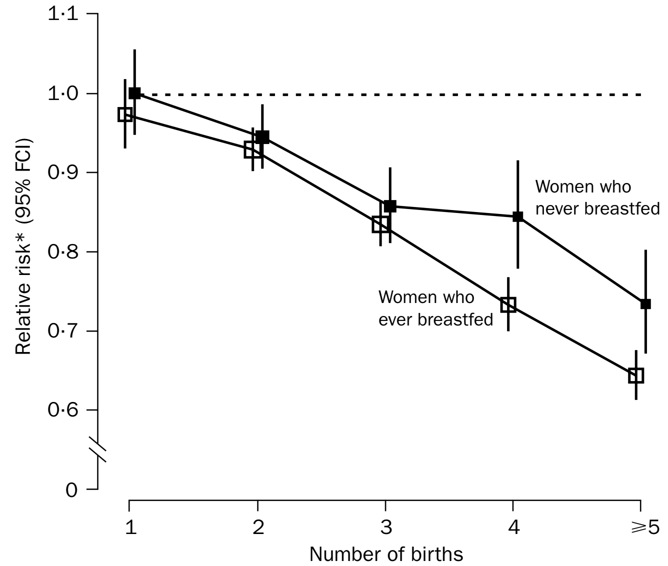
Table 1: **Relation between lifetime duration of breastfeeding and various other aspects of childbearing in parous cases and controls***

CIs. When more than two groups are compared, variances are estimated by treating the relative risks as floating absolute risks (FARs).[51] This approach yields floated standard errors (FSE) and floated CIs (FCI). The use of FARs rather than conventional methods does not alter the relative risks but slightly reduces the variances attributed to the relative risks that are not defined as 1·0, and also reduces unwanted covariances between them. Presentation of the results in this way enables valid comparisons between any two exposure groups, even if neither is the baseline group. Any comparison between groups must take the variation in each estimate into account by summing the variances of the logarithms of the two FARs.

To ensure that women in one study are compared directly only with similar women in the same study, all analyses are routinely stratified by study, by centre within study, by fine divisions of age (16–19, 20–24, 25–29, by single years from 30 to 79, 80–84, and 85–89 years), by age at first birth (<20, 20–24, 25–29, ⩾30), and by menopausal status (premenopausal, <5 or ⩾5 years since menopause, hysterectomy before natural menopause, unknown). Where appropriate, parous women are further stratified by fine divisions of parity (1, 2. . . 7, 8+).

To take into account the large proportion of women whose reported lifetime duration of breastfeeding was 6 months or less, and the tendency for the duration to be reported as multiples of 6 or 12 months (see the webfigure at http://image.thelancet.com/extras/01art9187webfigure.pdf), this variable was grouped into categories (0, ⩽6, 7–18, 19–30, 31–54, >54 months) for certain analyses. Most studies that recorded information on breastfeeding did not differentiate between exclusive breast-feeding and the use of supplementary feeds. There was some variation between studies in the definition of whether or not a woman had ever breastfed—ie, some studies defined a woman as having breastfed if she breastfed one child once, whereas other studies required that a woman had breastfed for at least a specified period, such as a week, a month, or even longer, before she was classified as having breastfed. For this reason, women who were reported to have never breastfed were grouped together with women whose total duration was 6 months or less for some analyses. Where appropriate, a trend in the relative risk of breast cancer with increasing duration of breastfeeding is calculated. In such instances, the duration of breastfeeding associated with a particular category is taken to be the median duration within that category.

In general, results in the text are presented as relative risks and their appropriate standard errors (SE or FSE). Where results are presented in the form of plots, relative risks and their corresponding CIs or FCIs are represented by squares and lines, respectively. The position of the square indicates the value of the relative risk and its area is inversely proportional to the variance of the logarithm of the relative risk, thereby providing an indication of the



Parous women who never breastfed					
Relative risk* (FSE)	1·00 (0·028)	0·94 (0·021)	0·86 (0·026)	0·84 (0·038)	0·73 (0·039)
Cases/controls (number)	3144/4338	4534/5898	2488/3500	1155/1647	893/1517
Parous women who ever breastfed					
Median duration of breastfeeding (months)	5	8	11	16	30
Relative risk* (FSE)	0·97 (0·023)	0·93 (0·015)	0·83 (0·016)	0·73 (0·020)	0·64 (0·020)
Cases/controls (number)	5410/9861	11086/19356	6737/14373	3091/8423	3044/11593

Figure 2: **Relative risk of breast cancer in parous women according to breastfeeding history and number of births**
*Calculated as floating absolute risk (FAR), and stratified by study, age, age at first birth, and menopausal status.

amount of statistical information available for that particular estimate. Owing to the large number of relative risk estimates calculated, results are generally given with their appropriate 99% CIs or 99% FCIs, with 95% CIs or 95% FCIs used for the main findings.

To investigate the contribution of childbearing and breastfeeding patterns prevalent in developed countries to the incidence of breast cancer in these countries, the incidence that would have occurred if the women had had the patterns of childbearing and breastfeeding that had been typical for Asian and African countries until recently,[53,54] is estimated by applying the relative risks obtained in this report to age-specific incidence rates for breast cancer in developed countries around 1990.[1–4,52] The cumulative incidence of breast cancer up to age 70 years is then calculated from the estimated age-specific results.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Altogether 50 302 women with invasive breast cancer (cases) and 96 973 women without breast cancer (controls) from 47 studies in 30 countries are included in these analyses (figure 1). Among the cases, the median year of diagnosis was 1988 and the average age at diagnosis was 50·1 years. Cases had, on average, fewer births than did controls (2·2 *vs* 2·6) and a greater proportion were nulliparous (16% vs 14%). The proportion of parous women who had ever breastfed was also lower in cases than in controls (71% *vs* 79%). The average parity and average total duration of breastfeeding in parous women varied across countries, largely reflecting the small family size and short lifetime duration of breastfeeding that have characterised women in many developed countries during the past century. The proportion of parous women who had ever breastfed was lowest in the USA, at around 50%, whereas in Japan, Scandinavia, and developing countries more than 90% of parous women had ever breastfed. Overall, the average lifetime duration of breastfeeding was 9·8 and 15·6 months, respectively, for parous cases and controls. As expected, the lifetime duration of breastfeeding was much shorter for women in developed than developing countries (average 8·7 and 29·2 months, respectively, in controls).

Table 1 shows, for parous cases and controls, the distribution of lifetime duration of breastfeeding and the relation of that factor to various other indices of childbearing. The mean parity and mean number of children breastfed were greater for women with longer lifetime durations of breastfeeding. The age women were when their first child was born decreased slightly with increasing duration of breastfeeding, but this aspect of childbearing is less strongly related to lifetime duration of breastfeeding than is parity or the number of children breastfed. Thus, there is considerable potential for any effect of breastfeeding on the risk of breast cancer to be confounded by the effects of each birth and, to a lesser extent, by the ages women were when their children were born.

To separate out the effects of breastfeeding from those of other aspects of childbearing, the first step was to describe the relation between breast cancer and certain reproductive factors, in the absence of breastfeeding. Then any additional contribution from breastfeeding is examined, taking account of the role of reproductive patterns and of other potential confounding factors. Having established, in the study population as a whole, what the independent effect of breastfeeding is, the consistency of the main results is examined across various subgroups of women and across studies and study designs.

Breast cancer in relation to childbearing in women who never breastfed

12 214 (29%) parous cases and 16 900 (21%) parous controls had never breastfed (table 1). Analyses restricted to these 29 114 women provide a description of the relation between breast cancer and childbearing patterns, that is not affected by breastfeeding. The younger such women were when they commenced childbearing, the lower was their relative risk of breast cancer; the relative risk declining by 3·0% (SE 0·3%; $p<0·0001$) for each year younger that women were when their first child was born. After stratifying by women's ages when their first child was born, as well as by study, age, and menopausal status, the relative risk of breast cancer also decreased with the number of births a woman had (figure 2). In the absence of breastfeeding, each birth reduces the relative risk of breast cancer by 7·0% (1·0%; $p<0·0001$).

Breast cancer in relation to breastfeeding

Figure 2 shows the relative risk of breast cancer by parity, for women who had breastfed, as well as for women who had never done so. Women with one child who had never breastfed are taken to have a relative risk of 1·0. The relative risk of breast cancer declines with increasing parity

Lifetime months of breastfeeding (median)	Number		Relative risk* (FSE)
	Women with breast cancer	Controls	
Never (0)	12 214	16 900	1·00 (0·019)
≤6 (3)	12 614	22 513	0·98 (0·017)
7–18 (12)	10 369	21 109	0·94 (0·016)
19–30 (24)	3362	8241	0·89 (0·025)
31–54 (40)	1996	6279	0·88 (0·033)
≥55 (72)	1027	5464	0·73 (0·049)

*Calculated as floating absolute risk (FAR), with corresponding floated standard error (FSE), and stratified by study, age, parity, age at first birth, and menopausal status.

Table 2: **Relative risk of breast cancer in parous women, in relation to lifetime duration of breastfeeding**

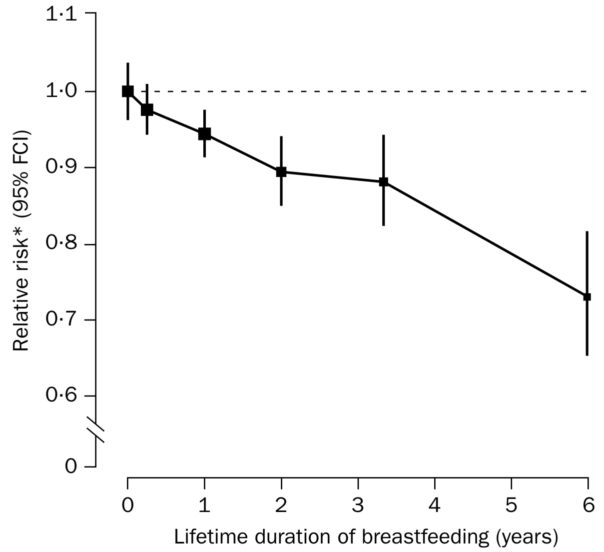
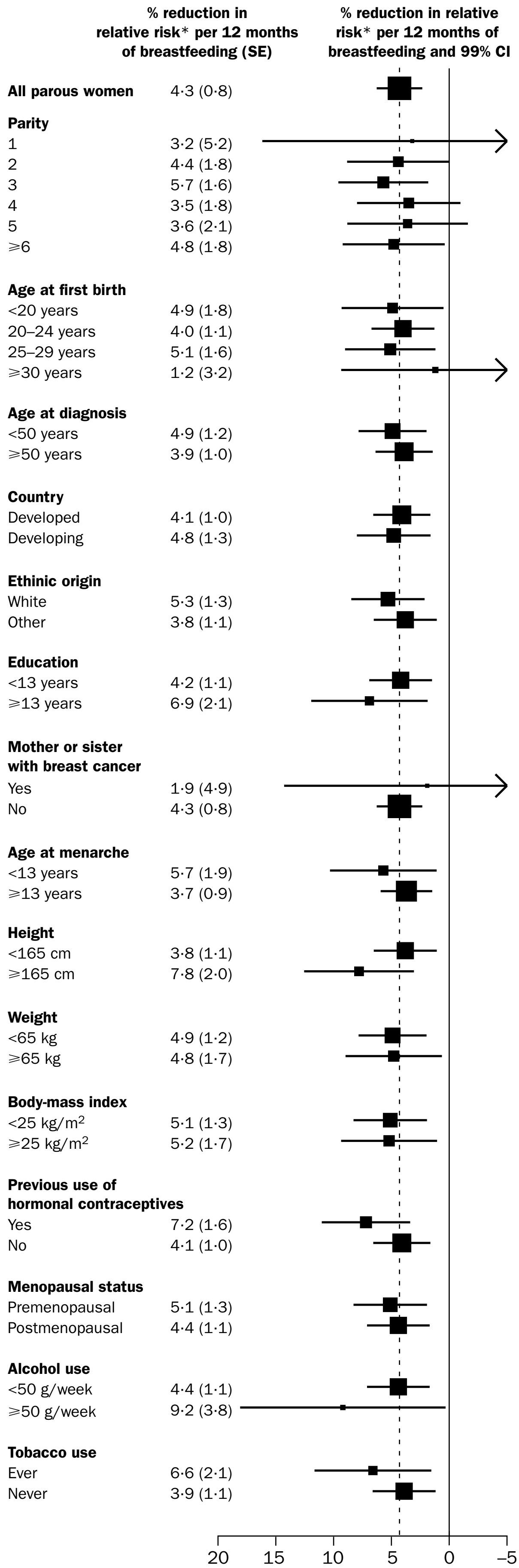


Figure 3: **Relative risk of breast cancer in parous women in relation to lifetime duration of breastfeeding**

*Calculated as floating absolute risk (FAR), and stratified by study, age, parity, age at first birth, and menopausal status.



in women who had ever and who had never breastfed. However, at each parity the relative risk is slightly lower for women who had breastfed than for women who had not (relative risk for ever versus never having breastfed, adjusted for parity and other factors shown in figure 2 is 0·96 (0·02, p=0·04).

Separating out the unique contribution of breastfeeding to the risk of breast cancer is not straightforward; women breastfeed only after they have had a birth, the lifetime duration of breastfeeding increases with increasing parity (table 1); and the independent effect of each birth on the risk of breast cancer is substantial in the absence of breastfeeding (figure 2). Hence, the effect of each birth needs to be considered carefully when looking at the relation between breastfeeding and breast cancer. Moreover, the reported lifetime duration of breastfeeding is not very accurate, with values often rounded to multiples of 6 or 12 months, especially for women who breastfed for long periods (see the webfigure at http://image.thelancet.com/extras/01art9187webfigure.pdf). Additionally, comparatively few women in the studies included here had breastfed for long periods—only 7% of the cases and 15% of the controls reported lifetime durations of breastfeeding of longer than 30 months (table 1). So, even in this large dataset, examination of the relation between breastfeeding and breast cancer is hampered by the potential for confounding, as well as by measurement errors and the limited numbers with substantial exposures.

The potential confounding by parity can be virtually eliminated by stratification of all analyses by fine divisions of parity. The estimated relative risks of breast cancer, according to lifetime duration of breastfeeding shown in table 2, are stratified by parity from 1 up to 8+, as well as by study, age, age at first birth, and menopausal status. The relative risk of breast cancer declines with increasing duration of breastfeeding, the estimated reduction in the relative risk per 12 months of breastfeeding being 4·5% (0·7%; p<0·0001; figure 3). Because there is some variation between studies in the classification of women whose lifetime duration of breastfeeding was short, sensitivity analyses were done, grouping together women with lifetime durations of 0 and 6 months or less. When this was done, the estimated decline in the relative risk of breast cancer was virtually unchanged, at 4·3% (0·8%; p<0·0001) per 12 months of breastfeeding. Because this latter approach provides a more consistent classification across studies than the former, women with reported lifetime durations of breastfeeding of 0 and 6 months or less are grouped together subsequently when trends are calculated.

Analyses similar to those in table 2 have been done separately for women of parity 1, 2, 3, 4, 5, and 6 or more (figure 4, and webtable 1 at http://image.thelancet.com/extras/01art9187webtable1.pdf). The relative risk of breast cancer declined with increasing duration of breastfeeding at each parity, and the magnitude of the decline did not vary significantly across women of different parity (χ^2_5 for heterogeneity 1·3; p=0·9). However, the standard errors and hence the confidence intervals for each parity-specific

Figure 4: **Reduction in the relative risk of breast cancer associated with breastfeeding in various subgroups of parous women**

*Stratified by study, age, parity, age at first birth, and menopausal status, where appropriate. The dotted vertical line represents the overall result for all parous women; information on each characteristic listed was not necessarily available for all women and averages of the subgroup-specific relative risks might therefore differ slightly from the result for all parous women.

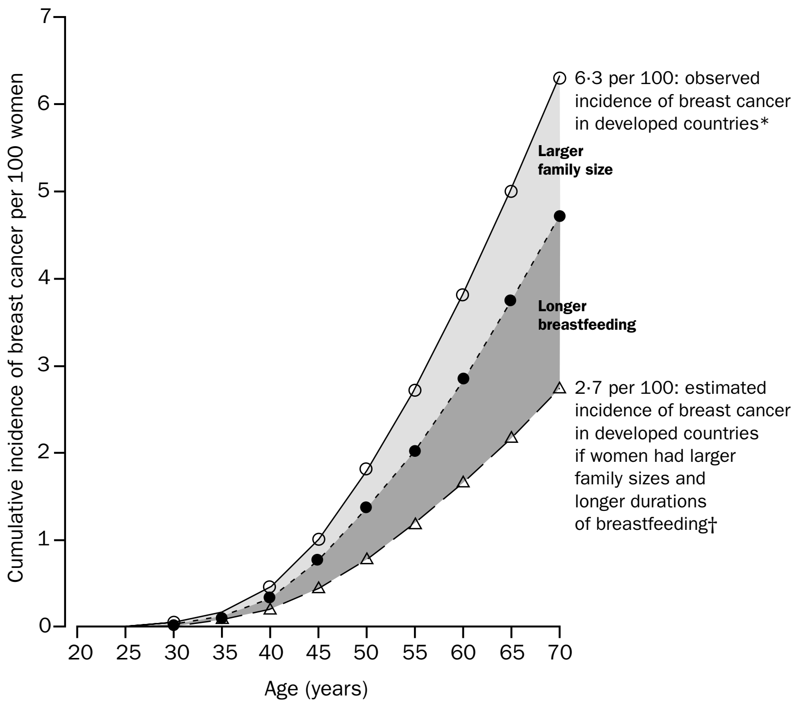


Figure 5: **Estimated cumulative incidence of breast cancer in developed countries if women had family sizes and breastfeeding patterns typical for developing countries**

*Cumulative incidence of breast cancer typical for women in developed countries around 1990;[1–4,52] †estimated incidence of breast cancer in developed countries if women had, on average, 6·5 births instead of 2·5, and if women breastfed each child, on average, for 24 months instead of a lifetime mean of 8·7 months; such values have been typical of developing and developed countries until recently.[53,54]

estimate are wide. Likewise, the decline in the relative risk of breast cancer associated with breastfeeding does not vary significantly according to the age women were when they began childbearing (webtable 1 on *The Lancet* website, figure 4; χ^2_3 for heterogeneity 1·5; p=0·7).

The relative risk of breast cancer declined by 3·4% (0·9%; p<0·0001) for each child breastfed. However, this association seems to be secondary to breastfeeding duration, since additional stratification by lifetime duration of breastfeeding substantially reduced the χ^2_1 test for trend with number of children breastfed, from 15·9, down to a non-significant value of 0·9. Conversely, the association of breast cancer with increasing duration of breastfeeding persisted after adjustment for the number of children breastfed (3·8% [1·0%] decline in the relative risk for each 12 months breastfeeding; p<0·0001).

The effect of ten other potential confounding factors (ethnic origin, education, family history of breast cancer, age at menarche, height, weight, body-mass index, and use of hormonal contraceptives, alcohol, and tobacco) on the trends shown in figure 3 was examined. Additional adjustment for each of these factors in turn did not materially alter the magnitude of the effect of breastfeeding on the relative risk of breast cancer (see webtable 2 at http://image.thelancet.com/extras/01art9187 webtable2.pdf).

Consistency of findings

The magnitude of the decline in the relative risk of breast cancer associated with each year of breastfeeding was calculated separately for various subgroups of women, including women from developed and developing countries, women of different ages, ethnic origins, familial patterns of disease, and 11 other possibly relevant factors, but none of the estimates varied significantly according to the factors examined (figure 4: global test for heterogeneity χ^2_{15} 16·8; p=0·3). For example, there was no strong evidence of heterogeneity between developed or developing countries (χ^2_1 0·2; p=0·7) by age at diagnosis (χ^2_1 0·5; p=0·5), menopausal status (χ^2_1 0·2; p=0·7), or family history of breast cancer (χ^2_1 0·3; p=0·6). Although the magnitude of the decline of the relative risk did not vary significantly across study designs (figure 1: χ^2_2 for heterogeneity 5·6 p=0·06), there was some variation across studies (χ^2_{42} 75·0; p=0·001).

The relative risk of breast cancer declined with increasing duration of breastfeeding for tumours localised to the breast and for tumours that had spread beyond the breast (decline in relative risk of breast cancer of 4·5% [1·6%] and 3·0% [1·7%], respectively, for each year of breastfeeding). There was no significant difference in the extent of tumour spread according to duration of breastfeeding among women with breast cancer (χ^2_1 2·7; p=0·1).

Cumulative incidence of breast cancer

Around 1990, the cumulative incidence of breast cancer up to age 70 years was 5–7 per 100 women in developed countries and 1–2 per 100 in Asian and African countries.[52] Women who would have been of childbearing age during the 1950s make substantial contributions to these estimates of cumulative risk. In 1955–60 women in developed countries had, on average, between two and three births, whereas women in Asian and African countries had, on average, between six and seven births.[53] Among parous women from developed countries in this study, the average duration of breastfeeding was about 3 months per child (the lifetime average duration of breastfeeding was 8·7 months for parous controls from developed countries), which contrasts with a median duration of breastfeeding of around 24 months per child in rural areas of Asia and Africa during the 1990s.[54]

To assess the contribution of the small family sizes and short lifetime duration of breastfeeding to breast cancer incidence in developed countries around 1990, the relative risks obtained here were applied to the age-specific incidence rates typical for developed countries at that time.[1,2] Figure 5 shows the cumulative incidence of breast cancer in developed countries and estimated cumulative incidence under the assumption that each woman had, on average, 6·5 births instead of 2·5, and that women breastfed each child for 24 months instead of 3 months. The contribution to the estimated reduction in the incidence of breast cancer from the additional births—ie, without breastfeeding—is distinguished from the contribution from breastfeeding itself in figure 5. Overall, the larger family sizes and longer lifetime duration of breastfeeding typical in developing countries until recently are estimated to more than halve the cumulative incidence of breast cancer in developed countries, from 6·3 to 2·7 per 100 women by age 70 years. Part of this estimated reduction in incidence is due to the additional births, but almost two-thirds is due to the longer lifetime duration of breastfeeding.

Discussion

Our analyses here show that the relative risk of breast cancer is reduced by 4·3% (95% CI 2·9–5·8) for each year that a woman breastfeeds, in addition to a reduction of 7·0% (5·0–9·0) for each birth. These relations are significant and are seen consistently for women from developed and developing countries, of different ages and ethnic origins, and with various childbearing patterns and other personal characteristics.

The 47 studies that contributed data were of different designs and included women with a wide range of reproductive and breastfeeding patterns. Since the decrease in the relative risk of breast cancer is comparatively small for each year of breastfeeding, some studies would, by chance alone, find significant associations and others would not; this possibility is particularly true for studies done in North America and many European countries, where women tend to breastfeed for a short time, if at all. When all studies are considered together, there was no significant variation in the results across study design; there was, however, some variation between studies, which could be due to differences between studies in the way that breastfeeding was defined. The overall results were not affected unduly by a single study or group of studies.

As far as can be ascertained, more than 80% of the worldwide epidemiological data on breast cancer and breastfeeding are included in this collaboration, and the findings from the ten studies that are not included[55–64] are generally consistent with these results. In the 1920s, Lane-Claypon in the UK[55] reported that the children of women with breast cancer were less likely to have been breastfed for 1 year or longer than the children of controls (19%, 172 of 921, *vs* 33%, 457 of 1392). The findings of a parallel study by Wainwright in the USA[56] showed a smaller difference in the same direction (28%, 472 of 1714, *vs* 29%, 718 of 2451). Six of the eight other studies not included here[57–62] published results on ever versus never breastfeeding adjusted by age, parity, and age at first birth, and the combined relative risk for ever having breastfed from these studies is 0·93 (95% CI 0·87–1·00; p=0·05). The other two studies[63,64] presented results according to duration of breastfeeding only, and the relative risk of breast cancer was seen to decline with increasing duration of breastfeeding in each study.

Confounding and bias

When studying the effect of each birth on the risk of breast cancer, potential confounding by breastfeeding can be eliminated by looking at the relation between parity and the relative risk of breast cancer in women who never breastfed. When this is done, it is clear that, in the absence of breastfeeding, each birth has an independent effect, reducing the relative risk of breast cancer by 7·0% per birth. When studying the effect of breastfeeding, however, there is potentially extensive confounding by parity and, to a lesser extent, by age at first birth. All analyses that examine the risk of breast cancer in relation to lifetime duration of breastfeeding have therefore stratified women into eight groups according to the number of births they had (1, 2 . . . 7, 8+), thereby effectively eliminating confounding by parity, and stratified further according to their age at first birth (<20, 20–24, 25–29, and ⩾30), thereby minimising counfounding due to that factor. Stratification of the data by finer divisions of age at first birth did not substantially alter the results. The trends according to duration of breastfeeding do not vary significantly by parity or age at first birth, indicating no strong interaction with these factors (figure 4).

Lifetime duration of breastfeeding is closely related to the number of children breastfed, and when the data are additionally stratified by the number of children breastfed the trend for the risk of breast cancer associated with increasing duration of breastfeeding remained significant. By contrast, the apparent association between breast cancer and the number of children breastfed was no longer significant after the data were additionally stratified by lifetime duration of breastfeeding.

Potential confounding by other factors such as age, study (and centre within study), and menopausal status are minimised by stratification. The fine stratification used in these analyses means that no direct comparisons are made between women in one study and women in another, and that breastfeeding patterns in women with breast cancer are compared only with the pattern in women of exactly the same age and parity, with a similar age at first birth and age at menopause. Although the stratification was fine enough to avoid substantial confounding, it was not excessively fine, since much of the statistical information content remained (an example of how to calculate the amount of statistical information lost by stratification is given elsewhere[4]). Potential confounding by ten additional factors was examined, but separate adjustment for each in turn did not materially alter the relative risk estimates (see webtable 2 at http://image.thelancet.com/extras/01art9187webtable2.pdf). Furthermore, the results did not suggest that any of the factors examined, including age, weight, family history of breast cancer, and menopausal status, significantly modified the magnitude of the relative risks, although there is limited power to detect such potential interactions.

Most women reliably report the number of children they have had, and hence differential reporting of births by cases and controls, or misclassification of parity is unlikely to be a serious problem. Even though stillbirths are not counted among the births for some studies, they represent about 1% of all births, and so the omission of stillbirths would have little effect on the findings with respect to parity. By contrast, women's reporting of the length of time that they breastfed is not so accurate, and there is a strong tendency for women to round to the nearest 6 months. Studies done in developing countries have shown that, even when women gave birth in the previous 3–5 years, they still tend to report their duration of breastfeeding as multiples of 6 or 12 months,[54] and that women who are educated tend to overestimate the length of time that they breastfed.[65] Most women included in this collaborative reanalysis would have given birth decades before they were asked about their breastfeeding practices, and no published data could be found investigating reporting errors in lifetime duration of breastfeeding in such circumstances. The inevitable misclassification of women would, if anything, be expected to lead to an underestimation of the true effect of breastfeeding on breast cancer.

There is no strong evidence in these data to suggest there might be differential recall or reporting of breastfeeding by cases and controls, since the results from cohort studies, in which breastfeeding details were collected prospectively, are in line with results from case-control studies, in which information was collected retrospectively (relative declines of 4·6% [1·8%] and 4·1% [0·7%], respectively, figure 1). The results for tumour stage show little difference in the extent of tumour spread according to duration of breastfeeding, which also suggests that there is little or no differential detection of breast cancer according to breastfeeding practices.

About half the women included in these analyses had breastfed for a total of 6 months or less, with only 7% of the cases and 15% of the controls breastfeeding for longer than 30 months. No distinction was made between exclusive breastfeeding and breastfeeding with supplementary feeds; this, taken together with likely measurement errors in the reported lifetime duration of breastfeeding, and the limited statistical power, means that there remains some uncertainty about the magnitude of the protective effect of breastfeeding on the risk of breast cancer. Measurement errors would, if anything, be expected to result in an underestimation of the true effect of breastfeeding on breast cancer. Because breastfeeding patterns could well account for a large part of the variation in breast-cancer incidence between developed and developing countries, there is a need for further research on this topic. Future epidemiological studies need to focus on populations in which breastfeeding was common for relatively long durations, and should attempt to collect information on the use of supplementary feeds and on errors in the reporting of lifetime duration of breastfeeding. Although this collaboration was not set up to consider mechanisms, laboratory research to elucidate how breastfeeding protects against breast cancer is of direct public-health relevance, since it might be possible to prevent a substantial proportion of breast cancers in developed countries if it were possible to mimic the effects of breastfeeding on the breast.

Public-health implications

Application of our results to incidence rates typical of developed countries around 1990 suggests that major reasons for the high incidence rates of breast cancer in such countries are the small family size and the short duration of breastfeeding that were characteristic of women in these countries during the past century. Indeed, if women had larger family sizes and longer lifetime durations of breastfeeding that were typical of developing countries until recently, the cumulative incidence of breast cancer in developed countries is estimated to be reduced by more than half (from 6·3 to 2·7 per 100 women) by age 70 years. Part of this estimated reduction in incidence is due to the large family size, but almost two-thirds is due to breastfeeding. Thus, much of the difference in breast-cancer incidence between developed and developing countries seems to be accounted for by these reproductive factors, since the cumulative risk of breast cancer by age 70 in most Asian and African countries around 1990 was between 1 and 2 per 100 women.[52] Nevertheless, the average family size and duration of breastfeeding are declining rapidly in such countries,[54,66] and breast-cancer incidence has subsequently begun to rise, especially in women aged younger than 50 years.[52]

For women to have a lifetime duration of breastfeeding that was typical of women in developing countries and yet have the small family sizes typical for women in developed countries would be virtually impossible. However, in that hypothetical situation, these findings suggest that the incidence of breast cancer in developed countries would be reduced by 42%, solely by the longer duration of breastfeeding. Thus, 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.

To expect that substantial reductions in breast-cancer incidence could be brought about today by women returning to the pattern of childbearing and breastfeeding that typified most societies until a century or so ago is unrealistic. However, if in the future the mechanism of the protective effect of breastfeeding on breast cancer were understood, it might be possible to prevent breast cancer by mimicking the effect of breastfeeding therapeutically or in some other way. In the meantime, important reductions in breast-cancer incidence could be achieved if women considered breastfeeding each child for longer than they do now. About 470 000 women in developed countries and 320 000 women in developing countries were diagnosed with breast cancer in 1990.[67] Based on the estimates obtained here, if women in developed countries had 2·5 children, on average, but breastfed each child for 6 months longer than they currently do, about 25 000 (5%) breast cancers would be prevented each year, and if each child were breastfed for an additional 12 months about 50 000 (11%) breast cancers might be prevented annually. There are obvious economic and social consequences to prolonging breastfeeding, and these results indicate that there are benefits to the mother, as well as the known benefits to the child.[68]

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Collaborators are listed in the webappendix at http://image.thelancet.com/extras/01art9187webappendix.pdf

Conflict of interest statement
None declared.

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