

Breast-Feeding and Cancer: The Boyd Orr Cohort and a Systematic Review With Meta-Analysis

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Background: Having been breast-fed has been suggested to influence cancer risk in adulthood. We investigated associations between breast-feeding during infancy and adult cancer incidence and mortality in a cohort study and meta-analyses of published studies. **Methods:** The Boyd Orr cohort consisted of 4999 subjects who were originally surveyed in 1937–39, when they were 0–19 years of age. Cancer outcomes from 1948 through 2003 were available for 4379 (88%) subjects, and 3844 had complete data on all covariates. Associations of breast-feeding with cancer were investigated using proportional hazards models. We also identified 14 studies on infant feeding and cancer published from 1966 through July 2005, of which 10 could be combined with the Boyd Orr cohort results in a meta-analysis of breast cancer using random-effect models. **Results:** In the Boyd Orr cohort, ever having been breast-fed, compared with never having been breast-fed, was not associated with the incidence of all cancers (hazard ratio [HR] = 1.07, 95% confidence interval [CI] = 0.89 to 1.28) or of any individual cancer type examined (prostate HR = 1.43, 95% CI = 0.58 to 3.52; breast HR = 1.62, 95% CI = 0.89 to 2.94; colorectal HR = 0.86, 95% CI = 0.45 to 1.63; gastric HR = 1.22, 95% CI = 0.47 to 3.15). In the meta-analysis, there was also no association between breast-feeding and breast cancer (regardless of menopausal status) (relative risk [RR] = 0.94, 95% CI = 0.85 to 1.04). However, breast-fed women had a reduced risk of premenopausal breast cancer (RR = 0.88, 95% CI = 0.79 to 0.98) but not of postmenopausal breast cancer (RR = 1.00, 95% CI = 0.86 to 1.16). **Conclusion:** Ever having been breast-fed was not associated with overall breast cancer risk, although the meta-analysis revealed a reduced risk of premenopausal breast cancer in women who had been breast-fed. [J Natl Cancer Inst 2005;97:1446–57]

Early-life environmental exposures may influence subsequent cancer risk (1,2). For example, taller individuals are at a 20%–60% increased risk of a range of cancers (3), indicating the possible importance of growth-promoting factors in the development of cancer. Increased height may be a marker for exposure to higher levels of insulin-like growth factor I (IGF-I) in childhood (4), and breast, prostate, and colorectal cancers have been positively associated with levels of IGF-I in adulthood in both cohort and case-control studies (5).

Another early-life exposure that can differ among individuals and possibly modify subsequent cancer risk is exposure to breast milk. Breast-feeding is positively associated with both stature (6,7) and circulating IGF-I levels (8) in later childhood, raising the possibility that breast-feeding may contribute to associations between height/IGF-I and cancer (5,9). Breast-feeding could, in theory, also affect cancer risk if it is the source

of a carcinogenic substance; in the 1930s, it was hypothesized that an oncogenic virus transmitted in breast milk causes subsequent breast cancer in offspring (10). Although the epidemiologic evidence of such an effect was limited (11), mothers with a family history of breast cancer were advised not to breast-feed their daughters. Results of subsequent studies relating having been breast-fed with breast cancer are inconclusive (12). Increasing interest in perinatal factors associated with testicular cancer has also led to an analysis of possible associations of breast-feeding with this tumor (13).

To gain a better understanding of possible cancer risks associated with having been breast-fed, we investigated the association of breast-feeding in infancy with adult cancer risk in a 65-year follow-up of the Boyd Orr cohort (14). This cohort is based on the long-term follow-up of the Carnegie (Lord Boyd Orr) study of Family Diet and Health in Pre-War Britain (1937–1939) (15), which was originally designed to investigate “the connection between economic factors and physical welfare” (16) and which was reconstructed as an historical cohort in 1988 to investigate a range of disease endpoints, particularly coronary heart disease and cancer, in relation to infant and childhood diet, to the socioeconomic conditions experienced by the children, and to markers of childhood nutritional status (body mass index [BMI], leg length, and height) (17).

Information on the breast-feeding history of cohort members is available, and the members are now at an age (range, 64–85 years) at which cancer is a substantial burden. Because breast-feeding is positively associated with height (6,7) and IGF-I (8) and because both are, in turn, positively associated with breast, prostate, and colorectal cancers (3,5), we hypothesized a priori that breast-feeding may be associated with an increase in the risk of these cancers. We also hypothesized an inverse relationship between breast-feeding and gastric cancer, because breast-feeding is associated with a lower prevalence of *Helicobacter pylori* infection (18), which has been implicated in gastric cancer etiology (19). We placed the results of the Boyd Orr cohort in context by conducting a systematic review and meta-analysis of the published literature on the relationship between breast-feeding in infancy and adult cancer.

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SUBJECTS AND METHODS

Boyd Orr Cohort

The methods used in the Boyd Orr cohort have been described previously (20). Briefly, the cohort comprised 4999 children who were aged 0–19 years at enrollment in 1937–1939. The cohort members came from 1343 families living in 16 urban and rural districts in Britain; they underwent a 1-week assessment of family diet and health at enrollment (the Carnegie Survey of Family Diet and Health in Pre-War Britain) (15). We used the National Health Service Central Register (NHSCR) to trace 4379 (88%) of the original study members (14), who have been followed up since the inception of the NHSCR in 1948 through February 28, 2003, and flagged for cancer registration and mortality. The United Bristol's Hospital Trust Local Research Ethics Committee provided ethical approval for flagging and tracing the Boyd Orr cohort.

From the original survey data, we obtained information on the method of infant feeding (recalled by the mother an average of 7 years after birth), age at baseline survey, sex, per capita weekly household food expenditure group (six categories), birth order, and survey district (15). Using the original survey records from 1937–1939, we coded history of infant feeding as either ever breast-fed or never breast-fed. Duration of breast-feeding was coded as follows: <6 months; 6–11 months; >11 months; or unknown. These cut points were chosen to assess the effects of both the currently recommended duration of breast-feeding (<6 months) and prolonged breast-feeding (>11 months). Socioeconomic status of the head of the household was assigned to one of eight categories (social class I, II, III, IV, or V; unemployed; armed forces; unclassifiable) using the Registrar General's 1931 classification (20). Based on single measurements of standing height, leg length, and body weight at the time of the original survey, internally age- and sex-standardized z-scores for measured childhood height, leg length, and BMI were computed (21). Because height measurement in children under 2 years of age tends to be unreliable and because of a large amount of missing data in children of this age and in the 15 and over age band, z-scores were calculated only for the subset of children aged between 2 and 14.75 years at the time of the original survey, as in previous reports ($n = 1191$ women and 1103 men in the current analysis) (21). Further information on diet, health, and lifestyle was obtained for 1648 subjects who completed a questionnaire in 1997–1998 (17).

Cancer incidence and cause of death in the Boyd Orr cohort members, based on data obtained from the NHSCR, were defined by the International Classification of Diseases Ninth (ICD-9) or Tenth (ICD-10) Revision. The outcomes included all cancers (ICD-9, 140–208; ICD-10, C0–C97); breast cancer (ICD-9, 174; ICD-10, C50); colorectal cancer (ICD-9, 153–154, excluding 154.2 and 154.3, which are cancers of the anal canal and anus; ICD-10, C18–20); prostate cancer (ICD-9, 185; ICD-10, C61); gastric cancer (ICD-9, 151; ICD-10, C16); all cancers thought to be etiologically related to smoking, including cancers of the mouth and oro-pharynx (ICD-9, 140–149 and 160; ICD-10, C0–C14 and C30–C31), larynx (ICD-9, 161; ICD-10, C32), other sections of the respiratory tract (ICD-9, 165; ICD-10, C39), pancreas (ICD-9, 157; ICD-10, C25), trachea and lung (ICD-9, 162; ICD-10, C33–C34), and bladder (ICD-9, 188; ICD-10, C67); and all cancers excluding those thought to be etiologically related to smoking. We subdivided cancers into those thought to be related to smoking and those thought to be unrelated

to smoking because smoking may confound associations between breast-feeding and smoking-related cancers and because information on smoking was available for only approximately 1000 subjects with breast-feeding data who were still alive for a questionnaire survey in 1997.

Complete data on all covariates were available for 3855 subjects (1889 males and 1966 females), and these subjects were included in the analyses relating having been breast-fed with cancer mortality ($n = 363$ cancer deaths). Eleven subjects with an incident cancer lacked a date for the outcome, and these subjects were therefore excluded from the total number of subjects included in the analyses of cancer incidence in relation to having been breast-fed ($n = 3844$ subjects; 1883 males and 1961 females; 587 incident cancers).

Statistical Analysis of the Boyd Orr Cohort

The outcomes were total and site-specific cancer incidence and mortality. Both endpoints were analyzed because cancer mortality is associated with socioeconomic position and because associations of having been breast-fed with cancer incidence may differ from associations with cancer mortality. The cancer incidence outcome was derived from the first cancer that was registered or, if no cancer had been registered prior to death, from the presence of a cancer code anywhere on the death certificate. Subsequent registered cancers were not included in the analysis because these could be secondary cancers or could have arisen due to adverse effects of treatment (in any event, only 22 of the 587 individuals with cancer had more than one cancer registration). For breast cancer, the main outcome was all cancers irrespective of menopausal status at diagnosis. We also separately examined breast cancers diagnosed in women under 50 years of age ($n = 13$) and in women 50 years of age and over ($n = 61$), but it was not possible to use a clinical definition of menopause because we had only the date of cancer diagnosis. The single case of male breast cancer was excluded from the analyses.

The association of breast-feeding initiation and duration with cancer outcomes was investigated using Cox proportional hazards models. Cohort members who were never breast-fed formed the reference group. Follow-up was censored on February 28, 2003. Subjects who had been traced but with whom contact via the NHSCR had been lost after 1948 (for example, if the subject is not currently registered with a Health Authority doctor) or who emigrated or died were included in the survival analysis up to the date of death, emigration, or last contact. Losses to follow-up were 11.3% among those breast-fed and 12.3% among those never breast-fed ($P = .3$).

Because age is a strong determinant of mortality risk, and because individuals entered the study over a 19-year range of ages (0–19 years) and over a 2-year period (1937–1939), we controlled for current age in all models. Because both the prevalence of breast-feeding (6) and cancer rates differed substantially between survey areas, all models were stratified by survey district, thus allowing for district-specific baseline rate parameters. Clustering effects may have arisen because most subjects in the cohort belonged to families that included other cohort members and therefore shared childhood conditions and possible genetic effects on cancer; we calculated robust standard errors to allow for a between-family component of variation (22).

The analyses controlling for age, survey district, and clustering form the simple models presented in the results. Multivariable

models were then developed that controlled additionally for sex (except for sex-specific cancers), socioeconomic status of the child's father at the time of the original survey, the child's birth order, and per capita weekly household food expenditure in childhood. The proportional hazards assumption was investigated both graphically and by formally testing that the log hazard ratio (HR) was constant over time for each model (23,24). There was no evidence against the proportional hazards assumption of a constant hazard ratio over time. We assessed whether the associations with breast-feeding differed according to sex and age at original survey using the likelihood ratio test in fully adjusted models.

Because differences in growth (6,7) and in circulating IGF-I levels (8) between those breast- and bottle-fed may be on the biologic pathway between mode of infant feeding and subsequent cancer risk, we examined the effect on breast-feeding-cancer associations of adjustment for age- and sex-standardized z-scores for measured childhood height and BMI in the subset of the cohort with available anthropometry in childhood. Any attenuation in effect estimates could indicate that childhood height or adiposity is an intermediary variable or marker for confounding factors operating in childhood.

Finally, changes in feeding patterns—for example, with respect to exclusivity of breast-feeding or alternatives to breast-feeding—may have occurred over the range of the years of births of the subjects (1918–1939). Therefore, we also tested for interaction by year of birth, which was dichotomized for this analysis as before 1930 or in 1930 or later (median year of birth).

Systematic Review

The data retrieved for the systematic review were based on a systematic search (completed by R.M.M.) of all published papers, letters, abstracts, and review articles on infant feeding and cancer using the MEDLINE database from January 1966 through to June 2004. We used a combined text word and MeSH heading search strategy, with terms for infant feeding combined with terms for cancer (see Appendix). We also manually searched the reference lists of all studies that fulfilled the inclusion criteria for further relevant publications. The search began in June 2004 and was repeated weekly through July 2005 using the automated OVID alert system.

Articles were included if they fulfilled the following criteria: 1) infants who had been breast-fed were compared with those never breast-fed; 2) the outcome was cancer incidence or mortality; and 3) quantitative estimates of the association of having been breast-fed and cancer outcomes were available or could be derived. Articles that related breast-feeding with cancers in childhood or adolescence (up to age 19 years) were excluded from the present analysis but are the subject of a separate report (25). R.M.M. extracted the data on two separate occasions to check the consistency of the data extraction.

A meta-analysis of the associations of breast-feeding with all cancers and with specific cancers was conducted that included the findings from the Boyd Orr study. Cancer in those who had ever or exclusively been breast-fed was compared with that in those who had never been breast-fed. If results for both ever and exclusive breast-feeding were presented, the exclusive breast-feeding association was used in the meta-analysis. For some studies, we calculated relative risks (RRs) from reported prevalence rates of cancer in different infant feeding groups or by using fixed-effects models to combine relative risks given for different durations of breast-feeding (13,26–28). To assess the

impact of extended breast-feeding, separate meta-analyses comparing any or exclusive breast-feeding of ≥ 6 months with never breast-feeding were undertaken.

We calculated the I^2 statistic as a quantitative measure of the degree of inconsistency across studies that is not dependent on the number of studies (29). An I^2 value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. Because it is conceivable that any associations of cancer with breast-feeding could depend on its duration or exclusivity, the population studied, or the era in which the subjects were born, effect estimates from the individual studies were pooled using random-effects models (although results from fixed-effects models were similar; data not shown). Random-effects models are appropriate in this instance because there was little evidence of publication bias. The Egger regression test was conducted to examine the relationship between sample size and observed cancer risk by infant feeding group (30,31).

Sensitivity Analysis

Because no generally accepted lists of appropriate quality criteria for observational studies are available, we investigated factors that might explain differences between studies as a way to gain clues to possible sources of systematic bias. Selected study characteristics, chosen a priori, were thus entered as indicator variables in separate meta-regression analyses (32) to assess their impact on between-study variation (heterogeneity). Meta-regression analysis offers a conservative test of the effect of certain exposures on outcome, assessed at study level (32). These characteristics were study design (case-control or cohort/nested case-control study, i.e., whether infant feeding information was obtained retrospectively or prospectively); study size (≤ 500 cases/ > 500 cases); reliance on maternal recall of breast-feeding beyond infancy (with infancy defined as < 1 years; coded as yes/no); whether effect estimates in the final models controlled for socioeconomic factors in childhood or adulthood (yes/no); whether effect estimates in the final models controlled for reproductive factors (yes/no); whether the study was population or hospital based (yes/no); and whether the response rate was less than 80% (yes/no). Other study characteristics that may be true effect modifiers of the association between breast-feeding and cancer were also examined, including the region in which the study was conducted (categorized as United Kingdom, North America, Europe, or other); the year of birth of the participants (dichotomized as 1970 or earlier versus after 1970); and whether the prevalence of any breast-feeding was at least 70%.

We used two-sided tests of statistical significance, and the precision of our estimates was based on 95% confidence limits throughout. No formal statistical approaches to account for multiple hypothesis testing were used, but we have quoted exact rather than threshold P values. All statistical analyses were performed using Stata 8.0 (33).

RESULTS

Boyd Orr Cohort

Of the 4999 original survey participants, 3844 (1961 females and 1883 males) included in the analysis of cancer incidence contributed 185 458 person-years of observation between January 1, 1948, and February 28, 2003. Of these, 2716 participants

(71%) were breast-fed and the median duration of breast-feeding was 9 months (range, 0.5–25 months). The prevalence and duration of breast-feeding did not differ by sex, socioeconomic status of the father, or decade of birth, but both were positively associated with household food expenditure (14).

Ever having been breast-fed was not associated with all cancers, with smoking-related cancers, or with non-smoking-related cancers (Table 1). There was weak evidence of an association between breast-feeding in infancy and risk of breast cancer in adulthood (HR = 1.62, 95% confidence interval [CI] = 0.89 to 2.94; $P = .11$). This association was the same regardless of the child's age when the mother was interviewed (P for age–outcome interaction = .8). The association also did not differ by the woman's age at cancer diagnosis (i.e., less than 50 years or 50 years or older; P for interaction = .5). The direction and size of the association with breast cancer mortality (HR = 1.53, 95% CI = 0.61 to 3.83; $P = .37$) was the same as that for breast cancer incidence. Adjusting for childhood BMI or height did not explain the association between breast-feeding and breast cancer (data not shown), suggesting that growth in childhood is unlikely to be on the causal pathway linking breast-feeding with breast cancer.

In addition, we found no evidence that ever having been breast-fed was associated with incident prostate, colorectal, or gastric cancer. As with breast cancer, however, the confidence limits were wide and, therefore, the results are consistent with the possibility that having been breast-fed is associated with increased or reduced risks of these cancers. There was no evidence that associations between breast-feeding and cancer outcomes varied by sex or year of birth (P for interaction $> .1$ for all cancer outcomes). There was no association between increased duration of breast-feeding and any of the cancers examined (data not shown).

Systematic Review

The search strategy (see Appendix) yielded 1415 hits, of which 78 articles met the inclusion criteria outlined in the Subjects and Methods. After detailed review of these 78 potentially relevant reports, 14 (13,26–28,34–43) were included in one or more of the meta-analyses (Table 2). For two of the studies, the outcome was all cancer (26,35), for 11 (including one of the studies that reported on all cancer), it was breast cancer (27,28,34–41,43), and for two, it was testicular cancer (13,42). Of the 64

Table 1. HRs (with 95% CIs) for cancer incidence and mortality in relation to ever having been breast-fed compared with never having been breast-fed in the Boyd Orr cohort*

Cancer type	Incidence (n = 3844)†		Mortality (n = 3855)	
	Events	HR (95% CI)	Deaths	HR (95% CI)
All cancers				
Simple model‡	587	1.05 (0.88 to 1.26)	363	1.08 (0.86 to 1.35)
Controlling for sex	587	1.05 (0.88 to 1.26)	363	1.08 (0.86 to 1.36)
Controlling for sex and childhood socioeconomic factors§	587	1.07 (0.89 to 1.28)	363	1.09 (0.86 to 1.37)
Smoking-related cancers				
Simple model‡	170	1.01 (0.73 to 1.40)	147	1.04 (0.88 to 1.41)
Controlling for sex	170	1.02 (0.75 to 1.47)	147	1.06 (0.74 to 1.54)
Controlling for sex and childhood socioeconomic factors§	170	1.05 (0.76 to 1.53)	147	1.08 (0.74 to 1.56)
Non-smoking-related cancers				
Simple model‡	417	1.07 (0.86 to 1.32)	216	1.10 (0.81 to 1.49)
Controlling for sex	417	1.06 (0.86 to 1.32)	216	1.10 (0.81 to 1.49)
Controlling for sex and childhood socioeconomic factors§	417	1.07 (0.86 to 1.32)	216	1.10 (0.81 to 1.50)
Breast cancer				
Simple model‡	74	1.64 (0.92 to 2.92)	32	1.59 (0.66 to 3.83)
Controlling for childhood socioeconomic factors§	74	1.62 (0.89 to 2.94)	32	1.53 (0.61 to 3.83)
Prostate cancer¶				
Simple model‡	28	1.54 (0.62 to 3.84)	17	1.37 (0.42 to 4.48)
Controlling for childhood socioeconomic factors§	28	1.43 (0.58 to 3.52)	17	1.34 (0.42 to 4.22)
Colorectal cancer				
Simple model‡	53	0.81 (0.42 to 1.57)	26	0.93 (0.39, 2.21)
Controlling for sex	53	0.81 (0.42 to 1.57)	26	0.93 (0.39, 2.20)
Controlling for sex and childhood socioeconomic factors§	53	0.86 (0.45 to 1.63)	26	0.96 (0.41, 2.21)
Gastric cancer				
Simple model‡	25	1.26 (0.49 to 3.23)	23	1.45 (0.53, 3.96)
Controlling for sex	25	1.27 (0.50 to 3.21)	23	1.45 (0.54, 3.92)
Controlling for sex and childhood socioeconomic factors§	25	1.22 (0.47 to 3.15)	23	1.43 (0.51, 4.01)

*HR = hazard ratio; CI = confidence interval. Standard errors used to derive 95% CIs were adjusted for possible within-family clustering of exposures and cancer incidence or mortality.

†Eleven subjects included in the mortality analyses were excluded from the incidence analyses because information on the date of the outcome was missing.

‡Simple models control for current age and are stratified by survey district.

§Childhood socioeconomic factors included socioeconomic status of the father, per capita weekly household food expenditure in childhood, and birth order; these analyses were stratified by survey district.

||Included 1961 women in incidence analysis and 1966 in mortality analysis.

¶Included 1883 men in incidence analysis and 1889 in mortality analysis.

Table 2. Studies of breast-feeding and cancers in adulthood included in the meta-analyses by cancer type and in descending order of year of publication*

Cancer type and study (reference)	Design	Year of birth	Age at which infant feeding was assessed (years)	Method of assessing infant feeding	Definitions of infant feeding	No. of cancers	Estimated odds or risk ratios (95% CI) for any or exclusive breast-fed versus bottle-fed	Variabes controlled for
All cancers Wingard et al., 1994 (26)	Historical cohort (main hypothesis)	1904–1915	11	Standardized questionnaire to parents	Any BF versus no BF; duration of BF	140	Risk ratios†: Males: 0.64 (0.36 to 1.15) Females: 2.25 (0.55 to 9.24) Duration males: <6 mo: 0.65 (0.32 to 1.34) ≥6 mo: 0.63 (0.40 to 1.00) Duration females: <6 mo: 1.89 (0.42 to 8.44) ≥6 mo: 2.44 (0.88 to 6.81) Odds in breast-fed: 66/2155 Odds in bottle-fed: 9/383 Odds ratio: 1.30 (0.64–2.63)	Age, birth weight, infant health, childhood SES
Tokuhata, 1969 (35)	Cross-sectional study of offspring of breast cancer probands and offspring of controls (multiple-hypothesis testing)	‡	Adulthood	Questionnaire to relatives of mother (husband, sibling or other informant)	Ever versus never BF	75		None
Breast cancer Michels et al., 2001 (27)	Population-based cohort (main hypothesis tested)	1921–1964	25–55	Self-reported on postal questionnaire (reports from the participants' mothers in a small subsample, $r = 0.74$ for self-report versus mothers' information on duration of breast-feeding)	Ever versus never BF	Premenopausal: 413 Postmenopausal: 660	Premenopausal: 0.97 (0.78 to 1.20) Duration: <9 mo: 0.85 (0.66 to 1.10) ≥9 mo: 0.88 (0.52 to 1.49) <i>P</i> for trend = 0.60 Postmenopausal: 1.12 (0.92 to 1.37) Duration: <9 mo: 1.06 (0.83 to 1.36) ≥9 mo: 1.30 (0.98 to 1.72) <i>P</i> for trend = 0.15 All ages‡: 1.05 (0.91 to 1.21) Duration: <9 mo: 0.95 (0.80 to 1.14) ≥9 mo: 1.19 (0.93 to 1.53)	Age, year of birth, premature birth, family history of breast cancer, height, BMI at 18 y, weight change since 18 y, history of benign breast disease, age at first child's birth, calorie intake, alcohol
Titus-Ermstoff et al., 1998 (34)	Population-based case-control (main hypothesis tested)	1911–1945	50–79	Telephone interview to subject	Ever versus never BF	Premenopausal: 205 Postmenopausal: 3803	Premenopausal: 0.65 (0.41 to 1.04) Postmenopausal: 0.95 (0.85 to 1.07) (<i>P</i> for interaction by menopausal status = .23) All ages‡: 0.93 (0.83 to 1.04) <45 y: 1.0 (0.8 to 1.3)¶ Duration: <6 mo: 1.04 (0.80 to 1.36) ≥6 mo: 1.0 (0.7 to 1.5)	Age, state, education, religion, family history of breast cancer, BMI, reproductive factors
Sanderson et al., 1998 (28)	Population-based case-control (multiple-hypothesis testing)	>1944	<45	Questionnaire to mother	Ever versus never BF	<45 y: 506		Age, birth year, BMI, family history of breast cancer, reproductive factors, infertility, use of OCPs, birth weight, maternal age, birth order, maternal smoking

(Table continues)

Table 2 (continued).

Cancer type and study (reference)	Design	Year of birth	Age at which infant feeding was assessed (years)	Method of assessing infant feeding	Definitions of infant feeding	No. of cancers	Estimated odds or risk ratios (95% CI) for any or exclusive breast-fed versus bottle-fed	Variables controlled for
Weiss et al., 1996 (36)	Population-based case-control (multiple-hypothesis testing)	1946–1972	20–44	Questionnaire to mother	Ever versus never BF	20–45 y: 508	<45 y: 0.74 (0.6–1.0)	Age, BMI, family history breast cancer, reproductive factors, previous breast biopsy, alcohol, no. of mammograms.
Freudenheim et al., 1994 (37)	Population-based case-control (main hypothesis tested)	1901–1951	40–85	Nurse interviews of subjects	Ever versus never BF	Premenopausal: 229 Postmenopausal: 299 All ages: 528	Premenopausal: 0.76 (0.52 to 1.12) Postmenopausal: 0.73 (0.47 to 1.13) All ages: 0.74 (0.56 to 0.99)	Age, education, BMI, family history breast cancer, reproductive factors, history of benign breast disease, duration breast-fed own infant, fat & carotenoid intake, height
Ekbom et al., 1993 (38)	Population-based nested case-control (main hypothesis tested)	1874–1954	Infancy	Hospital records completed by midwives/nurses	Feeding method at discharge (BF only, partly BF, not BF)	458 (<50 y: n = 212; ≥50 y: n = 246).	<50 y: 0.96 (0.37 to 2.49) ≥50 y: 1.23 (0.39 to 3.85) All ages: 1.03 (0.46 to 2.27)**	Maternal age, childhood SES, hospital stay, and reproductive factors
Brinton et al., 1983 (39)	Case-control study nested in screening programme (multiple-hypothesis testing)	Median 1991–1932	Median: 45–54 (range: <45→65)	Nurse interviews of subjects	Ever versus never BF	1192	All ages (mainly 45–54 y): 0.86 (0.7 to 1.1)	Age at diagnosis of study subjects
Henderson et al., 1974 (40)	Outpatient-based case-control (main hypothesis tested)	> 1906	Adulthood (<65)	Personal interviews of subjects	Ever versus never BF	235 (<40 y: n = 69)	<40 y: 1.18 (0.53 to 2.63) All ages: 1.27 (0.79 to 2.05)	Race, date of birth, SES
Tokuhata, 1969 (35)	Cross-sectional study of offspring of breast cancer probands versus offspring of controls (multiple-hypothesis testing)	‡	Adulthood	Interviews/questionnaires to relatives of mother (husband, sibling, or other)	Ever versus never BF	13	All ages Odds in breast-fed: 11/1133 Odds in bottle-fed: 2/181 Odds ratio: 0.88 (0.19–4.00)	None
Bucalossi et al., 1957 (41)	Hospital-based case-control study (multiple-hypothesis testing)	Early 1900s	Adulthood	Interviews/questionnaire to subjects, relatives, and/or family	Ever versus never BF	2969	All ages ^{††} Odds ratio: 1.09 (0.72 to 1.64)	None
Penrose et al., 1948 (43)	Case series (multiple-hypothesis testing)	‡	Mean: 55.2	Interviews of subjects	Ever BF	79 familial breast cancers; ‡‡ (control group: 360 women with nonfamilial breast cancers)	Odds ratio for familial breast cancer: 2.22 (0.85 to 5.77)	None

(Table continues)

Table 2 (continued).

Cancer type and study (reference)	Design	Year of birth	Age at which infant feeding was assessed (years)	Method of assessing infant feeding	Definitions of infant feeding	No. of cancers	Estimated odds or risk ratios (95% CI) for any or exclusive breast-fed versus bottle-fed	Variables controlled for
Testicular cancer Coupland et al., 2004 (73)	Population-based case-control (multiple-hypothesis testing)	1935-1972	15-49	Questionnaires to mothers	Ever BF; duration of any breast-feeding	446	Ever versus never: 0.81 (0.59 to 1.11); Duration: ≤6 mo: 0.83 (0.63 to 1.09) >6 mo: 0.65 (0.41 to 1.04) P for trend = .05	Age, region, social class, undescended testis or inguinal hernia before 15 y of age, maternal age at pregnancy.
Henderson et al., 1979 (42)	Population-based case-control (multiple-hypothesis testing)	1932-1959	15-40	Questionnaires to mothers	Ever BF	78	0.89 (0.46 to 1.71)	Sex, age, and neighborhood

*CI = confidence interval; BMI = body mass index; OCPs = oral contraceptive pills; SES = socioeconomic status; BF = breast-fed.

†For Wingard et al., standard errors for the calculation of CIs were derived from numbers of deaths given in their Table 3 (26) and assuming a Poisson distribution (59).

‡These studies lacked information on year of birth.

§In the studies by Michels et al. (27) and Titus-Ernstoff et al. (34), estimates of the association between breast-feeding and cancer at any age were derived by combining relative risks given separately for pre- and postmenopausal breast cancer using fixed-effects models.

||Includes age at menarche, age at first full-term pregnancy, parity, and age at menopause.

¶Because no evidence of confounding was found, the crude odds ratios are presented.

#From crude model; odds ratios and 95% CIs derived from Table II of the paper by Ekboom et al. (38) and are unadjusted.

**From fully adjusted model.

††Odds ratio and 95% CI derived from Table II of the paper by Bucalossi et al. (41) and are unadjusted.

‡‡One or more relatives with breast cancer were ascertained (mothers, sisters, grandmother, aunt).

potentially relevant studies that were excluded from these meta-analyses, 46 related to childhood cancers [and are the subject of a separate report (25)], 7 were reviews and 11 either did not report on breast-feeding-cancer outcomes or considered only breast cancers among breast-feeding mothers.

Breast-Feeding and All Cancers

In a meta-analysis of our Boyd Orr cohort findings together with the two published studies that examined the association of breast-feeding with all cancers (26,35), involving 802 cancer cases in total, there was no association between breast-feeding and all cancers (random-effects model: RR = 0.95, 95% CI = 0.71 to 1.26; $P = .7$) (Fig. 1, A). There was strong evidence of heterogeneity (I^2 statistic = 71%), and the possibility of a substantial increase or decrease in the risk of all cancers with breast-feeding cannot be discounted. An analysis of factors explaining this heterogeneity is not possible because meta-regression analyses based on only three studies could yield chance associations.

Breast-Feeding and Breast Cancer

Ten published studies (27,28,34–41) plus the Boyd Orr cohort, involving 11 564 breast cancer cases in total, were included in the meta-analyses of the association of breast-feeding with

breast cancer. [An additional published study (43) was not included in the meta-analysis because this study investigated the association of breast-feeding with familial compared with sporadic breast cancer rather than whether breast-feeding was associated with incident breast cancer per se.] Aspects of the quality of these studies are summarized in Table 3. Cohorts are considered to provide more robust estimates than case-control studies in the hierarchy of evidence, but only three cohort studies examining the breast-feeding–breast cancer association were identified: the Boyd Orr cohort, Michels et al. (the Nurses' Health Study) (27), and Ekblom et al. (a record-linkage study based on the Swedish cancer registry) (38). Nine studies relied on the long-term recall or reporting of having been breast-fed as a child among participants who were questioned after the diagnosis of breast cancer, so the responses may have been influenced by recall bias. The exceptions were the current Boyd Orr study and Ekblom's record-linkage study, in which infant feeding mode at discharge was recorded (on average 10 days after delivery) among infants born between 1874 and 1954 (38).

All studies of the breast cancer association defined breast-feeding as ever having been breast-fed; none examined exclusive breast-feeding beyond the first few days. Only some studies controlled for potentially important recognized confounders, including reproductive factors ($n = 6$) (27,28,34,36–38), family history of breast cancer ($n = 5$) (27,28,34,36,37) or a measure of

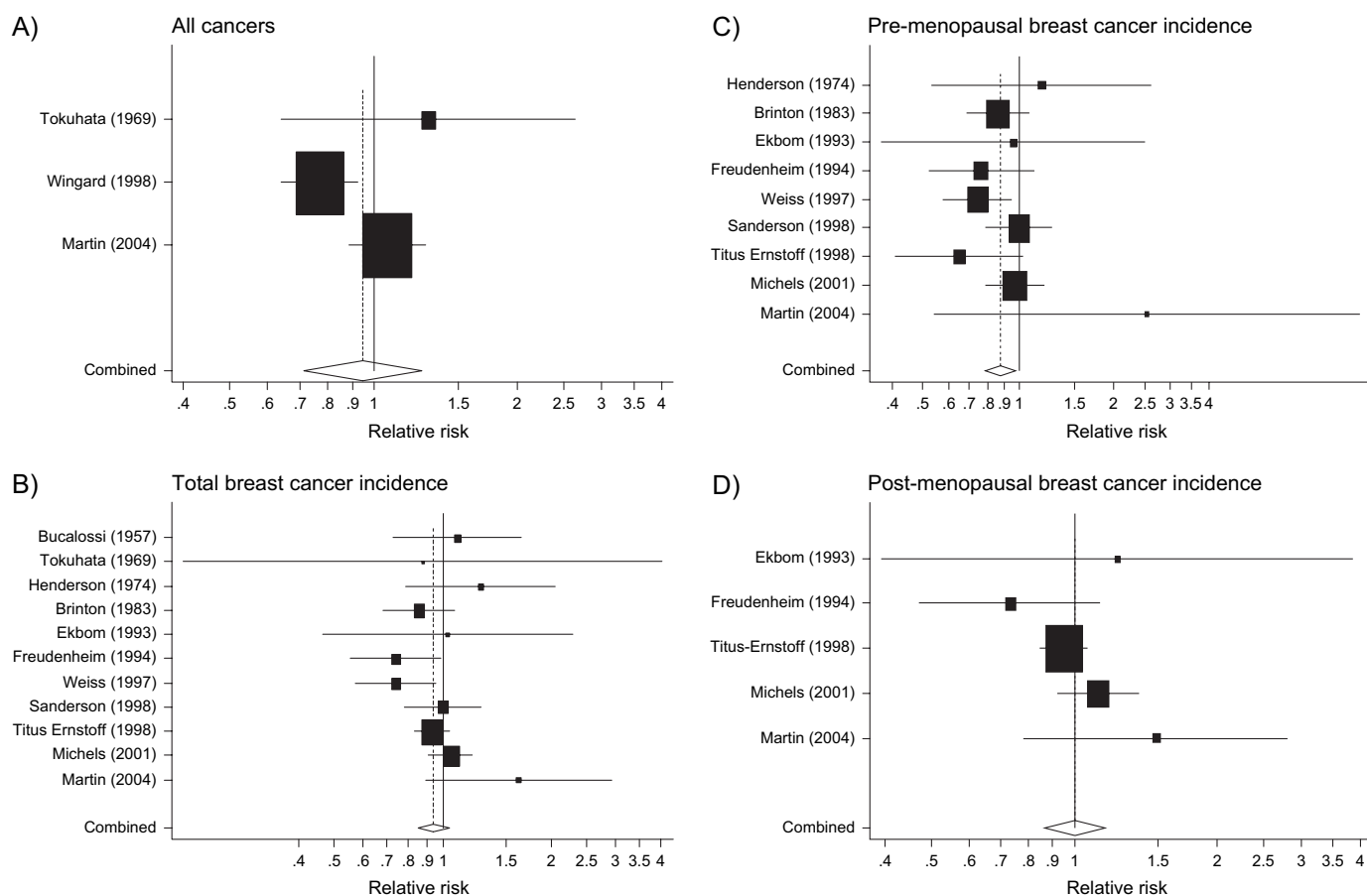


Fig. 1. Relative risks and 95% confidence intervals (CIs) for cancer incidence, comparing individuals who were ever breast-fed as infants with those who were never breast-fed, from a meta-analysis of published studies and Boyd Orr [shown as Martin (2004)]. **A)** Incidence of all cancer. **B)** Incidence of breast cancer. **C)** Incidence of premenopausal breast cancer. **D)** Incidence of postmenopausal

breast cancer. The study author is indicated on the y-axis (ordered by year of publication). The box for each study is proportional to the inverse of the variance; horizontal lines show 95% CIs on the relative risk. The pooled estimates, based on a random-effects model, are shown by a dashed vertical line and diamond (95% CI).

Table 3. Characteristics and quality of published studies relating ever having been breast-fed with breast cancer risk*

Characteristic	No.(%)
Year published (range)	1957–2004
Year of birth (range)	1874–1972
Cohort/nested studies	3 (27%)
Reliance on retrospective maternal/self recall	9 (82%)
Response rate in cases <80%†	6 (100%)
Response rate in controls <80%†	5 (100%)
Controlled for socioeconomic factors	5 (45%)
Controlled for maternal/reproductive factors	6 (55%)
Controlled for family history of breast cancer	5 (45%)
Controlled for family history of breast cancer and socioeconomic status and maternal/reproductive factors	3 (27%)
Population based	8 (73%)
Median (IQR) percent ever breast-fed	79% (49%–86%)
Median (IQR) % breast-fed >6 months	39% (13%–65%)

*IQR = interquartile range.

†For case-control studies, data on response rates in case patients were available for six studies and in control subjects for five studies.

socioeconomic/educational status ($n = 5$) (34,37,38,40) (and Boyd Orr). All six studies published since 1990, however, included multivariable adjustment for at least two of the following: reproductive factors, family history of breast cancer, or socioeconomic/educational status (27,28,34,36–38). Six case-control studies provided information on response rates (28,34,36,37,39,40), and in all of these studies the response rates among both case patients and control subjects were less than 80%, raising the possibility of selection bias.

Individually, five of the 11 studies included in the meta-analysis of breast cancer (34–37,39) suggested that women who had been breast-fed had a reduced risk of breast cancer (regardless of menopausal status), although the associations were statistically significant in only two studies (36,37). There was no evidence for an association between breast-feeding and breast cancer in the meta-analysis (RR = 0.94, 95% CI = 0.85 to 1.04; $P = .25$) (Fig. 1, B). There was moderate among-study heterogeneity ($I^2 = 31%$) but no evidence of small-study bias (Egger test $P = .7$).

Only three of the 11 studies (27,28) (and Boyd Orr) had information on duration of breast-feeding and breast cancer. In these studies, the association with breast cancer was similar in those breast-fed <6 months compared with those never breast-fed (RR = 0.99, 95% CI = 0.86 to 1.15) and in those breast-fed for 6 months or longer compared with those never breast-fed (RR = 1.21, 95% CI = 0.94 to 1.55), with little evidence of heterogeneity in each duration specific analysis ($I^2 = 0%$ and 29%, respectively).

Nine studies related having been breast-fed to premenopausal breast cancer (27,28,34,36–40) (and Boyd Orr), with a total of 3347 cases of premenopausal breast cancer. Of these studies, six (27,34,36–39) suggested a reduced risk of premenopausal breast cancer in women who had been breast-fed (Fig. 1, C). In random-effects meta-analysis, the RR was 0.88 (95% CI = 0.79 to 0.98; $P = .018$); the heterogeneity was low ($I^2 = 2%$), suggesting that the study results were consistent with one another. There was no evidence of small-study bias (Egger test $P = .6$). Five studies (27,34,37,38) (and Boyd Orr) examined associations of having been breast-fed with risk of postmenopausal breast cancer (5069 cases in total); in a meta-analysis, there was no association (RR = 1.00, 95% CI = 0.86 to 1.16; $P = 0.99$) (Fig. 1, D). These

studies were reasonably consistent with one another ($I^2 = 27%$), and there was no evidence of small-study effects (Egger test $P = .6$). An analysis of the two Nurses' Health Study cohorts (27) found weak evidence of a higher risk of postmenopausal breast cancer in women who had been breast-fed for at least 9 months versus those who had never been breast-fed, whether the analysis was based on self-reported infant feeding history (RR = 1.30, 95% CI = 0.98 to 1.72) or on information provided by the participants' mothers in a subsample of the cohorts (RR = 1.72, 95% CI = 0.99 to 3.00).

Four studies examined associations between having been breast-fed and familial compared with sporadic breast cancer (34,35,41,43). The data in three of these studies could be meta-analyzed (34,41,43) to assess whether a history of having been breast-fed is more common among women with familial breast cancer than women with sporadic breast cancers [a test of the Bittner hypothesis (10) that a breast cancer-causing agent is transmitted in breast milk]. The pooled relative risk for the association of having been breast-fed in relation to familial versus sporadic breast cancers was 1.05 (95% CI = 0.81 to 1.35; $I^2 = 35%$; $P = .7$), providing no evidence to support the suggestion that a transmissible agent in breast milk increases breast cancer risk. The study excluded from the above meta-analysis reported that the risks of breast cancer among breast-fed women compared with non-breast-fed women were the same regardless of maternal history of breast cancer (35).

Breast-Feeding and Testicular Cancer

A meta-analysis of the two studies that provided testicular cancer outcomes (with 524 cases of testicular cancer in total) provided only weak evidence of a lower risk of testicular cancer in breast-fed men (13,42) (pooled RR = 0.82, 95% CI = 0.62 to 1.10; $I^2 = 0%$; $P = .18$). One of the two studies, that of Coupland (13), suggested a duration-response relationship between breast-feeding and a lower risk of testicular cancer (P for trend = .05), but recall bias was possible because mothers provided information about method of infant feeding after the men were diagnosed at 15–49 years of age (13). The second study was relatively small (78 cases) (42). One small case-control study ($n = 37$), which was not included in the meta-analysis because the effect estimate was reported as an odds ratio per month of breast-feeding (44), suggested that breast-feeding was associated with an increased risk of testicular cancer: the odds ratio per month of breast-feeding was 1.05 (95% CI = 0.99 to 1.11; $P = .1$).

Sensitivity Analysis

Sensitivity analysis was restricted to the breast cancer meta-analyses because so few reports investigated all cancers or testicular cancers as outcomes. This analysis revealed that effect estimates differed according to study design, although the difference was borderline statistically significant (P for difference in effect estimates = .08). In the eight case-control studies (28,34–37,39–41), the pooled relative risk for the association of breast-feeding with breast cancer was 0.90 (95% CI = 0.82 to 0.99; $I^2 = 4%$). In the three cohort/nested case-control studies (27,38) (and Boyd Orr), the pooled relative risk was 1.07 (95% CI = 0.94 to 1.23; $I^2 = 0%$). There was no evidence that effects estimates differed by whether breast-feeding history was based on retrospective recall; by whether the study controlled for one or all of socioeconomic, family history, or reproductive factors; by

whether the study was population or hospital based; by the region in which the study was conducted; by the year of birth of the participants; or by whether or not the prevalence of any breast-feeding was at least 70% (all $P > .3$). Seven studies (27,28,34,36–38) (and Boyd Orr) presented both crude and adjusted estimates; the pooled relative risk for the association between breast-feeding and breast cancer using crude estimates (RR = 0.94, 95% CI = 0.80 to 1.09) was the same as that for the association using adjusted estimates (RR = 0.93, 95% CI = 0.82 to 1.06).

DISCUSSION

In this article, we describe two sets of analyses to examine associations between breast-feeding in infancy and subsequent adult cancer. First, our analysis of the Boyd Orr cohort provided no evidence that ever having been breast-fed or duration of breast-feeding is associated with incidence of all cancers or of prostate cancer, gastric cancer, or colorectal cancer. There was only weak, and not statistically significant, evidence from Boyd Orr in support of the hypothesis of a positive association between ever having been breast-fed in infancy and risk of breast cancer in adulthood.

Second, in a meta-analysis of published studies plus Boyd Orr (involving 11 564 breast cancer cases in total), ever having been breast-fed in infancy and the duration of breast-feeding were not associated with breast cancer risk (regardless of menopausal status). The meta-analyses showed that ever having been breast-fed was associated with a reduced risk of premenopausal breast cancer (RR = 0.88, 95% CI = 0.79 to 0.98) but was not associated with an alteration in the risk of postmenopausal breast cancer (RR = 1.00; 95% CI = 0.86 to 1.16). However, the confidence intervals for the two estimates overlap, and the differences in the risks of pre- and postmenopausal breast cancer could have arisen by chance. There was no statistical evidence of differences in associations of breast-feeding in infancy with breast cancer by menopausal status in the only study that formally tested for this interaction ($P = .23$) (34).

The analyses we conducted thus do not support the a priori hypothesis that ever having been breast-fed is linked with an increased risk of breast cancer. Neither was breast-feeding associated with a greater increase in breast cancer risk among women with a family history of breast cancer than among women with sporadic breast cancer, arguing against a transmissible agent in breast milk that increases breast cancer risk. Although breast-feeding was associated with a reduced risk of testicular cancer (RR = 0.82, 95% CI = 0.62 to 1.10), this reduction was not statistically significant. Moreover, the RR was derived from only two studies with retrospective ascertainment of exposure and multiple hypothesis testing. Hence, recall bias and chance cannot be excluded.

Both analyses in this article are subject to a number of limitations. In the Boyd Orr cohort, the confidence limits around the estimates for site-specific cancers were wide, indicating limited precision and low power to detect associations or interactions. The data did, however, add information to the breast cancer meta-analysis. We found no published studies relating having been breast-fed with prostate, colorectal, or gastric cancer; given the imprecise estimates from Boyd Orr and the absence of published data, definitive conclusions cannot be drawn for these cancers. Another limitation of the Boyd Orr study is the possibility that associations were confounded by adult risk factors such as smoking, body weight, and reproductive influences. However, the lack

of an association between breast-feeding and smoking-related cancers suggests that breast-feeding in infancy was not associated with smoking in adult life.

A limitation of the meta-analyses is that they were based on results from a group of studies of heterogeneous design and conduct. However, there was generally little variation in effect estimates between studies. Moderate between-study heterogeneity was found for the association of breast-feeding with all breast cancers ($I^2 = 31\%$). Although only 11 studies were involved in the breast cancer analysis, a relatively large number of breast cancers were included per study (total = 11 564; median = 508; interquartile range = 235–1192), allowing us to investigate this heterogeneity using meta-regression (discussed below).

There are a number of possible alternative explanations for the associations observed in the meta-analyses. First, in meta-regression analysis, we found some evidence ($P = .08$) that effect estimates from case-control studies (which suggested a 10% reduction in risk of breast cancer associated with having been breast-fed) were qualitatively different than those from the cohort/nested case-control studies (which suggested no association). Cohort studies are less likely than case-control studies (where breast-feeding history is obtained retrospectively following the diagnosis of cancer) to be affected by recall or selection biases, and the findings from these studies may be more robust. The possibility that retrospective versus prospective exposure ascertainment is a potential source of recall bias is suggested by the finding that long-term recall of breast-feeding history differs by socioeconomic status (45). Indeed, an apparent association between breast-feeding and type 1 diabetes was discounted once studies with prospective measurement of exposure were conducted (46). Moreover, in all case-control studies providing this information, response rates were less than 80% in both case and control subjects, a potential source of selection bias.

Second, because the mother's choice to breast-feed may be related to other factors influencing the future health of the child, the possibility of confounding in the studies included in the meta-analysis, particularly by socioeconomic status, needs to be considered. Approximately half of the reports with breast cancer outcomes controlled for at least one of the following: socioeconomic status, reproductive history, or a family history of breast cancer. There was no evidence that estimates adjusted for selected confounding factors differed from crude effect estimates, either within or between studies. Most studies included no or only limited information on childhood diet or factors during infancy (e.g., age at introduction of solids, birth weight, and length), and residual or uncontrolled confounding remains a concern. It has recently been recognized that growth patterns in early life may underlie associations relating early-life factors with breast cancer (3,47,48). None of the published studies reviewed here investigated the role of childhood growth in the relationship between breast-feeding and cancer risk, although two studies adjusted for final height (27,37). In the Boyd Orr cohort, adjustment for height and BMI in childhood did not alter the point estimates of the associations between breast-feeding and breast cancer (data not shown), arguing against childhood growth as an intermediate factor on the causal pathway or for a confounding effect of factors associated with childhood growth, such as diet.

Third, many of the studies had collected data on a large number of exposures. At the individual study level, chance findings in the context of multiple hypothesis testing and low prior probability that any one hypothesis is correct are a distinct possibility (49).

Fourth, publication bias may occur when small studies are differentially published only when they report large differences between feeding groups. Other undiscovered or unpublished studies may have included breast-feeding among a large number of variables tested for statistically significant associations. However, there was no evidence of small-study bias (i.e., the tendency for the smaller studies in a meta-analysis to provide larger estimates of the effect size) on the Egger tests (31).

Finally, there are several limitations to interpreting the infant feeding exposure data. The participants in these reports were born between 1874 and 1972, during which time alternatives to breast-feeding were likely to be predominantly unmodified cow's milk preparations. Formula feeds changed considerably from the late 1970s onward. Thus, the relevance of these analyses to babies born since then is unclear. Also, historic breast-feeding rates were far higher than current rates, so babies who were bottle-fed were likely to be a highly selected group, especially in the earlier part of the twentieth century. Nevertheless, we found no evidence that associations altered in studies with different breast-feeding prevalence rates. Moreover, although the studies were conducted on babies born during a period of considerable socioeconomic transition, the effect sizes were consistent over time.

Another limitation to the infant feeding exposure data is that most studies defined breast-feeding as any breast-feeding and did not specify the timing of breast-feeding initiation. Such information would be important to assess whether colostrum, which is dense with immunologic factors, is important to cancer outcomes. Most studies also did not address whether breast-feeding was exclusive, the duration of exclusive breast-feeding, and the quantities of supplementary feeds. Distinguishing between exclusive and partial breast-feeding, and assessing its duration, would help to assess whether the amount of breast milk exposure is associated with cancer outcomes.

Confounding in observational epidemiologic studies of the long-term effects of breast-feeding is a major limitation of existing reports (50). Two broad strategies could be used to overcome the problem of confounding. First, the relationship could be explored in populations in which breast-feeding is not socially patterned (51). The Boyd Orr cohort presented in this paper involved subjects born between 1918 and 1939, an era during which social and educational factors played little part in a mother's decision to breast- or bottle-feed (52). Therefore confounding by social, educational, and economic factors is likely to be less of an issue in this cohort than in more recent cohorts (53). Second, the relationship between breast-feeding and markers of later cancer risk [such as the IGF axis (4,8,54)] could be investigated in large, randomized, controlled trials of measures to promote breast-feeding. For example, long-term follow-up of the 17000 children in the PROBIT trial (55) would provide an experimental setting in which to rigorously test the association between breast-feeding and markers of cancer risk. Given our largely null findings, the beneficial influence of breast-feeding on infant and child health (56,57) and cognitive development (58) support its promotion as the infant feeding method of choice.

In summary, we found that breast-feeding has little or no association with development of adult cancer. There are limitations in the current epidemiologic evidence relating having been breast-fed with cancer, and the generalizability of the results to modern cohorts is unclear. Better measurement of infant feeding is required if future studies are to improve understanding of the association between breast-feeding and cancer.

Appendix. Search terms used in systematic review

Infant nutrition	Cancer
exp Breast Feeding	exp Neoplasms
exp Infant Nutrition	exp Breast Neoplasms
exp Milk, Human	exp Prostatic Neoplasms
(breast adj2 fed).tw	exp Colonic Neoplasms
breast feed\$.tw	prostat\$ cancer.tw
(human adj2 milk).tw	breast cancer.tw
breast milk.tw	colon\$ cancer.tw
breastfeeding.tw	cancer.tw
breastfed.tw	neoplas\$.tw
breastmilk.tw	

REFERENCES

- (1) Schwartzbaum JA, George SL, Pratt CB, Davis B. An exploratory study of environmental and medical factors potentially related to childhood cancer. *Med Ped Oncol* 1991;19:115–21.
- (2) Potischman N, Troisi R, Vatten L. A lifecourse approach to cancer epidemiology. In: Kuh D, Ben Shlomo Y, editors. *A life course approach to chronic disease epidemiology*. 2nd ed. Oxford (England): Oxford University Press; 2004. p. 260–80.
- (3) Gunnell D, Okasha M, Davey Smith G, Oliver SE, Sandhu J, Holly JMP. Height, leg length, and cancer risk: a systematic review. *Epidemiol Rev* 2001;23:313–41.
- (4) Davey Smith G, Gunnell D, Holly J. Cancer and insulin-like growth factor-I. *BMJ* 2000;321(7265):847–8.
- (5) Renehan AG, Zwahlen M, Minder PC, O'Dwyer ST, Shalet PS, Egger PM. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. *Lancet* 2004;363(9418):1346–53.
- (6) Martin RM, Davey Smith G, Mangtani P, Frankel S, Gunnell D. Association between breast feeding and growth: the Boyd-Orr cohort study. *Arch Dis Child Fetal Neonatal Ed* 2002;87:F193–F201.
- (7) Wadsworth ME, Hardy RJ, Paul AA, Marshall SF, Cole TJ. Leg and trunk length at 43 years in relation to childhood health, diet and family circumstances; evidence from the 1946 national birth cohort. *Int J Epidemiol* 2002;31:383–90.
- (8) Martin RM, Holly JMP, Davey Smith G, Ness AN, Emmett P, Rogers I, et al. Could associations between breastfeeding and insulin-like growth factors underlie associations of breastfeeding with adult chronic disease? The Avon Longitudinal Study of Parents and Children. *Clin Endocrinol* 2005;62:728–37.
- (9) Gunnell D. Can adult anthropometry be used as a biomarker for prenatal and childhood exposures? *Int J Epidemiol* 2002;31:390–4.
- (10) Bittner JJ. Mammary tumours in mice in relation to nursing. *Am J Cancer* 1937;30:530–8.
- (11) Fraumeni JF Jr, Miller RW. Breast cancer from breast-feeding. *Lancet* 1971;2:1196–7.
- (12) Potischman N, Troisi R. In-utero and early life exposures in relation to risk of breast cancer. *Cancer Causes Control* 1999;10:561–73.
- (13) Coupland CAF. Maternal risk factors for testicular cancer: a population-based case-control study (UK). *Cancer Causes Control* 2004;15:277–83.
- (14) Martin RM, Davey Smith G, Tilling K, Frankel S, Gunnell D. Breastfeeding and cardiovascular mortality: the Boyd Orr cohort and a systematic review with meta-analysis. *Eur Heart J* 2004;25:778–86.
- (15) Rowett Research Institute. *Family diet and health in pre-war Britain*. Dunfermline (United Kingdom): Carnegie United Kingdom Trust; 1955.
- (16) Smith D. The Carnegie Survey: background and intended impact. In: Fenton A, editor. *Order and disorder: the health implications of eating and drinking in the nineteenth and twentieth centuries*. East Linton (United Kingdom): Tuckwell Press Ltd; 2000. p. 64–80.
- (17) Martin RM, Gunnell D, Pemberton J, Frankel S, Davey Smith G. Cohort profile: the Boyd Orr cohort—an historical cohort study based on the 65 year follow-up of the Carnegie Survey of Diet and Health (1937–39). *Int J Epidemiol* 2005;34:742–9.
- (18) Fall CHD, Goggin PM, Hawtin P, Fine D, Duggleby S. Growth in infancy, infant feeding, childhood living conditions, and *Helicobacter pylori* infection at age 70. *Arch Dis Child* 1997;77:310–4.

- (19) Kelley JR, Duggan JM. Gastric cancer epidemiology and risk factors. *J Clin Epidemiol* 2003;56:1–9.
- (20) Gunnell DJ, Frankel S, Nanchahal K, Braddon FEM, Davey Smith G. Lifecourse exposure and later disease: a follow-up study based on a survey of family diet and health in pre-war Britain (1937–1939). *Public Health* 1996;110:85–94.
- (21) Gunnell DJ, Davey Smith G, Frankel S, Nanchahal K, Braddon FEM, Pemberton J, et al. Childhood leg length and adult mortality: follow-up study of the Carnegie (Boyd Orr) survey of diet and health in pre-war Britain. *J Epidemiol Commun Health* 1998;52:142–52.
- (22) Cluster. In: *Stata reference manual release 7. Vol 1 A-G*. College Station (TX): Stata Press; 2001. p. 224–35.
- (23) StataCorp. *Stata survival analysis and epidemiological tables*. Reference manual release 8.0. College Station (TX): Stata Corporation; 2003.
- (24) Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika* 1994;81:515–26.
- (25) Martin RM, Gunnell D, Owen CG, Davey Smith G. Breastfeeding and childhood cancer: a systematic review with meta-analysis. *Int J Cancer* 2005;June 28 [epub ahead of print].
- (26) Wingard DL, Criqui MH, Edelstein SL, Tucker J, Tomlinson-Keasey C, Schwartz JE, et al. Is breast-feeding in infancy associated with adult longevity? *Am J Public Health* 1994;84:1458–62.
- (27) Michels KB, Trichopoulos D, Rosner BA, Hunter DJ, Colditz GA, Hankinson SE, et al. Being breastfed in infancy and breast cancer incidence in adult life: results from the two nurses' health studies. *Am J Epidemiol* 2001;153:275–83.
- (28) Sanderson M, Williams MA, Daling JR, Holt VL, Malone KE, Self SG, Moore DE. Maternal factors and breast cancer risk among young women. *Paediatr Perinat Epidemiol* 1998;12:397–407.
- (29) Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327(7414):557–60.
- (30) Sterne JAC, Egger M, Davey Smith G. Investigating and dealing with publication and other biases. In: Egger M, Davey Smith G, Altman DG, editors. *Systematic reviews in health care: meta-analysis in context*. 2nd ed. London (England): BMJ Publishing Group; 2001. p. 189–208.
- (31) Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315(7109):629–34.
- (32) Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Davey Smith G, Altman DG, editors. *Systematic reviews in health care: meta-analysis in context*. 2nd ed. London (England): BMJ Publishing Group; 2003. p. 285–312.
- (33) StataCorp. *Stata statistical software: release 8.0*. College Station (TX): Stata Corporation; 2003.
- (34) Titus-Ernstoff L, Egan KM, Newcomb PA, Baron JA, Stampfer M, Greenberg ER, et al. Exposure to breast milk in infancy and adult breast cancer risk. *J Natl Cancer Inst* 1998;90:921–4.
- (35) Tokuhata GK. Morbidity and mortality among offspring of breast cancer mothers. *Am J Epidemiol* 1969;89:139–53.
- (36) Weiss HA, Potischman NA, Brinton LA, Brogan D, Coates RJ, Gammon MD, et al. Prenatal and perinatal risk factors for breast cancer in young women. *Epidemiology* 1997;8:181–7.
- (37) Freudenheim JL, Marshall JR, Graham S, Laughlin R, Vena JE, Bandera E, et al. Exposure to breastmilk in infancy and the risk of breast cancer. *Epidemiology* 1994;5:324–31.
- (38) Ekbohm A, Hsieh CC, Trichopoulos D, Yen YY, Petridou E, Adami HO. Breast-feeding and breast cancer in the offspring. *Br J Cancer* 1993;67:842–5.
- (39) Brinton LA, Hoover R, Fraumeni JF Jr. Reproductive factors in the aetiology of breast cancer. *Br J Cancer* 1983;47:757–62.
- (40) Henderson BE, Powell D, Rosario I, Keys C, Hanisch R, Young M, et al. An epidemiologic study of breast cancer. *J Natl Cancer Inst* 1974;53:609–14.
- (41) Bucalossi P, Veronesi U. Some observations on cancer of the breast in mothers and daughters. *Br J Cancer* 1957;11:337–47.
- (42) Henderson BE, Benton B, Jing J, Yu MC, Pike MC. Risk factors for cancer of the testis in young men. *Int J Cancer* 1979;23:598–602.
- (43) Penrose LS, MacKenzie HJ, Karn MN. A genetic study of human mammary cancer. *Br J Cancer* 1948;2:168–76.
- (44) Mori M, Davies TW, Miyake H, Masuoka H, Kumamoto Y, Tsukamoto T. Maternal factors of testicular cancer: a case-control study in Japan. *Jpn J Clin Oncol* 1990;20:72–7.
- (45) Vobecky JS, Vobecky J, Froda S. The reliability of the maternal memory in a retrospective assessment of nutritional status. *J Clin Epidemiol* 1988;41:261–5.
- (46) Norris JM. A meta-analysis of infant diet and insulin-dependent diabetes mellitus: do biases play a role? *Epidemiology* 1996;7:87–92.
- (47) De Stavola BL, dos Santos Silva I, McCormack V, Hardy RJ, Kuh DJ, Wadsworth ME. Childhood growth and breast cancer. *Am J Epidemiol* 2004;159:671–82.
- (48) Ahlgren M, Melbye M, Wohlfahrt J, Sorensen TIA. Growth patterns and the risk of breast cancer in women. *N Engl J Med* 2004;351:1619–26.
- (49) Sterne JAC, Smith Davey G, Cox DR. Sifting the evidence—what's wrong with significance tests? *BMJ* 2001;322(7280):226–31.
- (50) Kramer MS, Guo T, Platt RW, Shapiro S, Collet JP, Chalmers B, et al. Breastfeeding and infant growth: biology or bias? *Pediatrics* 2002;110(2 Pt 1):343–7.
- (51) Davey Smith G, Ebrahim S. Data dredging, bias, or confounding. *BMJ* 2002;325:1437–8.
- (52) Baxter-Jones ADG, Cardy AH, Helms PJ, Phillips DO, Smith WC. Influence of socioeconomic conditions on growth in infancy: the 1921 Aberdeen birth cohort. *Arch Dis Child* 1999;81:5–9.
- (53) Simmons D. NIDDM and breastfeeding. *Lancet* 1997;350:157–8.
- (54) Holly JMP, Gunnell DJ, Davey Smith G. Growth hormone, IGF-I and cancer. Less intervention to avoid cancer? More intervention to prevent cancer? *J Endocrinol* 1999;162:321–30.
- (55) Kramer MS, Chalmers B, Hodnett ED, Sevkovskaya Z, Dzikovich I, Shapiro S, et al. Promotion of Breastfeeding Intervention Trial (PROBIT): a randomized trial in the Republic of Belarus. *JAMA* 2001;285:413–20.
- (56) Raisler J, Alexander C, O'Campo P. Breast-feeding and infant illness: a dose-response relationship? *Am J Public Health* 1999;89:25–30.
- (57) WHO Collaborative Study Team on the Role of Breastfeeding on the Prevention of Infant Mortality. Effect of breastfeeding on infant and child mortality due to infectious diseases in less developed countries: a pooled analysis. *Lancet* 2000;355:451–5.
- (58) Anderson JW, Johnstone BM, Remley DT. Breast-feeding and cognitive development: a meta-analysis. *Am J Clin Nutr* 1999;70:525–35.
- (59) Kirkwood B. *Essentials of medical statistics*. London (England): Blackwell Science Ltd; 1988.

NOTES

G.D.S. and Stephen Frankel established the adult follow-up phase of the Carnegie Survey of Diet and Health in Pre-War Britain using original records loaned by the Rowett Research Institute. R.M.M. and N.M. currently maintain the Boyd Orr cohort database. R.M.M., G.D.S., D.G., and C.G.O. developed the hypothesis. N.M. analyzed the Boyd Orr dataset. R.M.M. undertook the literature search, identified eligible papers, undertook data extraction, and did the analysis for the systematic review. R.M.M. wrote the first draft of the paper and coordinated completion. All authors contributed to, and approved, the final version.

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