

Breastfeeding and childhood cancer

UK Childhood Cancer Study Investigators*

*V Beral, NT Fear, F Alexander and P Appleby. A complete list of investigators is given in: The United Kingdom Childhood Cancer Study: objectives, material, and methods. *Br J Cancer* 2000; 82(5): 1073–1102

Summary The relationship between childhood cancer and having been breastfed in infancy was investigated in the UK Childhood Cancer Study (UKCCS), a national, population-based case-control study. Analyses included 3500 children with cancer (cases) of whom 1637 were diagnosed with leukaemia, 114 with Hodgkin's disease, 228 with non-Hodgkin's lymphoma and 1521 with other cancer and 6964 controls. 62% cases and 64% controls were reported to have ever been breastfed. There was weak evidence, of borderline statistical significance, that having been breastfed was associated with a small reduction in the odds ratios for leukaemia (odds ratio = 0.89, 95% CI 0.80–1.00, $P = 0.06$), and for all cancers combined (odds ratio = 0.92, 95% CI 0.84–1.00, $P = 0.05$). Combining data from the UKCCS with results from other published studies showed a small reduction in the odds ratios for leukaemia, Hodgkin's disease, non-haematological cancers, and all childhood cancers combined, associated with ever having been breastfed. It is unclear whether the apparent small reduction in the odds ratio for these various types of childhood cancer is a generalized effect of breastfeeding or whether it reflects some systematic bias in the majority of studies that have investigated the question. © 2001 Cancer Research Campaign <http://www.bjcancer.com>

Keywords: breastfeeding; childhood cancer

The identification of leukaemia and lymphoma viruses in various animal species (Gross, 1951; Vogt and Ishizaki, 1965) prompted the search for viral causes of human leukaemia and lymphoma. The Epstein Barr virus has been associated with Burkitt's lymphoma in children (Epstein et al, 1964) and the human T-cell leukaemia virus with a rare form of adult leukaemia/lymphoma (Poiesz et al, 1980) but, as yet, no specific infectious agent has been associated with the majority of human leukaemias or lymphomas. Recently, attention has focused on the association between surrogate markers of exposure to infectious agents and the risk of childhood leukaemia (Greaves and Alexander, 1993; Kinlen, 1995).

Breastfed infants are at a reduced risk of gastrointestinal and respiratory infections (WHO Collaborative Study Team on the Role of Breastfeeding on the Prevention of Infant Mortality, 2000), but are also at an increased risk of mother-to-child transmission of certain infectious agents (Ruff, 1994; Nduati et al, 2000). Several case-control studies of children with leukaemia have reported a significantly reduced risk associated with having been breastfed as infants (Shu et al, 1999; Smulevich et al, 1999; Infante-Rivard et al, 2000; Bener et al, 2001), although not all studies have noted such a relationship (van Steensel-Moll et al, 1986; McKinney et al, 1987; Davis et al, 1988; Magnani et al, 1988; Shu et al, 1995; Petridou et al, 1997; Dockerty et al, 1999; Schüz et al, 1999; Rosenbaum et al, 2000; Hardell and Dreifaldt, 2001). Others have reported a significantly reduced risk of Hodgkin's disease (Grufferman et al, 1998) and non-Hodgkin's lymphoma (Bener et al, 2001) in breastfed children.

We report here the results of an analysis of breastfeeding patterns in infancy among children with leukaemia and other

cancers and among control children in the UK Childhood Cancer Study (UK Childhood Cancer Study Investigators, 2000). An a priori hypothesis was that any association with breastfeeding should be seen for childhood leukaemia, and possibly for childhood lymphoma, but not for other childhood cancers.

MATERIALS AND METHODS

Subjects

The UKCCS is a national population-based case-control study. Details of the study design are given elsewhere (UK Childhood Cancer Study Investigators, 2000). Briefly, children aged 0–14 with cancer diagnosed in England and Wales (1992–96) and Scotland (1991–94) were eligible for inclusion in the study. Detailed diagnostic review information was obtained from multiple sources, including histopathology reviews and clinical trial data. Subtyping of leukaemia was made possible by collecting together and reviewing cytogenetic and molecular details (UK Childhood Cancer Study Investigators, 2000). For each case, two controls were randomly selected from Family Health Services Authorities (in England and Wales) and Health Boards (in Scotland) matched to the case by month and year of birth, sex and region of residence at diagnosis. Eligible controls who did not participate in the study were replaced by another matched control until, where possible, two controls had been enrolled for each participating case. Participation rates were 87% for cases and 72% for first-choice controls.

The mothers of 3838 cases and 7629 controls were interviewed, using a standard questionnaire, that included questions about social, medical and behavioural factors. Included among the questions to the mothers were 'Did you ever breastfeed (the child)? How old was (the child) when you gave your last breast feed? Did you ever use formula milk? If so, how old was (the child) when he/she had his/her first

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Correspondence to: V Beral, Imperial Cancer Research Fund Cancer Epidemiology Unit, Gibson Building, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE, UK

*See Appendix for Management Committee, Regional Investigators and Data Management Processing Group

formula feed? Was (the child) ever given expressed milk from a milk bank?" Responses to these questions are examined in this report.

Analysis

A total of 943 children aged under 12 months at diagnosis/pseudodiagnosis were excluded from the analyses to prevent the introduction of possible biases if breastfeeding were to cease prematurely in children aged under 12 months with cancer. A further 60 children were excluded because information about breastfeeding had not been provided by their biological mother. Overall 338 cases and 665 controls were excluded leaving 3500 cases and 6964 controls – 91% of all interviewed and potentially eligible subjects.

Analyses were carried out for all cancers combined (3500 cases), and separately for leukaemia (1637 cases), Hodgkin's disease (114 cases), non-Hodgkin's lymphoma (228 cases) and all other cancers (1521 cases). For certain analyses children with leukaemia were subdivided into those with acute lymphoblastic leukaemia (ALL, 1401 cases) and acute myeloid leukaemia (AML, 214 cases). Those with ALL were subclassified further, as having common ALL (cALL, 879 cases), T cell ALL (134 cases), and those with B-lineage ALL were further subclassified as TEL-AML 1 (95 cases) or hyperdiploidy (358 cases).

Since the hypotheses concerning the role of infectious agents in childhood cancer are chiefly concerned with leukaemia and lymphoma, and because of the possible differential participation of the parents of children with and without cancer and differential recall of events in childhood, some analyses were restricted to children with cancer. In these restricted analyses, the breastfeeding histories of children with leukaemia or lymphoma were compared with those of children with other cancers, i.e. taking the children with other cancers as 'controls'.

Odds ratios (ORs) and their 95% confidence intervals (CIs) were estimated using unconditional logistic regression (StataCorp, 1999) and adjusted for region (10 in total), sex, age at diagnosis (in single years), birth order (1, 2, 3, 4+) and deprivation index (7 levels). For certain analyses, additional adjustments were

performed for the mother's age at leaving school and at the time of the child's birth, child's birthweight, whether or not the child had been admitted to a special care baby unit, and had attended day care in the first year of life, and maternal smoking when the child was 1 year old. Trends were assessed using likelihood ratio tests.

Results showing data from more than one study are presented in the form of plots of odds ratios. Each odds ratio is plotted as a black square, the area of which is proportional to the amount of statistical information for that particular estimate, i.e. the reciprocal of the variance of the log odds ratio, which reflects the reliability with which the odds ratio is estimated. The corresponding 95% CIs are shown as horizontal black lines. Where CIs are so narrow as to be contained entirely in the black box, they are plotted as white lines. Summary odds ratios are plotted in the form of a diamond, the width of which indicates the corresponding 95% CIs, and the dotted vertical line indicates the value of the summary odds ratio.

RESULTS

Table 1 shows the distribution of children with leukaemia, Hodgkin's disease, non-Hodgkin's lymphoma, other cancers, all cancers and controls, according to whether or not they were reported to have ever been breastfed and the reported duration that they had been breastfed; it also shows the corresponding adjusted odds ratios, with 95% confidence intervals, and the results of tests for trend by duration of breastfeeding. About two thirds of the children were reported to have been breastfed, with almost one fifth for longer than 6 months. The adjusted odds ratios associated with ever having been breastfed were below 1.0 and of borderline statistical significance for leukaemia (OR = 0.89, 95%CI 0.80–1.00, $P = 0.06$) and for all cancers combined (OR = 0.92, 95% CI 0.84–1.00, $P = 0.05$). For each cancer type shown in Table 1, none of the trends with increasing duration of breastfeeding was statistically significant. The odds ratios in Table 1 were not materially altered after additional adjustment for maternal education, maternal age, birthweight, admission to a special care baby unit, attendance at day care, or maternal smoking.

Table 1 Distribution of children with cancer and controls, according to cancer type and breastfeeding history, and the associated odds ratios* (ORs) and 95% confidence intervals (CIs)

	Leukaemia <i>n</i> = 1637	Hodgkin's disease <i>n</i> = 114	Non-Hodgkin's lymphoma <i>n</i> = 228	Other cancers <i>n</i> = 1521	All cancers <i>n</i> = 3500	Controls <i>n</i> = 6964
a) Number (%)						
never breastfed	629 (38.4)	43 (37.7)	79 (34.7)	592 (38.9)	1343 (38.4)	2500 (35.9)
ever breastfed	1008 (61.6)	71 (62.3)	149 (65.4)	929 (61.1)	2157 (61.6)	4464 (64.1)
duration < 1 month	251 (15.3)	23 (20.2)	33 (14.5)	241 (15.8)	548 (15.7)	1015 (14.6)
duration 1–6 months	454 (27.7)	29 (25.4)	75 (32.9)	389 (25.6)	947 (27.1)	2034 (29.2)
duration ≥ 7 months	302 (18.5)	19 (16.7)	41 (18.0)	298 (19.6)	660 (18.9)	1410 (20.3)
unknown	1 (0.1)	–	–	1 (0.1)	2 (0.1)	5 (0.1)
b) ORs* (95% CIs)						
never breastfed (reference)	1.0	1.0	1.0	1.0	1.0	
ever breastfed	0.89 (0.80–1.00)	1.01 (0.67–1.53)	1.03 (0.77–1.38)	0.90 (0.80–1.02)	0.92 (0.84–1.00)	
duration < 1 month	0.96 (0.81–1.14)	1.50 (0.88–2.57)	1.04 (0.68–1.59)	1.01 (0.86–1.20)	1.01 (0.89–1.14)	
duration 1–6 months	0.88 (0.77–1.02)	0.85 (0.51–1.40)	1.12 (0.80–1.50)	0.83 (0.72–0.96)	0.88 (0.79–0.98)	
duration ≥ 7 months	0.85 (0.73–1.00)	0.90 (0.50–1.60)	0.90 (0.60–1.34)	0.93 (0.79–1.08)	0.89 (0.79–1.01)	
c) Test for trend						
with duration of breastfeeding*	$\chi_1^2 = 1.11$ $P = 0.29$	$\chi_1^2 = 1.22$ $P = 0.27$	$\chi_1^2 = 1.07$ $P = 0.30$	$\chi_1^2 = 0.10$ $P = 0.75$	$\chi_1^2 = 1.50$ $P = 0.22$	

*Adjusted by age at diagnosis, sex, region, birth order and deprivation index. *Excludes never breast fed and unknown duration categories, based on median duration within each duration category (9 days, 91 days and 304 days) for the control population.

Table 2 shows results, for various subtypes of leukaemia, for children who had ever versus never been breastfed and according to the reported duration of breastfeeding. The numbers in each category are comparatively small and none of the odds ratios or tests for trend with duration of breastfeeding was statistically significant.

The results for leukaemia were also examined separately for first born children and the odds ratio associated with ever having been breastfed in this subgroup was 0.98 (95% CI 0.82–1.18).

Table 3 shows age-specific results according to whether or not the children were breastfed, separately for children with

Table 2 Distribution of children with leukaemia, according to the type of leukaemia and breastfeeding history, and the associated odds ratios* (ORs) and 95% confidence intervals (CIs)

	Acute myeloid leukaemia (AML) n = 214	Acute lymphoblastic leukaemia (ALL) n = 1401	Sub-categories of acute lymphoblastic leukaemia			
			T cell ALL n = 134	Common ALL n = 879	Sub-categories of B-lineage ALL	
					TEL-AML 1 n = 95	Hyperdiploidy n = 358
a) Number (%)						
never breastfed	92 (43.0)	529 (37.8)	48 (35.8)	320 (36.4)	34 (35.8)	131 (36.6)
ever breastfed	122 (57.0)	872 (62.2)	86 (64.2)	559 (63.6)	61 (64.2)	227 (63.4)
duration < 1 month	29 (13.6)	217 (15.5)	15 (11.2)	149 (17.0)	13 (13.7)	64 (17.9)
duration 1–6 months	61 (28.5)	388 (27.7)	43 (32.1)	243 (27.7)	23 (24.2)	100 (27.9)
duration ≥ 7 months	32 (15.0)	266 (19.0)	28 (20.9)	167 (18.9)	25 (26.3)	63 (17.6)
unknown	–	1 (0.1)	–	–	–	–
b) ORs* (95% CIs)						
never breastfed (reference)	1.0	1.0	1.0	1.0	1.0	1.0
ever breastfed	0.78 (0.58–1.05)	0.91 (0.81–1.04)	1.14 (0.78–1.66)	0.96 (0.82–1.11)	0.97 (0.62–1.50)	0.96 (0.76–1.22)
duration < 1 month	0.82 (0.53–1.26)	0.98 (0.82–1.17)	0.86 (0.47–1.55)	1.09 (0.88–1.34)	0.87 (0.45–1.67)	1.14 (0.83–1.57)
duration 1–6 months	0.85 (0.60–1.20)	0.90 (0.77–1.04)	1.27 (0.82–1.95)	0.91 (0.76–1.09)	0.80 (0.46–1.38)	0.93 (0.71–1.23)
duration ≥ 7 months	0.65 (0.43–1.00)	0.89 (0.75–1.05)	1.20 (0.73–1.97)	0.92 (0.75–1.13)	1.31 (0.76–2.25)	0.87 (0.63–1.19)
c) Test for trend						
with duration of breastfeeding*	$\chi_1^2 = 1.46$ P = 0.23	$\chi_1^2 = 0.50$ P = 0.48	$\chi_1^2 = 0.29$ P = 0.59	$\chi_1^2 = 0.52$ P = 0.47	$\chi_1^2 = 2.72$ P = 0.10	$\chi_1^2 = 1.47$ P = 0.23

*Adjusted by age at diagnosis, sex, region, birth order and deprivation index. *Excludes never breast fed and unknown duration categories, based on median duration within each duration category (9 days, 91 days and 304 days) for the control population.

Table 3 Age-specific distribution of children with cancer and controls, and associated odds ratios* (ORs) and 95% confidence intervals (CIs)

	Leukaemia	Hodgkin's disease	Non-Hodgkin's lymphoma	Other cancers	All cancers	Controls
Age 1 year						
a) Numbers (%)						
never breastfed	59 (44.0)	–	2 (66.7)	67 (32.5)	128 (37.3)	261 (37.9)
ever breastfed	75 (56.0)	–	1 (33.3)	139 (67.5)	215 (67.7)	427 (62.1)
b) ORs* (CIs) for ever vs never breastfed						
vs never breastfed	0.76 (0.51–1.12)	–	1.76 (0.09–35.9)	1.48 (1.04–2.09)	1.12 (0.84–1.48)	
c) P value (ever vs never)						
	0.17	–	0.71	0.03	0.44	
Ages 2–5 years						
a) Numbers (%)						
never breastfed	332 (37.3)	8 (53.3)	20 (30.8)	236 (42.9)	596 (39.2)	1088 (36.1)
ever breastfed	558 (62.7)	7 (46.7)	45 (69.2)	314 (57.1)	924 (60.8)	1926 (63.9)
b) ORs* (CIs) for ever vs never breastfed						
vs never breastfed	0.95 (0.81–1.11)	0.57 (0.19–1.69)	1.24 (0.71–2.15)	0.75 (0.62–0.91)	0.88 (0.79–1.00)	
c) P value (ever vs never)						
	0.52	0.31	0.45	0.004	0.05	
Age 6+ years						
a) Numbers (%)						
never breastfed	238 (38.8)	35 (35.4)	57 (35.6)	289 (37.8)	619 (37.8)	1151 (35.3)
ever breastfed	375 (61.2)	64 (64.7)	103 (64.4)	476 (62.2)	1018 (62.2)	2111 (64.7)
b) ORs* (CIs) for ever vs never breastfed						
vs never breastfed	0.85 (0.70–1.02)	1.12 (0.71–1.75)	0.99 (0.70–1.41)	0.92 (0.77–1.09)	0.91 (0.80–1.04)	
c) P value (ever vs never)						
	0.09	0.62	0.97	0.34	0.16	

*Adjusted by age of diagnosis, sex, region, birth order and deprivation index.

leukaemia, Hodgkin's disease, non-Hodgkin's lymphoma, other cancers, and all cancers combined. The divisions by age were determined a priori, with the specific hypothesis that the effects of any infectious agent would be greatest for cALL at ages 2–5 (Greaves and Alexander, 1993). For leukaemia the odds ratios did not differ significantly from 1.0 at any age and there is no statistical evidence that the results varied according to age at diagnosis. Most children with leukaemia were diagnosed at ages 2–5 years and in this age group the odds ratios for the various leukaemia subtypes for ever having been breastfed versus never having been breastfed were: 0.95 (0.80–1.12) for ALL; 0.95 (0.55–1.64) for AML; 1.03 (0.83–1.25) for cALL; 1.18 (0.64–2.18) for T cell ALL; 0.84 (0.50–1.40) for TEL-AML 1; and 1.03 (0.77–1.37) for hyperdiploidy. Thus there was no strong evidence of heterogeneity between the subtypes at those ages. Nor was there evidence that the findings for the lymphomas varied by age, although there was some evidence of heterogeneity in all other cancer categories. Detailed examination for specific cancers within this category

revealed no consistent pattern. Of these, the most common cancers before the age of 6 were tumours of the central nervous system (57 cases at age 1, OR = 1.79, 95% CI 0.94–3.41; and 210 cases at age 2–5, OR = 0.91, 95% CI 0.67–1.23) and renal tumours (39 cases at age 1, OR = 1.85, 95% CI 0.85–4.02 and 99 cases at age 2–5, OR = 0.68, 95% CI 0.44–1.04). Both these tumour types contributed to the comparatively high odds ratio for children aged 1 and the comparatively low odds ratio at ages 2–5, and these may well be chance findings.

Table 4 shows results according to whether or not the child was ever given formula feed and, if so, the age the child was when such feeds were introduced. No consistent pattern is evident, and no results are statistically significant. Nor did the risk of childhood cancer appear to be influenced by having been given expressed milk from a milk bank. The results are, however, based on small numbers (about 2% of children ever received milk from a milk bank), the respective odds ratios were: 0.89 (0.57–1.39) for leukaemia; 1.50 (0.46–4.95) for Hodgkin's disease; 1.17 (0.46–2.93) for non-

Table 4 Distribution of children with cancer and controls, according to the type of cancer and age at introduction of first formula feed, and the associated odds ratios* (ORs) and 95% confidence intervals (CIs)

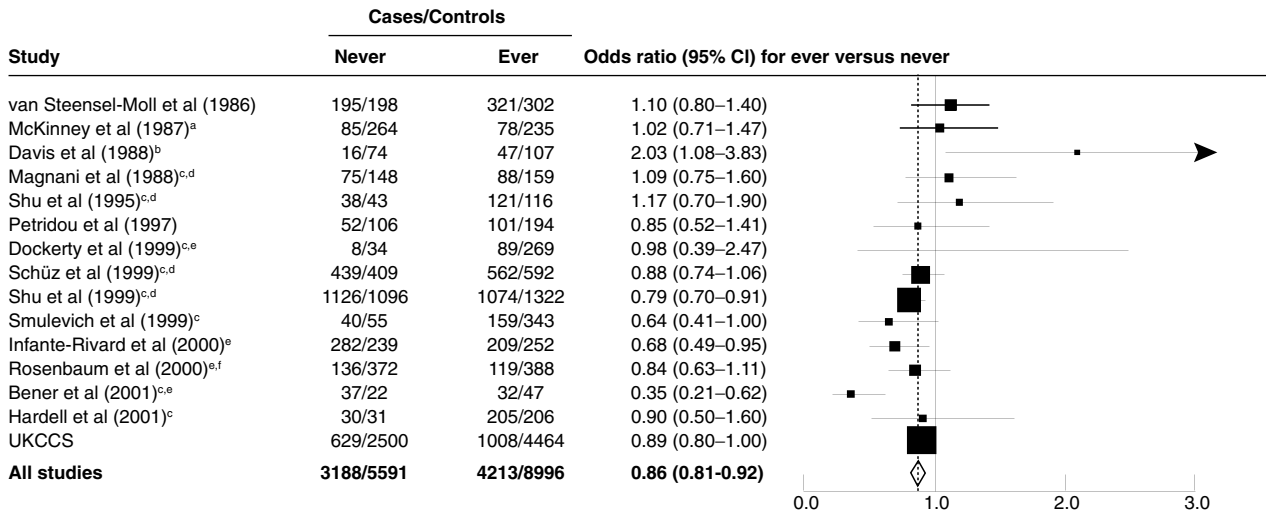
	Leukaemia n = 1637	Hodgkin's disease n = 114	Non-Hodgkin's lymphoma n = 228	Other cancers n = 1521	All cancers n = 3500	Controls n = 6964
a) Number (%)						
no formula feeds	223 (13.6)	16 (14.0)	32 (14.0)	216 (14.2)	487 (13.9)	1047 (15.0)
first use <1 month	1024 (62.6)	73 (64.0)	135 (59.2)	960 (63.1)	2192 (62.6)	4136 (59.4)
first use ≥ 1 month	390 (23.8)	25 (21.9)	61 (26.8)	345 (22.7)	821 (23.5)	1778 (25.5)
unknown	–	–	–	–	–	3 (<0.1)
b) ORs* (95% CIs)						
no formula feeds	1.0	1.0	1.0	1.0	1.0	
first use <1 month	1.11 (0.94–1.31)	1.28 (0.72–2.26)	1.22 (0.82–1.84)	1.09 (0.92–1.29)	1.11 (0.98–1.26)	
first use ≥ 1 month	0.98 (0.81–1.18)	1.11 (0.58–2.11)	1.30 (0.83–2.03)	0.93 (0.77–1.12)	0.98 (0.86–1.13)	
c) P value						
(ever vs never)	P = 0.44	P = 0.48	P = 0.27	P = 0.65	P = 0.28	

*Adjusted by age at diagnosis, sex, region, birth order and deprivation index.

Table 5 Distribution of children with cancer, according to cancer type and breastfeeding history, and the associated odds ratios* (ORs) and 95% confidence intervals (CIs) for leukaemia and lymphoma compared to all other cancers

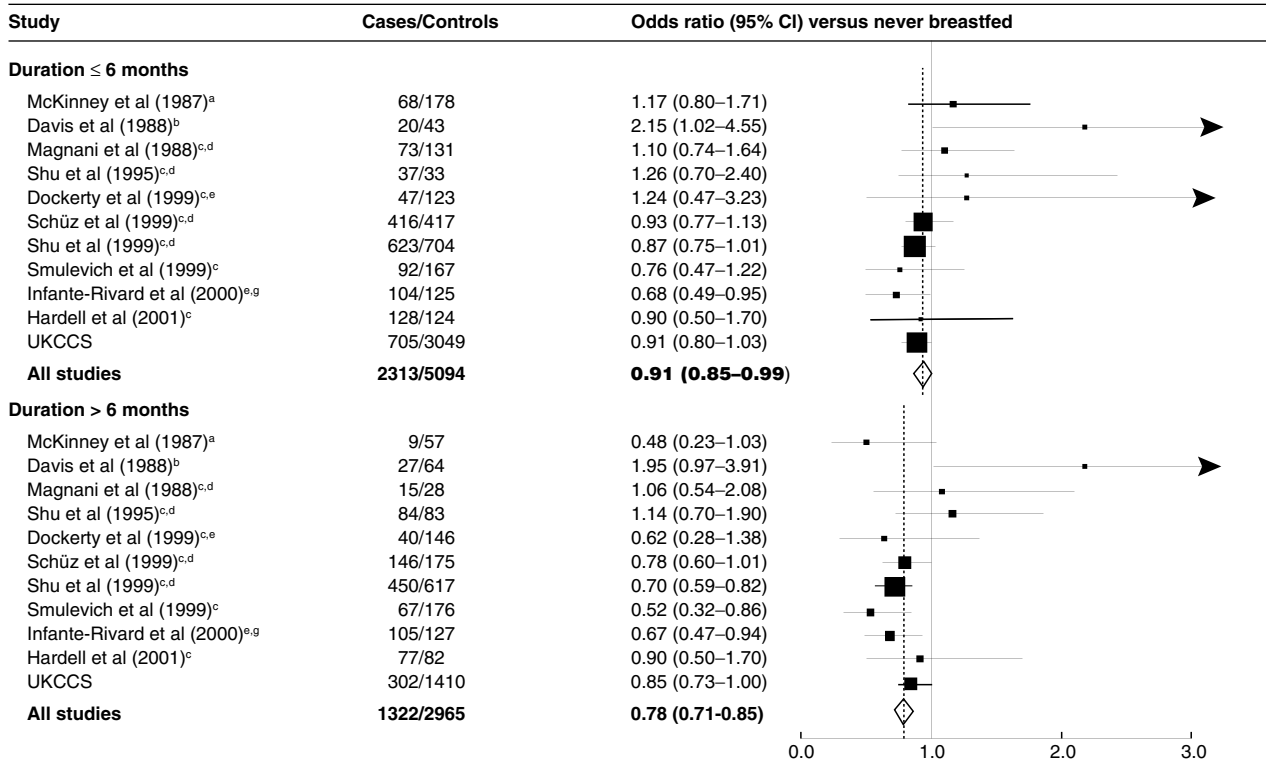
	Leukaemia n = 1637	Hodgkin's disease n = 114	Non-Hodgkin's lymphoma n = 228	Other cancers n = 1521
a) Number (%)				
never breastfed	629 (38.4)	43 (37.7)	79 (34.7)	592 (38.9)
ever breastfed	1008 (61.6)	71 (62.3)	149 (65.4)	929 (61.1)
duration < 1 month	251 (15.3)	23 (20.2)	33 (14.5)	241 (15.8)
duration 1–6 month	454 (27.7)	29 (25.4)	75 (32.9)	389 (25.6)
duration ≥ 7 months	302 (18.5)	19 (16.7)	41 (18.0)	298 (19.6)
unknown	1 (0.1)	–	–	1 (0.1)
b) ORs* (95% CIs)				
never breastfed (reference)	1.0	1.0	1.0	
ever breastfed	1.00 (0.85–1.17)	1.24 (0.79–1.95)	1.26 (0.91–1.75)	
duration < 1 month	0.96 (0.77–1.19)	1.65 (0.92–2.98)	1.20 (0.75–1.90)	
duration 1–6 month	1.09 (0.90–1.31)	1.07 (0.62–1.86)	1.56 (1.07–2.28)	
duration ≥ 7 months	0.91 (0.74–1.13)	1.11 (0.59–2.10)	0.94 (0.60–1.47)	
c) Test for trend				
with duration	$\chi_1^2 = 0.52$	$\chi_1^2 = 0.82$	$\chi_1^2 = 2.63$	
of breastfeeding*	P = 0.47	P = 0.36	P = 0.11	

*Adjusted by age at diagnosis, sex, region, birth order and deprivation index, using as the control population children with other cancers. *Excludes never breast fed and unknown duration categories, based on median duration within each duration category (11 days, 106 days and 330 days) for the control population (children with other cancers).

Figure 1 Odds ratio for childhood leukaemia by history of having been breastfed

Test for heterogeneity: $\chi^2_{10} = 30.21$; $P < 0.01$

Odds ratio for childhood leukaemia by duration of breastfeeding compared to never breastfed



Test for heterogeneity \leq 6 months: $\chi^2_{10} = 13.01$; $P > 0.1$; NS

Test for heterogeneity $>$ 6 months: $\chi^2_{10} = 17.92$; $P < 0.1$

Test for heterogeneity between short-term and long-term breastfeeding: $\chi^2_1 = 6.90$; $P < 0.01$

^aData provided by McKinney (personal communication)

^bNumbers of cases and controls derived from data presented by the authors

^c"Never" includes breastfed for $<$ 2 days (Dockerty et al 1999); $<$ 1 month (Magnani et al 1988, Shu et al 1995, Schüz et al 1999, Shu et al 1999, Hardell et al 2001); $<$ 2 months (Smulevich et al 1999); \leq 6 months (Bener et al 2001)

^dAcute leukaemia only

^eAcute lymphatic leukaemia only

^fData from meeting abstract

^gDuration \leq 3 months and $>$ 3 months

Hodgkin's lymphoma; 1.03 (0.68–1.58) for other childhood cancers; and 0.99 (0.72–1.36) for all cancers combined.

When children with other cancers are taken as the comparison group, the odds ratios associated with ever having been breastfed

are 1.00, 1.24 and 1.26, respectively for leukaemia, Hodgkin's disease and non-Hodgkin's lymphoma (Table 5).

The results from the UKCCS study with respect to breastfeeding were compared with relevant results from other epidemiological studies of childhood cancer (van Steensel-Moll et al, 1986; McKinney et al, 1987; Davis et al, 1988; Hartley et al, 1988; Magnani et al, 1988; Golding et al, 1990; Shu et al, 1995; Petridou et al, 1997; Grufferman et al, 1998; Dockerty et al, 1999; Schüz et al, 1999; Shu et al, 1999; Smulevich et al, 1999; Infante-Rivard et al, 2000; Rosenbaum et al, 2000; Bener et al, 2001; Hardell and Dreifaldt, 2001). The UKCCS results did not differ significantly from those of previous studies, they have been combined with these and the overall results are shown for leukaemia (Figure 1), Hodgkin's disease (Figure 2), non-Hodgkin's lymphoma (Figure 3), other childhood cancers (Figure 4) and all childhood cancers combined (Figure 5). Not all studies published separate results for each cancer type and so the totals for each type do not add up to the 'all cancer' values. For childhood leukaemia, there is evidence of a statistically significant reduction in the odds ratio associated with ever having been breastfed (OR = 0.86, 95% CI 0.81–0.92) and having been breastfed for more than 6 months (OR = 0.78, 95% CI 0.71–0.85). However, there is also evidence of a reduction in the odds ratio of similar magnitude associated with ever having

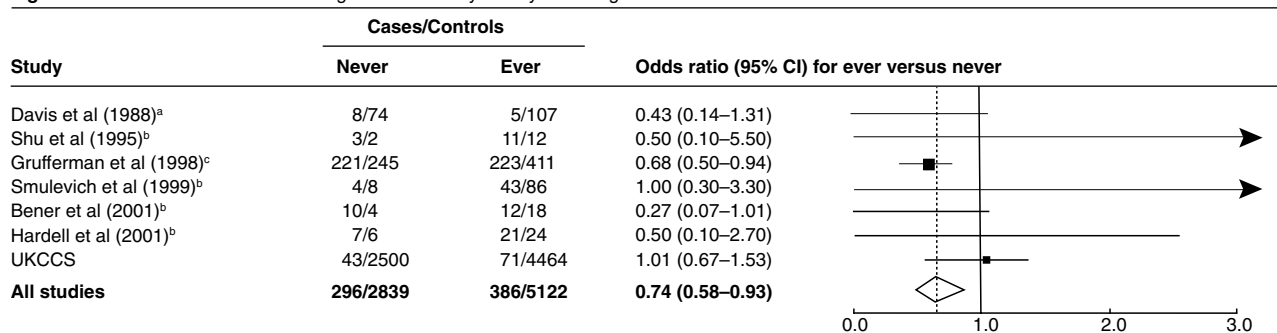
been breastfed for Hodgkin's disease (OR = 0.74, 95% CI 0.58–0.93), all non-haematological cancers (OR = 0.85, 95% CI 0.76–0.95) and for all childhood cancers combined (OR = 0.90, 95% CI 0.84–0.97).

DISCUSSION

Breastfeeding provides a range of immunological benefits to the infant (Jelliffe and Jelliffe, 1978; Goldman, 1993; Cuthbertson, 1999; WHO Collaborative Team on the Role of Breastfeeding on the Prevention of Infant Mortality, 2000). In the first hours after birth, breast milk contains anti-microbial immunoglobulins; subsequently it also contains lymphocytes, macrophages and soluble factors, such as cytokines, lactoferrin, lysozyme, complement components, that may alter response to infection (Goldman, 1993; Hanson, 2000). However, breastfeeding also predisposes to the transmission of various infectious agents from mother to child (Ruff, 1994; Nduati et al, 2000).

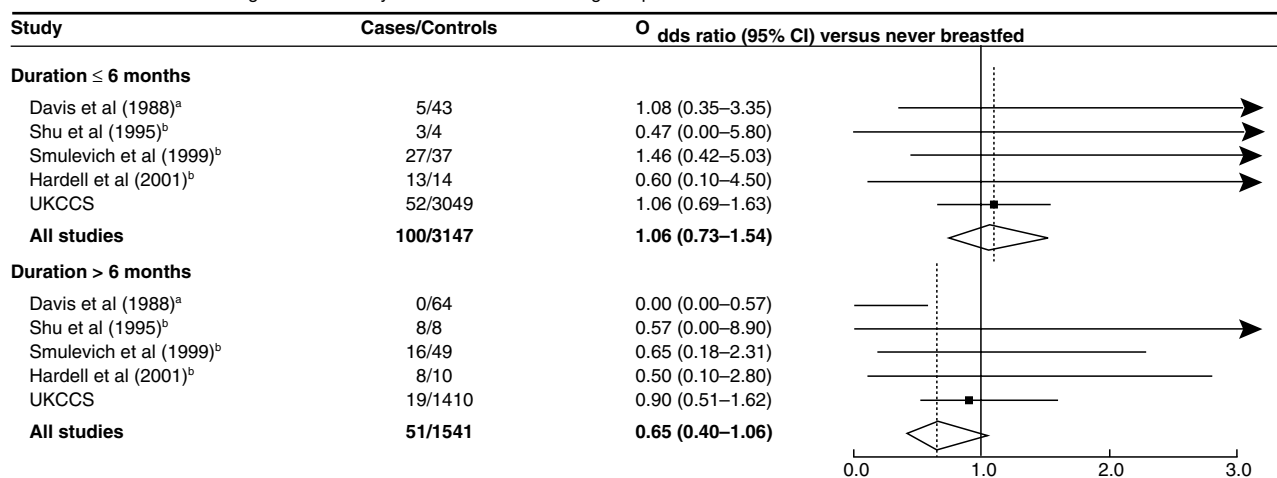
Greaves' delayed exposure hypothesis predicts a protective effect for protracted breastfeeding specifically for childhood acute lymphoblastic leukaemia as a consequence of priming of the developing immune system by both vertical transmission of infective agents and immunological properties of breast milk (Greaves, 1997). The results from the UKCCS provide, however, equivocal

Figure 2 Odds ratio for childhood Hodgkin's disease by history of having been breastfed



Test for heterogeneity: $\chi^2_6 = 6.16$; $P > 0.1$; NS

Odds ratio for childhood Hodgkin's disease by duration of breastfeeding compared to never breastfed



Test for heterogeneity ≤ 6 months: $\chi^2_4 = 0.80$; $P > 0.1$; NS

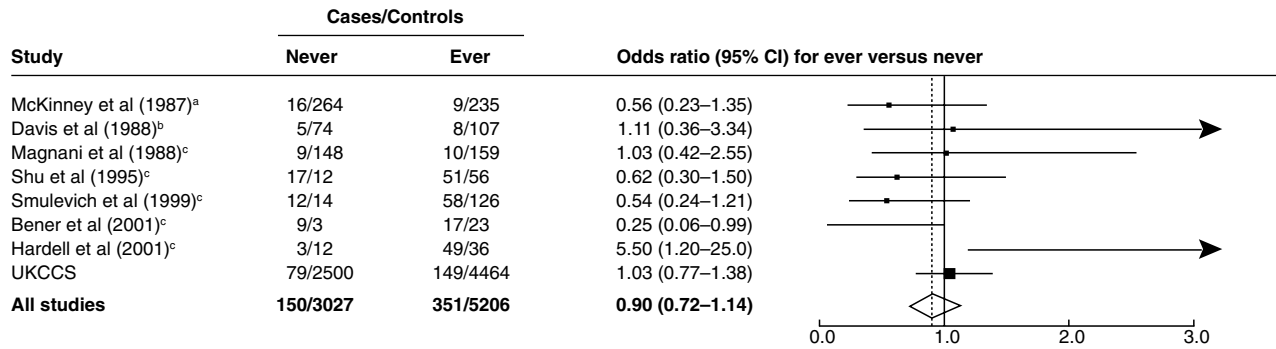
Test for heterogeneity > 6 months: $\chi^2_4 = 17.55$; $P < 0.01$

Test for heterogeneity between short-term and long-term breastfeeding: $\chi^2_1 = 2.44$; $P > 0.1$; NS

^aNumbers of cases and controls derived from data presented by the authors

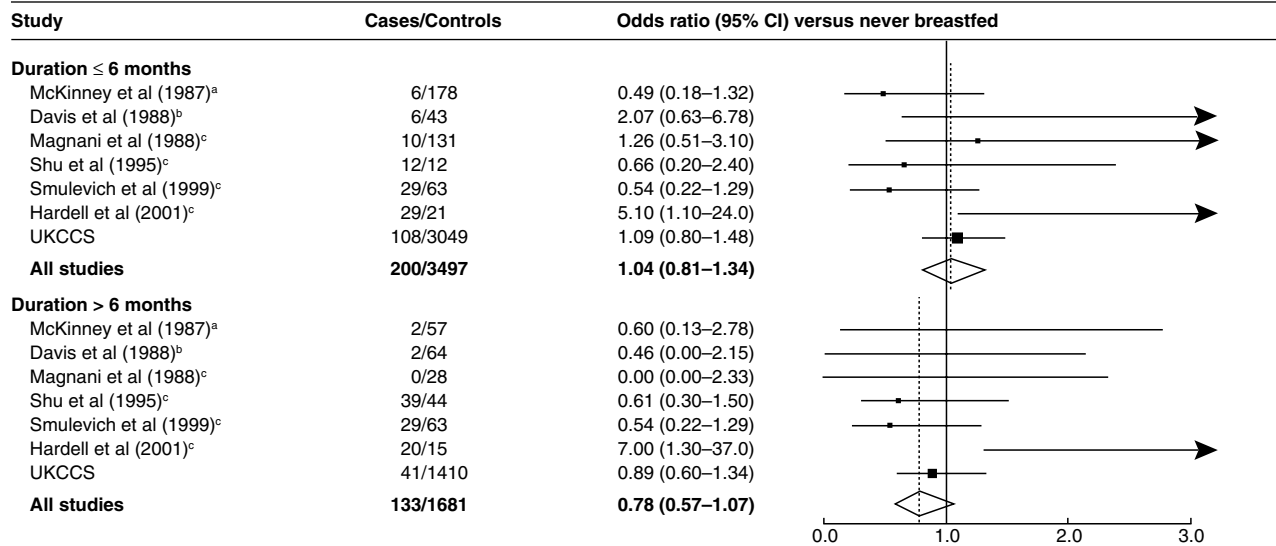
^b'Never' includes breastfed for < 1 month (Shu et al 1995, Hardell et al 2001); < 2 months (Smulevich et al 1999); ≤ 6 months (Bener et al 2001)

^cData from meeting abstract

Figure 3 Odds ratio for childhood non-Hodgkin's lymphoma by history of having been breastfed

Test for heterogeneity: $\chi^2 = 13.17$; $P < 0.1$

Odds ratio for childhood non-Hodgkin's lymphoma by duration of breastfeeding compared to never breastfed



Test for heterogeneity ≤ 6 months: $\chi^2 = 10.46$; $P > 0.1$; NS

Test for heterogeneity > 6 months: $\chi^2 = 18.64$; $P < 0.01$

Test for heterogeneity between short-term and long-term breastfeeding: $\chi^2 = 1.89$; $P > 0.1$; NS

^aData provided by McKinney (personal communication)

^bNumbers of cases and controls derived from data presented by the authors

^c"Never" includes breastfed for < 1 months (Magnani et al 1988, Shu et al 1995, Hardell et al 2001); < 2 months (Smulevich et al 1999); ≤ 6 months (Bener et al 2001)

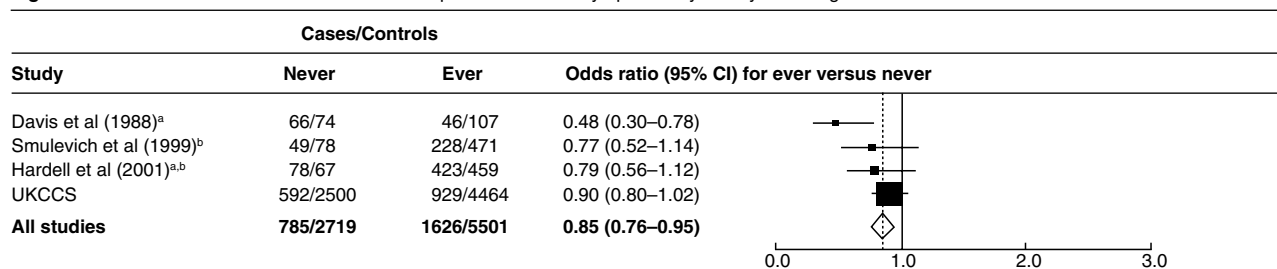
support for the role of breastfeeding in the aetiology of childhood leukaemia. Although there is weak evidence, of borderline statistical significance, of a small reduction in the odds ratio for leukaemia in children who were breastfed, a reduction in the odds ratio of a similar magnitude was also found for all childhood cancers. Furthermore, the combined results from all relevant published studies suggest that, although having been breastfed is associated with an apparent small reduction in the odds ratio for childhood leukaemia (Figure 1), it is also associated with a small reduction in the odds ratio for Hodgkin's disease (Figure 2), non-haematological childhood cancers (Figure 4) and for all childhood cancers combined (Figure 5).

Information on breastfeeding practices were reported by mothers at the time of interview. Although there are known inaccuracies in such reporting (DHS Comparative Studies, 1999), it is unknown whether this is biased between the mothers of cases and controls. Studies comparing the duration of breastfeeding reported by mothers with the duration that was recorded at the time when their children were young indicate that women tend to round the

reported durations to the nearest 6 months (DHS Comparative Studies, 1999).

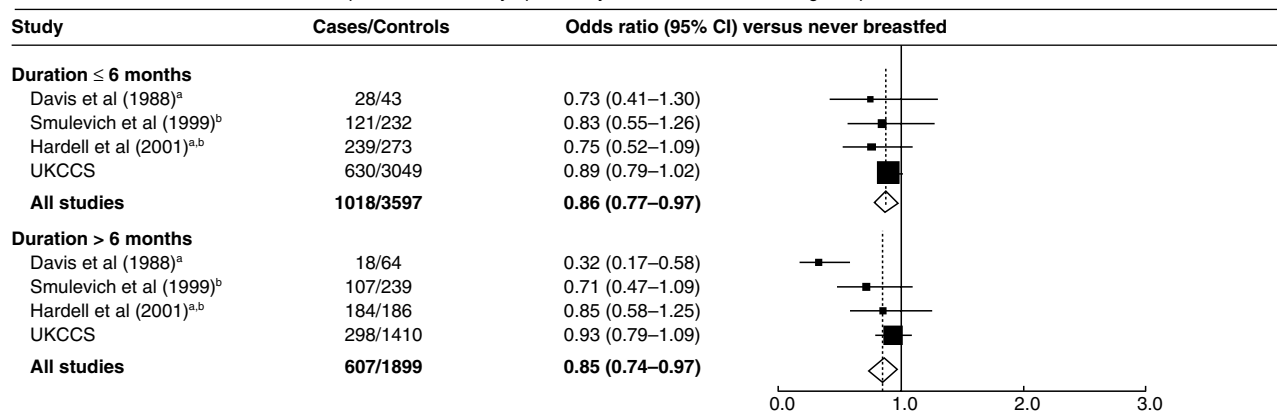
Furthermore, 8 years after the birth of a child there is an overall tendency for women to report somewhat longer durations of breastfeeding than had been recorded at the time when the child was young (Vobecky et al, 1988). A review of the role of infant feeding in the aetiology of childhood diabetes mellitus showed that in studies where there was a substantially lower participation rate in controls than cases there was a tendency for the odds ratio associated with ever having been breastfed to be reduced (Norris and Scott, 1996). Participation in the UKCCS was lower in controls than cases (UK Childhood Cancer Study, 2000). Furthermore, participating controls were of higher socio-economic status than the first choice controls eligible for this study, but whether or not these factors produced bias is unknown.

In conclusion, it is unclear whether the apparent small reduction in the risk of each type of childhood cancer reported here is a non-specific effect of breastfeeding on childhood cancer or whether it reflects some systematic bias shared by the majority of the case-control studies that have investigated aetiological factors in

Figure 4 Odds ratio for all childhood cancers except leukaemia and lymphoma by history of having been breastfed

Test for heterogeneity: $\chi^2_3 = 6.76$; $P < 0.1$

Odds ratio for all childhood cancers except leukaemia and lymphoma by duration of breastfeeding compared to never breastfed



Test for heterogeneity ≤ 6 months: $\chi^2_3 = 1.13$; $P > 0.1$; NS

Test for heterogeneity > 6 months: $\chi^2_3 = 11.64$; $P < 0.01$

Test for heterogeneity between short-term and long-term breastfeeding: $\chi^2_1 = 0.05$; $P > 0.1$; NS

^aNumbers of cases and controls derived from data presented by the authors

^b"Never" includes breastfed for < 1 month (Hardell et al 2001); < 2 months (Smulevich et al 1999)

childhood cancer. We are unable to decide which of these possibilities is the more likely.

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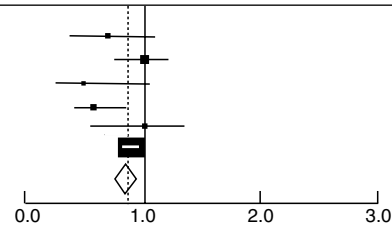
APPENDIX

Management Committee: KK Cheng, Central region; NE Day, East Anglia region; R Cartwright and A Craft, North East region; JM Birch and OB Eden, North West region; PA McKinney, Scotland; J Peto, South East region; V Beral and E Roman, South Midlands region; P Elwood, South Wales region; FE Alexander, South West region; CED Chilvers, Trent region; R Doll, Epidemiological Studies Unit, University of Oxford, Oxford; CMTaylor, Immunogenetics Laboratory, University of Manchester, Manchester; M Greaves, Leukaemia Research Fund Centre, Institute of Cancer Research; D Goodhead, Radiation and Genome Stability Unit, Medical Research Council, Harwell; FA Fry, National Radiological Protection Board; G Adams, UK Coordinating Committee for Cancer Research.

Regional Investigators: KK Cheng and E Gilman, Central region; NE Day, J Skinner and D Williams, East Anglia region; R Cartwright and A Craft, North East region; JM Birch and OB Eden, North West region; PA McKinney, Scotland; J Deacon and J Peto, South East region; V Beral and E Roman, South Midlands region; P Elwood, South Wales region; FE Alexander and M Mott,

Figure 5 Odds ratio for all childhood cancers by history of having been breastfed

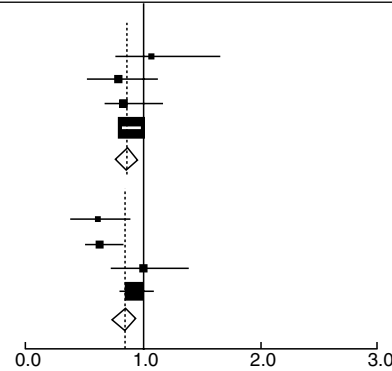
Study	Cases/Controls		Odds ratio (95% CI) for ever versus never
	Never	Ever	
Davis et al (1988) ^a	95/74	106/107	0.77 (0.51–1.16)
Hartley et al (1988)	230/464	290/586	1.00 (0.80–1.24)
Golding et al (1990)	24/53	9/46	0.43 (0.19–1.01)
Smulevich et al (1999) ^b	105/155	488/1026	0.70 (0.54–0.92)
Hardell et al (2001) ^b	119/116	716/744	1.00 (0.70–1.30)
UKCCS	1343/2500	2157/4464	0.92 (0.84–1.00)
All studies	1916/3362	3766/6973	0.90 (0.84–0.97)



Test for heterogeneity: $\chi^2_5 = 8.54$; $P > 0.1$; NS

Odds ratio for all childhood cancers by duration of breastfeeding compared to never breastfed

Study	Cases/Controls	Odds ratio (95% CI) versus never breastfed
Duration ≤ 6 months		
Davis et al (1988) ^a	59/43	1.07 (0.65–1.75)
Smulevich et al (1999) ^b	269/499	0.80 (0.60–1.06)
Hardell et al (2001) ^b	421/444	0.90 (0.70–1.30)
UKCCS	1495/3049	0.92 (0.84–1.02)
All studies	2244/4035	0.91 (0.84–0.99)
Duration > 6 months		
Davis et al (1988) ^a	47/64	0.57 (0.35–0.93)
Smulevich et al (1999) ^b	219/527	0.61 (0.46–0.82)
Hardell et al (2001) ^b	295/300	1.00 (0.70–1.40)
UKCCS	660/1410	0.90 (0.79–1.01)
All studies	1221/2301	0.85 (0.76–0.94)



Test for heterogeneity ≤ 6 months: $\chi^2_3 = 1.25$; $P > 0.1$; NS

Test for heterogeneity > 6 months: $\chi^2_3 = 9.30$; $P < 0.05$

Test for heterogeneity between short-term and long-term breastfeeding: $\chi^2_1 = 1.15$; $P > 0.1$; NS

^aNumbers of cases and controls derived from data presented by the authors

^b"Never" includes breastfed for < 1 month (Hardell et al 2001); < 2 months (Smulevich et al 1999)

South West region; CED Chilvers and K Muir, Trent region; NT Fear, G Law, J Simpson and E Roman, Leukaemia Research Fund Data Management Processing Group.

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