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Birth Size and Breast Cancer Risk: Re-analysis of Individual Participant Data from 32 Studies

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Abbreviations: BMI, body mass index; CI, confidence interval; PI, ponderal index; RR, relative risk; SD, standard deviation; SES, socioeconomic status

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ABSTRACT

Background

Birth size, perhaps a proxy for prenatal environment, might be a correlate of subsequent breast cancer risk, but findings from epidemiological studies have been inconsistent. We re-analysed individual participant data from published and unpublished studies to obtain more precise estimates of the magnitude and shape of the birth size–breast cancer association.

Methods and Findings

Studies were identified through computer-assisted and manual searches, and personal communication with investigators. Individual participant data from 32 studies, comprising 22,058 breast cancer cases, were obtained. Random effect models were used, if appropriate, to combine study-specific estimates of effect. Birth weight was positively associated with breast cancer risk in studies based on birth records (pooled relative risk [RR] per one standard deviation [SD] [= 0.5 kg] increment in birth weight: 1.06; 95% confidence interval [CI] 1.02–1.09) and parental recall when the participants were children (1.02; 95% CI 0.99–1.05), but not in those based on adult self-reports, or maternal recall during the woman's adulthood (0.98; 95% CI 0.95–1.01) (p for heterogeneity between data sources = 0.003). Relative to women who weighed 3.000–3.499 kg, the risk was 0.96 (CI 0.80–1.16) in those who weighed $<$ 2.500 kg, and 1.12 (95% CI 1.00–1.25) in those who weighed $\geq$ 4.000 kg (p for linear trend = 0.001) in birth record data. Birth length and head circumference from birth records were also positively associated with breast cancer risk (pooled RR per one SD increment: 1.06 [95% CI 1.03–1.10] and 1.09 [95% CI 1.03–1.15], respectively). Simultaneous adjustment for these three birth size variables showed that length was the strongest independent predictor of risk. The birth size effects did not appear to be confounded or mediated by established breast cancer risk factors and were not modified by age or menopausal status. The cumulative incidence of breast cancer per 100 women by age 80 y in the study populations was estimated to be 10.0, 10.0, 10.4, and 11.5 in those who were, respectively, in the bottom, second, third, and top fourths of the birth length distribution.

Conclusions

This pooled analysis of individual participant data is consistent with birth size, and in particular birth length, being an independent correlate of breast cancer risk in adulthood.

The Editors' Summary of this article follows the references.

Introduction

In 1990 Trichopoulos [1] suggested that prenatal exposure to high levels of pregnancy oestrogens might affect the risk of breast cancer. This hypothesis, which has since evolved to include other in utero hormonal and biological factors [2], sparked a considerable amount of research on the prenatal origins of breast cancer, relying mainly on birth size measures as indirect markers of the in utero environment. Published estimates of the strength of the association between birth size and breast cancer, however, have been far from consistent [3–33], and several unanswered questions remain, including uncertainty regarding the magnitude and shape of the association as well as the extent to which it may be mediated, confounded, and/or modified by known breast cancer risk factors.

We set up a collaborative group to bring together and re-analyse the original individual participant data from published and unpublished studies on pre- and perinatal factors and subsequent risk of breast cancer. This paper reports on the birth size–breast cancer association. This re-analysis provides several scientific advantages over previously published overviews [34–36]. First, it is large and comprehensive, comprising published and unpublished information on over 22,000 breast cancer cases from 32 studies, many of which have been enlarged since their original publications. Second, the availability of primary data from each individual participant provided a unique opportunity to estimate study-specific effects using similar definitions and adjustments across studies. Third, it allowed a detailed investigation of between-study heterogeneity and its possible sources. Fourth, study-specific data could be combined, if appropriate, to produce far more precise estimates of the association of birth size with breast cancer risk than those obtained from any single study.

Methods

Identification of Studies and Data Extraction

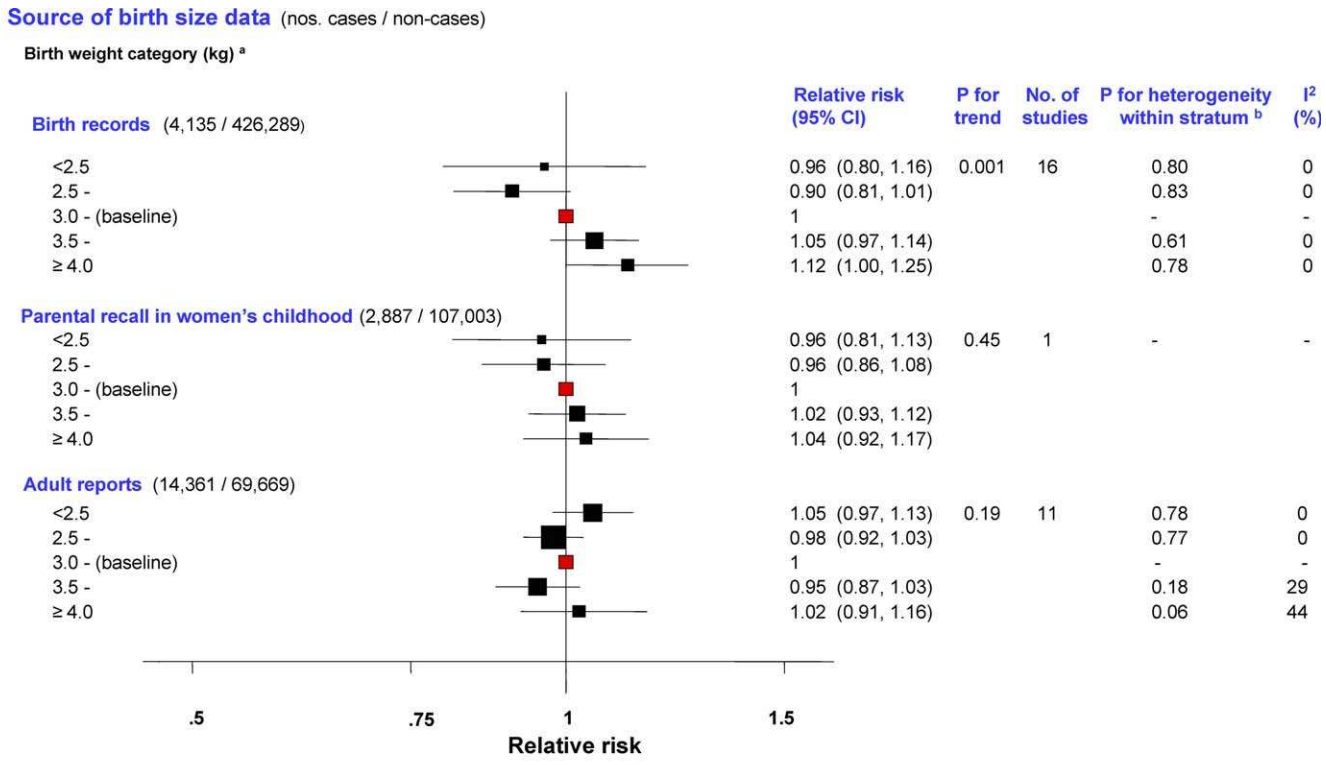
We attempted to identify studies that collected information on at least one measure of birth size and were based on incident breast cancer cases. Studies were identified by computer-assisted searches (including PubMed and Embase) up to the end of June 2007, manual searches of reference lists, personal communication with investigators, and publicity regarding our collaboration in international conferences. The search strategy used the term "breast cancer" in combination with "birth weight," "birth size," "birth length," "head circumference," "ponderal index [PI]," and "gestational age" (details of search strategy available on request). A total of 27 published and seven unpublished cohort and case-control studies [3–33] were identified, including two twin studies [10,11] and a cohort of premature or very low birth weight babies [9,21]. One study [32] was excluded because most of its participants contributed to a larger unpublished study (Swedish Young Female Breast Cancer [SYFBC], Table S1) and another [33] because its original individual participant data could not be retrieved. The included studies refer to independent study populations, with the exception of two (Seattle Breast Cancer in Young Women [BCYW] [4] and Seattle Perinatal Factors and Breast Cancer [PFBC] [7], Table S1) that were conducted in the same population but used different sources of birth size information. Data from the smallest one (Seattle PFBC; 442 cases and 393 non-cases) were excluded from the analyses whenever appropriate (as indicated in Figures 1, 2, S1, and S2). Each participating study had previously obtained all relevant ethics approvals; only nonidentifiable data were sent to the London School of Hygiene & Tropical Medicine (LSHTM).

Data on individual participants were obtained in a standardised format. They included measures of birth size (i.e., weight, length, and head circumference) and, if available, data on potential confounding factors, mediators, and effect modifiers (Tables 1, S1–S3). These individual-level data were centrally collated and crosschecked at LSHTM, with data quality queries clarified by the principal investigators. As the birth size distributions were very different in the twin studies [10,11] and in the cohort study of premature/low birth weight babies [9,21] (Tables S4–S6), these were examined separately. Analyses were restricted to singletons in the remaining studies and will hereafter be referred to as singleton studies. Participants were further excluded from all studies if they had a known history of cancer other than nonmelanoma skin cancer at entry into the study (i.e., at recruitment/start of follow-up), and if all birth size data were missing. For the two Nurses Health Studies [31], only nested case-control data were provided for the pooled analyses. Because of these exclusions and updated follow-up/recruitment in some studies [22,23,27,31], study sizes may differ from those reported in the original study-specific publications.

Statistical Methods

The primary exposure of interest was birth size as measured by weight (kg), length (cm), head circumference (cm), and PI (defined as weight [kg]/height [m]^3) at birth. These measures were examined as quantitative (for increments of approximately one standard deviation [SD], i.e., 0.5 kg for weight, 2 cm for length, 1.5 cm for head circumference, and 2.5 kg/m^3 for PI) and as categorical variables. In the analyses of singleton studies, birth weight was categorised according to commonly used categories ($<$2.500, 2.500–2.999, 3.000–3.499 [baseline], 3.500–3.999, and $\geq$4.000 kg); for four studies [29–31] birth weight data were only available as predefined categories equivalent to these except in one study [30] in which the three middle categories were collapsed into a single one (Table S4). Categories for birth length, head circumference, and PI were defined by quartiles of their overall distributions among all participants in cohort studies and non-cases in case-control studies. Study-specific quartiles for birth weight, length, and PI (no data were available for head circumference) were similarly generated in each twin study [10,11] and in the cohort of premature/low birth weight babies [21].

Assessment of birth size–breast cancer associations was performed primarily using a two-stage approach [37,38]. Study-specific effects were first estimated and, if appropriate, pooled using a random effects model under the assumption that individual studies estimate different exposure effects because of potential heterogeneities in populations and data quality, but with the interest focused on their mean value. These pooled effects will hereafter be referred to as "two-stage," with the standard errors calculated from the inverse of the sum of the adjusted weights [38]. Study-specific effects were estimated as rate ratios in cohort studies and odds ratios



[a] Contributing studies (abbreviations as in Supporting Table S1): Birth records: SPNFBC, NYSEOBC, MRC NSHD, HBCS I, PSWG, TBPCCS, DPCCS, UBCoS Multigen, CBCS, MDCS, SOUHCB, NCI DES, ACONF, HBCS II, HBCS III, SYFBC; Parental recall in women's childhood: CSHRR; Adult reports: NHS I, NHS II, Seattle BCYW, Seattle BCMW, SBCS, CmsBCS, WEB, PBCS, UKWCS, CARE, EPIC-Norfolk (excludes Seattle PFBC)

[b] Between source of birth size data heterogeneity for categorical birth weight: P=0.49 for category <2.5; P=0.46 for category 2.5-; P=0.09 for category 3.5-; and P=0.48 for category ≥4.0; for linear trend: P=0.002.

Figure 1. Minimally Adjusted Pooled Breast Cancer RRs Stratified by Source of Birth Size Data in Relation to Categorical Birth Weight (Singleton Studies Only)

The area of the black squares is inversely proportional to the variance (on the log scale).
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in case-control studies (hereafter referred to as relative risks [RRs]) using models appropriate for each study design (i.e., Cox proportional hazard or Poisson regression for cohort studies; conditional logistic regression for nested [all based on risk-set sampling] and individually matched case-control studies; and logistic regression for frequency-matched case-control studies) [39].

The analytical time scale for cohort studies was age, with the beginning of the follow-up defined as the age at recruitment into the study or the age when outcome ascertainment became possible (e.g., through linkage to cancer registries). Follow-up ended at the age of breast cancer diagnosis, death, emigration, or last follow-up, whichever occurred earlier. RRs for cohort studies were thus adjusted for age at diagnosis. The proportional hazards assumption was checked in Cox models graphically, by comparing stratum-specific cumulative incidence curves before fitting the models, and formally via the test of proportionality based on Schoenfeld residuals [40]. In Poisson models the assumption of time-constant effects (i.e., proportionality) was assessed by testing the significance of interactions between birth size measures and age. RRs for cohort studies were additionally adjusted for calendar year by stratification. The matching variables specified for each case-control study (e.g., year of birth, calendar period, recruitment centre, area of residence, or ethnicity) were accounted for in the estimation of RRs either through matched analyses (for individually matched studies) or adjustment (for frequency-matched studies). The RRs quoted in the text refer to these minimally adjusted RRs unless otherwise specified. The statistical significance of each birth size–breast cancer association, and of quadratic departures from the assumption of linearity of effects, were assessed within each study by likelihood ratio tests and for pooled estimates by Wald tests. Possible sources of between-study heterogeneity were investigated and formally tested using the Cochran Q statistic and the I^2 quantity based on standard cut-off points [41,42]. Two-stage pooled estimates of groups of RRs were only calculated if there was no statistically significant evidence of systematic heterogeneity. The influence of individual studies was assessed by sequentially dropping each one before pooling study-specific estimates.

To increase statistical precision, one-stage pooled analyses, in which overall pooled estimates are derived from a single model, were also conducted on the subset of cohort studies of singleton women with birth records information. Random effects multivariable Cox regression (frailty) models [43], which account for within study clustering, were fitted to assess exposure-response relationships for each birth size variable and to estimate their joint associations with breast

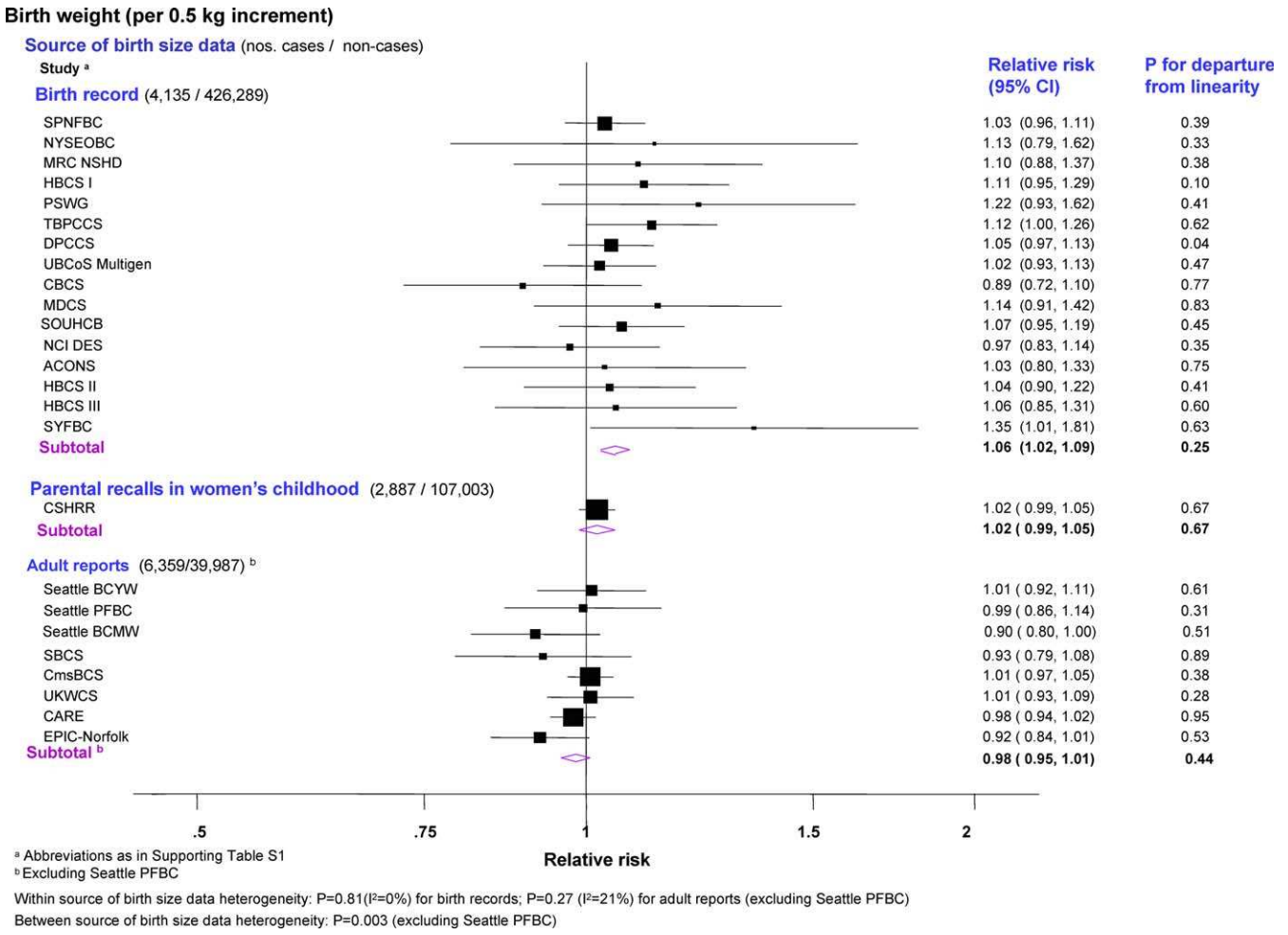

Figure 2. Minimally Adjusted Study-Specific and Pooled Breast Cancer RRs Stratified by Source of Birth Size Data in Relation to Continuous Birth Weight (Singleton Studies Only)

The area of the black squares is inversely proportional to the variance (on the log scale).
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cancer risk. These models were also used to estimate the breast cancer cumulative incidence curve corresponding to the baseline birth length category (i.e., 49.0–49.9 cm). Cumulative incidence curves for the other birth length categories were obtained by multiplying the baseline curve by the corresponding category-specific RRs. A similar approach was used to calculate cumulative incidence curves for the five birth weight categories (taking the 3.000–3.999 kg category as the baseline).

As the availability and classification of potential confounders varied from study to study, adjustment for confounding was performed separately for each variable, or group of variables, within each study and then pooled using the two-stage procedure. Consequently, the number of cases and non-cases involved in each analysis varied accordingly. To assess whether the birth size associations were modified by age, analyses were stratified by age at breast cancer diagnosis (<45 y; 45–54 y, ≥55 y) for case-control studies and by a time-changing indicator of current age for cohort studies. Analyses were similarly stratified by menopausal status at diagnosis in the subset of studies with this information.

Two-stage and one-stage pooled analyses were repeated after excluding extreme birth size observations (i.e., values outside the singleton/twins/premature-specific means ± 4 SDs). Small study bias was assessed via the Egger funnel plot asymmetry test [44] and other forms of publication bias by meta-regression. All statistical analyses were performed in Stata [45]. All tests of significance are two-sided.

Results

Characteristics of the Study Participants

A total of 32 studies contributed to these analyses, including 22,058 women with newly diagnosed invasive or in situ breast cancer and 604,854 non-cases. The characteristics of the participating studies are summarised in Table 1 (further details in Tables S1–S3). Information on birth weight was based on birth records, parental recall when the women were 6–7 y old, mother's recall during the woman's adulthood, and on self-reports in adulthood. In analyses by source of birth weight data, the two last categories produced similar effect estimates and thus were combined into one single category of adult reports. Data on categorical birth weight were available for all 32 studies, whereas data on continuous birth weight and on other measures of birth size were available for a smaller number of studies (Tables 1 and S2).

Table 1. Summary Characteristics of the 32 Participating Studies

Characteristic	Category	Sub-Category	Number of Studies	Cases		Non-Cases		All	
				n	Percent	*n*	Percent	*n*	Percent
All	—	—	**32**	22,058	100	604,854	100	626,912	100
Study design	**Cohort** [a]	—	**14**	5,116	23.2	560,483	92.7	565,599	90.2
	Nested case-control	—	**3**	5,247	23.8	26,196	4.3	31,443	5.0
	Individually matched case-control[b]	—	**6**	2,517	11.4	7,608	1.3	10,125	1.6
	Frequency matched case-control	—	**9**	9,178	41.6	10,567	1.8	19,745	3.2
Year of publication	**1996–2000**	—	**8**	7,755	35.2	32,517	5.4	40,272	6.4
	2001–2007	—	**17**	10,445	47.3	149,856	24.8	160,301	25.6
	Unpublished	—	**7**	3,858	17.5	422,481	69.8	426,339	68.0
Geographical region	**Western Europe**	**Nordic countries**[c]	**15**	6,759	30.6	521,653	86.2	528,412	84.3
	—	**UK**	**4**	805	3.7	40,758	6.7	41,563	6.6
	Eastern Europe	**Poland**	**1**	1,764	8.0	1,792	0.3	3,556	0.6
	North America	**US**	**11**	12,488	56.6	40,348	6.7	52,836	8.4
	Asia	**China**	**1**	242	1.1	303	0.1	545	0.1
Ethnicity	—	—	**32**	—	—	—	—	—	—
	European descent	—	**—**	19,888	90.2	597,529	98.8	617,417	98.5
	Non-European descent	—	**—**	1,569	7.1	3,545	0.6	5,114	0.8
	Missing	—	**—**	601	2.7	3,780	0.6	4,381	0.7
Source of birth data	**Birth records**	—	**19**	4,368	19.8	427,789	70.7	432,157	68.9
	Parental recall when woman was a child	—	**1**	2,887	13.1	107,003	17.7	109,890	17.5
	Adult reports[d]	—	**12**	14,803	67.1	70,062	11.6	84,865	13.5
Year of birth	—	—	**32**	—	—	—	—	—	—
	<1940	—	**—**	9,367	42.5	59,259	9.8	68,626	11.0
	1940–1949	—	**—**	6,450	29.2	70,962	11.7	77,412	12.4
	1950–1959	—	**—**	4,522	20.5	58,302	9.6	62,824	10.0
	1960–1969	—	**—**	588	2.7	20,085	3.3	20,673	3.3
	1970–	—	**—**	85	0.4	393,565	65.1	393,650	62.8
	Missing[e]	—	**—**	1,046	4.7	2,681	0.4	3,727	0.6
Age at diagnosis (y)	—	—	**32**	—	—	—	—	—	—
	<30	—	**—**	312	1.4	—	—	—	—
	30–39	—	**—**	2,951	13.4	—	—	—	
	40–49	—	**—**	5,154	23.4	—	—	—	—
	50–59	—	**—**	5,904	26.8	—	—	—	—
	60–	—	**—**	6,672	30.3	—	—	—	—
	Missing[e]	—	**—**	1,065	4.8	—	—	—	—
Year of diagnosis	—	—	**32**	—	—	—	—	—	—
	1958–1979	—	**—**	776	3.5	—	—	—	—
	1980–1989	—	**—**	3,355	15.2	—	—	—	—
	1990–1999	—	**—**	11,825	53.6	—	—	—	—
	2000–	—	**—**	4,591	20.8	—	—	—	—
	Missing[e]	—	**—**	1,511	6.9	—	—	—	—
Birth weight (kg)[f,g]	—	—	**29**	—	—	—	—	—	—
	<2.500	—	**—**	1,659	7.6	28,654	4.8	30,313	4.9
	2.500–2.999	—	**—**	4,117	18.9	91,327	15.1	95,444	15.3
	3.000–3.499	—	**—**	9,402	43.1	228,763	37.9	238,165	38.1
	3.500–3.999	—	**—**	4,626	21.2	182,697	30.3	187,323	30.0
	≥4.000	—	**—**	2,021	9.3	71,913	11.9	73,934	11.8
Birth length (cm)[f,h]	—	—	**11**	—	—	—	—	—	—
	<49.0	—	**—**	469	13.0	82,677	20.0	83,146	20.0
	49.0–49.9	—	**—**	412	11.4	63,974	15.5	64,386	15.5
	50.0–50.9	—	**—**	764	21.2	90,293	21.9	91,057	21.9
	≥51.0	—	**—**	1,968	54.5	175,968	42.6	177,936	42.7
Head circumference (cm)[h,i]	—	—	**9**	—	—	—	—	—	—
	<33.0	—	**—**	99	6.7	41,647	10.3	41,746	10.3
	33.0–33.9	—	**—**	214	14.4	66,779	16.5	66,993	16.4
	34.0–34.9	—	**—**	387	26.1	109,372	26.9	109,759	26.9
	≥35.0	—	**—**	785	52.9	188,180	46.4	188,965	46.4

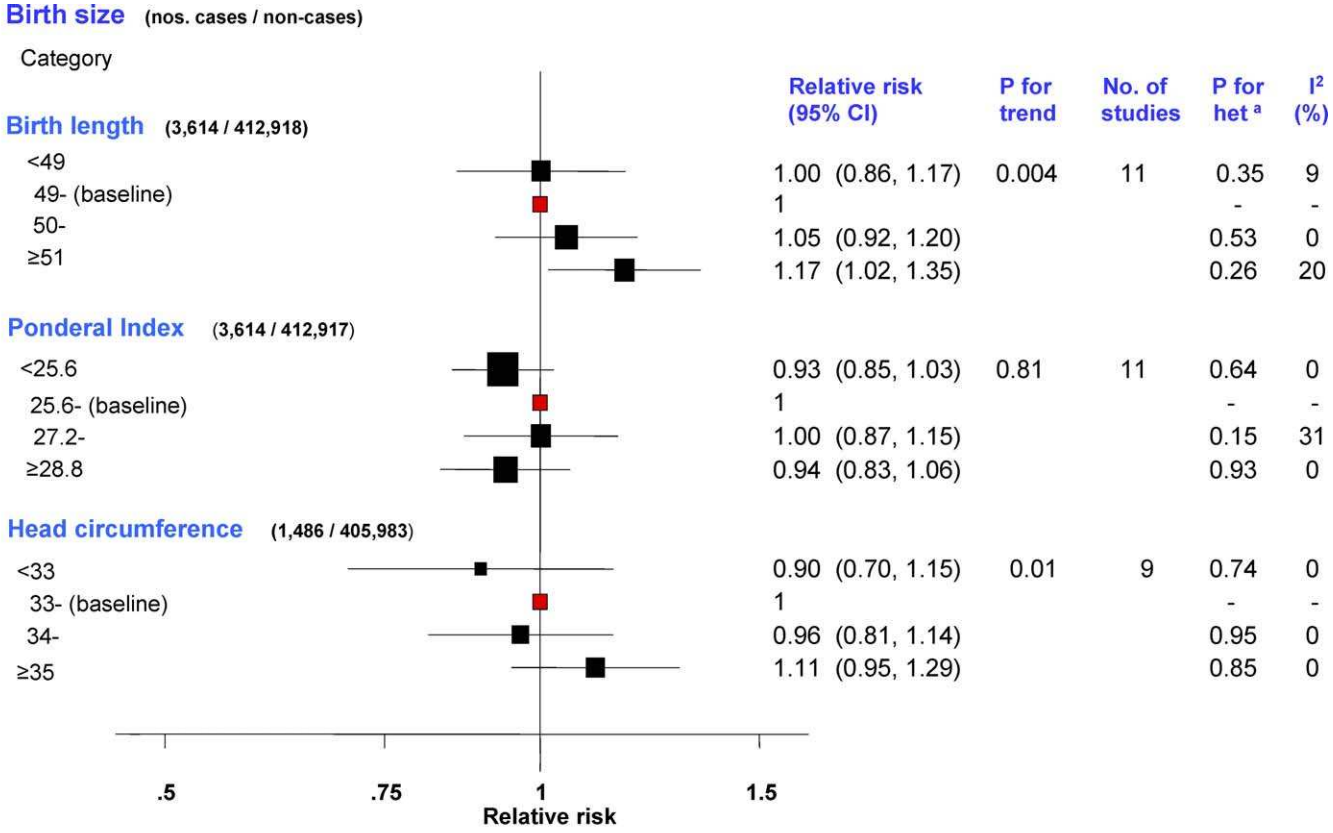
[a]Includes 47 cases and 1,319 non-cases from a Swedish cohort of premature/low birth weight babies (SPVLBW).
[b]Includes 186 cases and 186 non-cases from two Swedish twin studies (Swedish Like-Sexed Twin Study [SLSTS] and Swedish Opposite-Sexed Twin Study [SOSTS]).
[c]Denmark, Finland, Norway, Sweden.
[d]Based on self-reports in adulthood except for 20% of the participants in one small cohort (National Cancer Institute Diethylstilbestrol Combined Cohort Study [NCI DES]) and all individuals in two frequency-matched case-control studies (Seattle Perinatal Factors and Breast Cancer [PFBC]: 442 cases; 393 non-cases; Shanghai Breast Cancer Study [SBCS]: 242 cases; 303 non-cases) in which birth size data were based on maternal recalls during the woman's adulthood.
[e]Missingness was mainly due to one study for which no information was available on date of birth and diagnosis.
[f]Values shown in the table are for singletons; corresponding categorical distributions in the two twin studies (SLSTS and SOSTS) and in the cohort of premature/low birth weight babies (Swedish cohort of Premature and Very Low Birth Weight [SPVLBW]) are given in Tables S4 and S5.
[g]Median (25th and 75th percentile) for continuous birth weight (in kg), in all the 25 singleton studies with such data, is 3.300 (2.977, 3.639) in cases and 3.400 (3.070, 3.730) in non-cases; in

the 16 studies with birth records: 3.400 (3.060, 3.730) in cases and 3.430 (3.110, 3.750) in non-cases; in the study with parental recall when women were 6-7 y old: 3.300 (3.000, 3.650) in cases and 3.300 (3.000, 3.600) in non-cases; in the eight studies with adult reports: 3.182 (2.863, 3.629) in cases and 3.175 (2.889, 3.629) in non-cases.
[h]Categories based on quartiles of the overall distribution among all participants in cohort studies and non-cases in case-control studies. The median (25th and 75th percentile) of continuous birth length (in cm) is 51 (50, 52) in cases and 50 (49, 51) in non-cases; the median (25th and 75th percentile) of continuous head circumference (in cm) is 35 (34, 36) in cases and 34 (33, 35) in non-cases.
[i]Data available only in singleton studies.
doi:10.1371/journal.pmed.0050193.t001

Birth Size and Breast Cancer Risk

Two-stage pooled analyses of RRs, stratified by source of birth size information, showed that the risk of breast cancer in singletons increased with increasing birth weight categories in studies based on birth records or on parental recalls in childhood (although significant only for the first, p for linear trend (p_t) = 0.001), but not in those based on adult reports (Figure 1; study-specific estimates available in Table S4). Continuous analysis of birth weight (restricted to 25 studies; Figure 2) revealed a similar pattern. A 0.5-kg increment (about one SD) in birth weight was associated with a statistically significant increase in risk in studies based on birth records (pooled RR = 1.06 [95% confidence interval (CI) 1.02–1.09]; $p = 0.002$) and a borderline significant increase in those based on parental recalls when the women were children, but not in studies based on adult reports, with statistical evidence of heterogeneity between birth weight data sources ($p = 0.003$). Categorical and continuous analyses of birth weight stratified by study design revealed a positive trend in risk with increasing birth weight categories in data from cohort, nested case-control, and individually matched case-control studies (albeit only statistically significantly for the latter), but not in data from frequency-matched case-control studies (Figures S1 and S2). There was evidence of between study-design heterogeneity of the continuous birth weight effect ($p = 0.03$), but it was accounted for by differences in birth data sources when examined via meta-regression of the birth weight RRs on both study design and birth data sources (p-value for study-type heterogeneity = 0.67; for adult reports versus other sources = 0.08).

Data on birth length and head circumference were available, respectively, for 11 and nine singleton studies, all derived from birth records. Two-stage pooled analyses stratified by study design showed no statistical evidence of heterogeneity within or between strata in either categorical or continuous analyses (Figures 3, 4, and S4; study-specific estimates available in Tables S5 and S7) and, thus, overall pooled RRs were estimated. Breast cancer risk increased with increasing birth length ($p_t = 0.004$; Figure 3), with women ≥ 51 cm long at birth having 17% (95% CI 2%–35%) higher risk



[a] P for heterogeneity within stratum
Contributing studies for birth length and PI analyses as in Figures 4 and S3; for head circumference as in Figure S4.

Figure 3. Minimally Adjusted Pooled Breast Cancer RRs in Relation to Categorical Birth Length, PI, and Head Circumference (Singleton Studies Only)
The area of the black squares is inversely proportional to the variance (on the log scale).
doi:10.1371/journal.pmed.0050193.g003

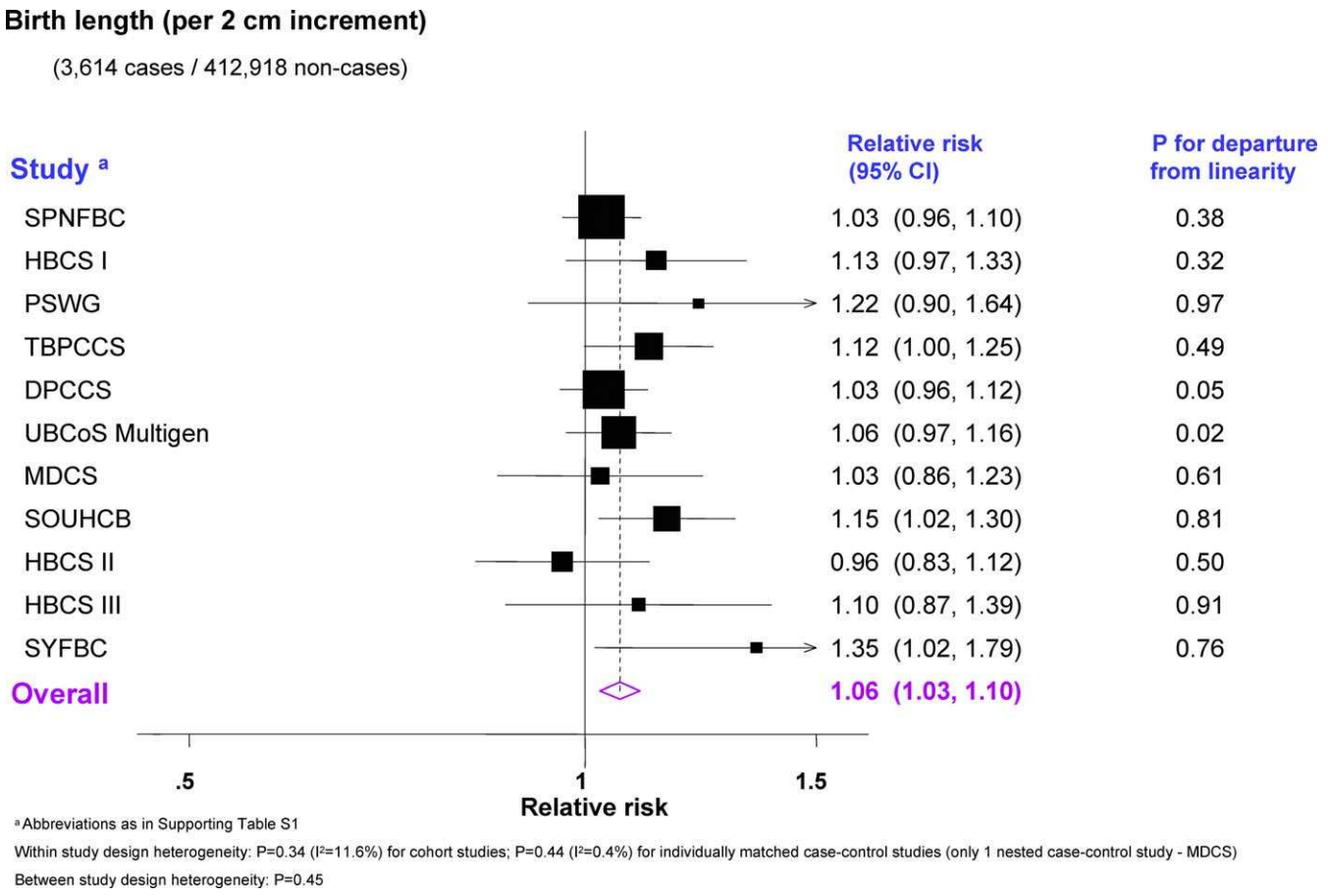


Figure 4. Minimally Adjusted Study-Specific and Pooled Breast Cancer RRs in Relation to Continuous Birth Length (Singleton Studies Only)
The area of the black squares is inversely proportional to the variance (on the log scale).
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of developing breast cancer relative to those in the baseline category. Women with a head circumference ≥35 cm had an 11% increase (95% CI −5% to 29%) in risk relative to those in the baseline category, whereas those with a head circumference <33 cm had a 10% decrease (95% CI −30% to 15%) ($p_t = 0.01$) (Figure 3). These estimates corresponded to pooled RRs of 1.06 (95% CI 1.03–1.10) per one SD (= 2 cm) increment in birth length (Figure 4) and 1.09 (1.03–1.15) per one SD (= 1.5 cm) increment in head circumference (Figure S4). In contrast, there was no association with categorical (Figure 3) or continuous PI (pooled RR per 2.5 kg/m^3 increment = 1.01; 0.97–1.04; Figure S3; study-specific estimates available in Table S6).

The two twin case-control studies, both based on birth records, showed stronger associations of breast cancer risk with continuous birth weight (pooled RR per one SD increment = 1.57; 95% CI 1.20–2.07) and continuous birth length (1.23; 1.01–1.49) than those found among singleton studies, and a positive association with PI (1.36; 1.06–1.75) that was not observed in the latter (Figure S5). No association

Table 2. Separate (Univariable) and Mutually Adjusted (Multivariable) Breast Cancer Incidence Rate Ratios for Continuous Weight, Length, and Head Circumference at Birth in Singletons

Variable	Univariable		Multivariable	
	Rate Ratio[a]	(95% CI)	Rate Ratio[a]	(95% CI)
Birth weight (per 0.5 kg increment)	1.07	(1.01–1.14)	0.98	(0.89–1.08)
Birth length (per 2 cm increment)	1.10	(1.03–1.16)	1.09	(1.00–1.19)
Head circumference (per 1.5 cm increment)	1.07	(1.01–1.14)	1.03	(0.96–1.12)

[a]Estimated using random effects Cox proportional hazards models fitted on the age timescale on seven cohort studies (1,210 cases/404,970 non-cases) with continuous birth size data from birth records (Population Study of Women in Gothenburg [PSWG], Helsinki Birth Cohort Study [HBCS] I, II, and III, Uppsala Birth Cohort Multigenerational Study [UBCoS Multigen], Saint Olav's University Hospital Birth Cohort [SOUHBC], and The Swedish Young Female Breast Cancer Study [SYFBC]).
doi:10.1371/journal.pmed.0050193.t002

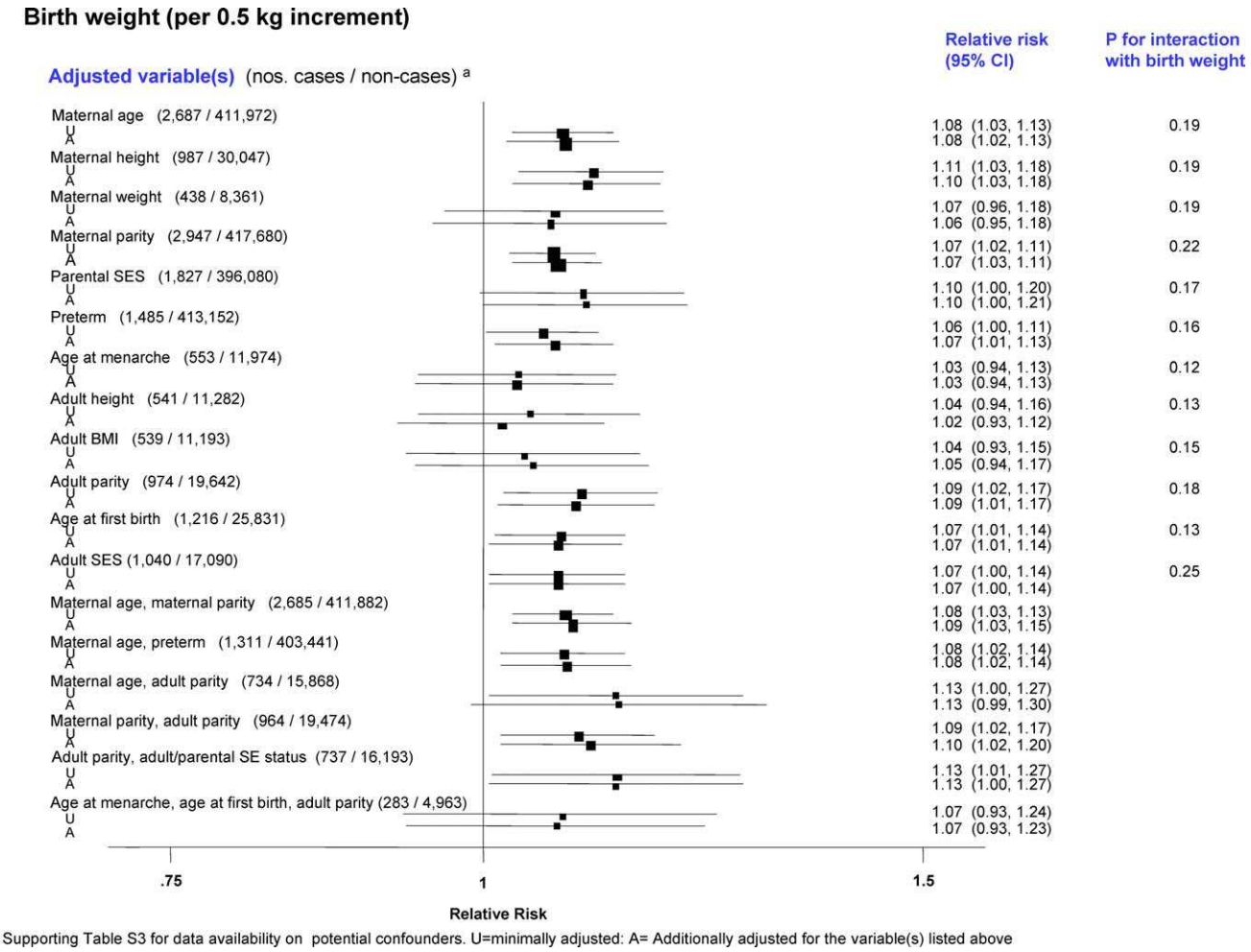

Figure 5. Pooled Breast Cancer RRs, Minimally Adjusted and Further Adjusted for Various Potential Confounding Factors in Relation to Continuous Birth Weight (Restricted to Singleton Studies Based on Birth Records)

Adjustments for maternal age (continuous), maternal height (continuous), maternal weight (continuous), maternal parity (categorical: 0, 1, 2, ≥3), parental SES (study-specific categories: paternal SES for Medical Research Council National Survey of Health and Development [MRC NSHD]; maternal SES for Saint Olav's University Hospital Birth Cohort [SOUHCB], Trondheim & Bergen Population-based Case-Control Study [TBPCCS], and Swedish study on Pre-Natal Factors and Breast Cancer [SPNFBC]; and parental/paternal occupation for Carolina Breast Cancer Study [CBCS]), preterm (binary), age at menarche (categorical: <12 y, 12.0–12.9 y, ≥13 y), adult height (continuous), adult BMI (continuous), adult parity (categorical: 0, 1, 2, ≥3), age at first birth (categorical: nulliparous, <20 y, 20–29 y, ≥30 y), and adult SES (study-specific categories: adult SES for MRC NSHD, Helsinki Birth Cohort Study [HBCS] I, Population Study of Women in Gothenburg [PSWG]; and occupation for Malmö Diet and Cancer Study [MDCS]).
doi:10.1371/journal.pmed.0050193.g005

between any of these birth size measures and breast cancer risk was found in the cohort study of premature/low birth weight babies, which was also based on birth records (Figure S5; study-specific estimates available in Tables S4–S6).

Shape of the Birth Size–Breast Cancer Association in Singletons

In the subset of singletons in cohort studies based on birth records, all with continuous birth size data, the one-stage pooled dose-response plot for birth weight suggested a nonlinear (quadratic) relationship, with RR for women at the extremes of the distribution being slightly lower than predicted by the linear model. However, the test for deviation from linearity was not statistically significant ($p = 0.20$; Figure S6). The plots for birth length and head circumference were more consistent with a linear association (p-value for departure from linearity: 0.39 and 0.58, respectively; Figure S6).

Independence of Effects of the Various Birth Size Measures in Singletons

Birth weight and birth length were strongly correlated with each other ($r = 0.79$, $p < 0.001$, in the subset of cohorts with birth record data), and both were correlated with head circumference ($r = 0.61$ and $r = 0.51$, respectively; $p < 0.001$ for both). Simultaneous one-stage pooled analysis of these three variables in the subset of cohort studies of singletons based on birth records showed that birth length was the measure with the strongest independent association with breast cancer risk (Table 2). The association with birth weight disappeared after adjustment for birth length and head circumference, while the association with birth length persisted, and remained of borderline significance, after adjustment for birth weight and head circumference.

In this subset of cohort studies, all from developed countries, the cumulative incidence of breast cancer by age

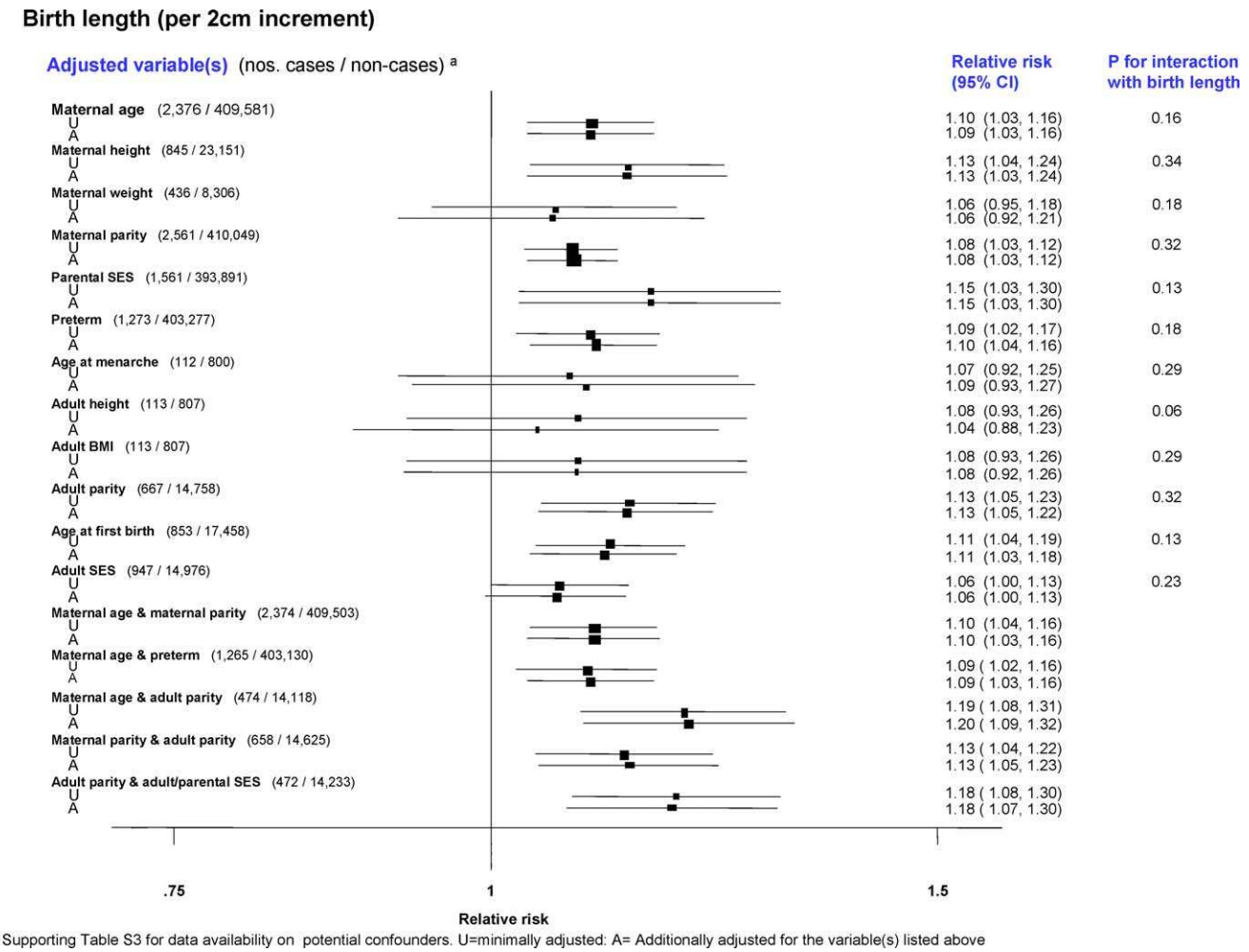

Figure 6. Pooled Breast Cancer RRs, Minimally Adjusted and Further Adjusted for Various Potential Confounding Factors in Relation to Continuous Birth Length (Restricted to Singleton Studies Based on Birth Records)

Adjustments for maternal age (continuous), maternal height (continuous), maternal weight (continuous), maternal parity (categorical: 0, 1, 2, ≥3), parental SES (study-specific categories: paternal SES for Medical Research Council National Survey of Health and Development [MRC NSHD]; maternal SES for Saint Olav's University Hospital Birth Cohort [SOUHCB], Trondheim & Bergen Population-based Case-Control Study [TBPCCS] and Swedish study on Pre-Natal Factors and Breast Cancer [SPNFBC]; and parental/paternal occupation for Carolina Breast Cancer Study [CBCS]), preterm (binary), age at menarche (categorical: <12 y, 12.0–12.9 y, ≥13 y), adult height (continuous), adult BMI (continuous), adult parity (categorical: 0, 1, 2, ≥3), age at first birth (categorical: nulliparous, <20 y, 20–29 y, ≥30 y), and adult SES (study-specific categories: adult SES for MRC NSHD, Helsinki Birth Cohort Study [HBCS] I, Population Study of Women in Gothenburg [PSWG]; and occupation for Malmö Diet and Cancer Study [MDCS]).

doi:10.1371/journal.pmed.0050193.g006

80 y is estimated to be 10.0 per 100 singleton women in those who were shorter than 49 cm at birth and 10.0, 10.4, 11.5, respectively, per 100 singleton women who were 49.0–49.9, 50.0–50.9, and ≥51.0 cm at birth. Similarly, and as data on birth weight are more widely available, the cumulative incidence is estimated to change from 10.0 per 100 singleton women in those who weighed less than 2.500 kg at birth to 9.4, 10.4, 10.9, and 11.6, respectively, per 100 singleton women who weighed 2.500–2.999, 3.000–3.499, 3.500–3.999, and ≥4.000 kg at birth. About 45%–50% of women in these cohorts were ≥ 50 cm long, or ≥ 3.5 kg, at birth. If the observed effect estimates are valid, and assuming that birth size reflects some underlying process that is causally related to breast cancer, it is estimated that about 4.5%–5.0% of breast cancers by age 80 y in these study populations are attributable to length ≥ 50 cm, or weight ≥ 3.5 kg, at birth.

Consistency of the Findings

There was little evidence that the associations between the various birth size variables and breast cancer risk in singletons were confounded or modified by other peri- and postnatal factors in data from birth records (Figures 5 and 6), or adult reports (Figure S7). Even variables that were significantly associated with birth size, such as maternal height and maternal parity (e.g., correlation coefficients with birth length: $r = 0.24$ and $r = 0.07$, respectively; $p < 0.001$ for both), woman's adult height ($r = 0.29$, $p < 0.001$) and parental and woman's adulthood measures of socioeconomic status (SES) ($p < 0.01$ and $p < 0.05$, respectively), did not explain the positive association with breast cancer risk. In particular, adjustment for maternal height or the woman's adult height attenuated only slightly the effects of birth weight and length (Figures 5 and 6). Similarly, adjustment for the woman's adult

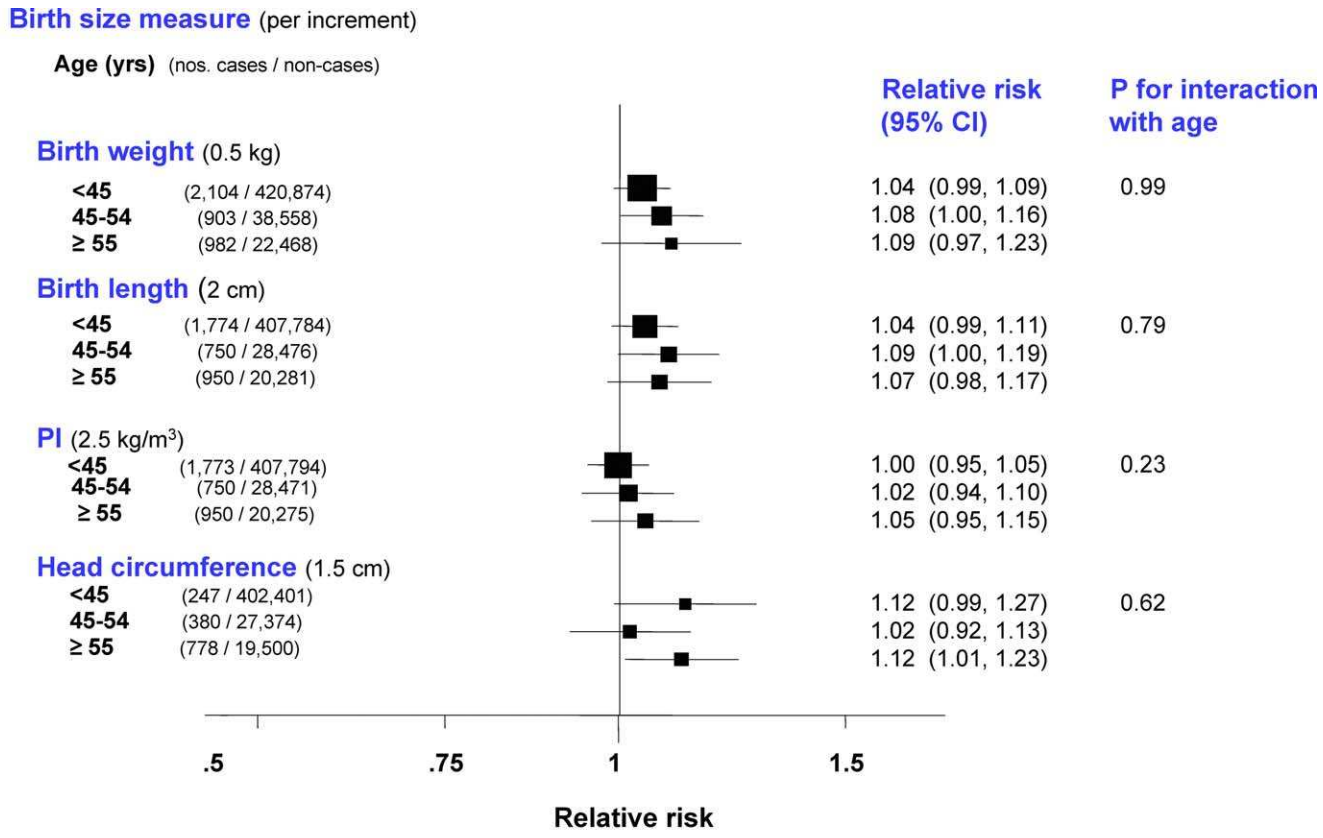

Figure 7. Minimally Adjusted Pooled Breast Cancer RRs in Relation to Continuous Weight, Length, PI, and Head Circumference at Birth Stratified by Age (Restricted to Singleton Studies Based on Birth Records)
doi:10.1371/journal.pmed.0050193.g007

body mass index (BMI) did not affect the birth size effects (Figures 5 and 6). Neither continuous gestational age (pooled RR per 1 wk increment = 0.99; 95% CI 0.96–1.03) or being preterm (unpublished data) was associated with breast cancer risk. Few studies collected data on the woman's use of oral contraceptives (OC) or hormone replacement therapy (HRT) (Table S3), but their findings indicate that the birth size–breast cancer associations reported here are unlikely to have been confounded by ever use of these exogenous hormones (minimally adjusted and OC-adjusted pooled RRs per 2 cm increment in birth length: 1.14 (95% CI 0.82–1.61) and 1.14 (0.82–1.61), respectively; similarly, minimally adjusted and HRT-adjusted pooled RRs: 1.08 (0.92–1.25) and 1.07 (0.86–1.34), respectively).

The effect of categorical (Figure S8; study-specific estimates available in Table S8) or continuous birth weight (Figure 7) was not modified by age (defined as current age for cohort studies and age at diagnosis for case-control studies). There was also no evidence of any interaction between age and continuous birth length, PI, or head circumference (Figure 7). Menopausal status was known for 33% of the cases, but analysis restricted to the subset of studies with this information showed no difference in the birth size effects between pre- and postmenopausal women.

Sensitivity analysis showed that none of the categorical or continuous pooled birth size associations reported here was dominated by any single study. The association of birth size with breast cancer risk in birth record data persisted after exclusion of 1,510 in situ tumours among the case-control studies and censoring 28 diagnoses of in situ tumours in cohort studies (6% of all cases). Birth cohort (defined by the median year of birth in each study) and geographical area (North America, Western Europe, Eastern Europe, and Asia) did not explain any further between-study heterogeneity beyond that accounted for by source of birth size data.

The findings did not appear to be affected by study size bias (Egger funnel plot asymmetry test: $p = 0.20$). There was no statistical evidence of publication bias among the studies included in these analyses (Table S9).

Discussion

We analysed individual participant data on over 22,000 women with breast cancer from 32 epidemiological studies of the association between birth size and breast cancer. This pooled analysis provided evidence of moderate positive trends in the risk of breast cancer among studies based on birth records, with risk increasing with increasing birth weight, length, and head circumference. Source of birth size data was identified as the main source of between-study heterogeneity, with positive associations of birth size with breast cancer risk found only in data from birth records and,

to a lesser extent, in data from parental recalls when the women were aged 6–7 y, but not in data from self-reports or maternal recalls when the women were adults.

Simultaneous adjustment for weight, length and head circumference at birth showed that length, perhaps as a measure of linear growth, was the strongest predictor of risk despite the fact that the latter tends to be more poorly measured than weight or head circumference [46,47]. Such finding should not however be overinterpreted because of the strong collinearities among these variables.

The birth size effect did not appear to be confounded or modified by known breast cancer risk factors. In particular, and contrary to previous reports [18,23,31], there was no evidence that the birth size effect was stronger for premenopausal breast cancer. The association between birth size and breast cancer risk was observed consistently in women born over a period of several decades, and in different geographical areas.

Strengths and Limitations

Because of its large size this pooled analysis provided greater statistical power than any of the contributing individual studies and, therefore, more precise estimates than those previously published. It was also possible to standardise the way in which the exposure and confounding variables were defined and coded, the choice of which variables to control for, and the type of analysis conducted, thereby removing these potential sources of heterogeneity across studies. The possible influence of bias needs to be considered. Publication bias is a general problem for pooled analyses. Because inclusion in this pooled analysis was not dependent on publication, this re-analysis is likely to have been less affected by publication bias than meta-analyses of the published literature. The two nonparticipating studies [32,33] showed no association between birth weight and breast cancer, but they were based on small numbers of cases (12 and 74, respectively). We found no evidence of publication bias when examining the effect of study size, or year and type of publication.

Bias within studies, such as information or selection bias, might also have influenced the results. Exposure measurement error could have been a problem as we found evidence of statistical heterogeneity of effects by source of birth size data. Reports of birth weight by the participants themselves in adulthood, or by their mothers when the participants were adults, are likely to be more prone to measurement error than those based on birth records or on parental recall when the participants were children. This remark is consistent with the clear digit preference patterns found in the birth weight data reported by the women themselves, or their parents, but not in those from birth records (unpublished data). These errors are, however, likely to be mainly nondifferential and so likely to impose an attenuating bias in univariable analyses that use these sources of data as exposure measurements. Although differential misclassification is possible in studies in which exposure information was collected after diagnosis, it is unlikely that participants would have been aware of a possible link of birth size with breast cancer risk. Thus, the variability in results across the various sources of birth weight data might simply reflect different degrees of attenuation of the true birth weight effect due to different levels of random exposure misclassification. Selection bias could have been a problem, particularly in case-control studies. Although all case-control studies in this re-analysis were population-based, selection bias might still have occurred in studies with relatively low participation. We did not find evidence that studies with low participation levels provided systematically discrepant results (p for heterogeneity = 0.88). Bias due to incomplete follow-up is unlikely because all cohorts had high degrees of completeness.

Finally, the impact of potential confounding factors was evaluated by comparing effect estimates unadjusted and adjusted for single or multiple potential confounders. The results showed little variation. The availability of information on many potential confounding variables is a major strength of our pooled analysis. One drawback is that information for many of them was restricted to a few studies and therefore we could only assess the impact of each potential confounder separately, or only of groups with few of them at a time, when pooling data. Moreover, some of these factors were probably measured with some error. Thus, we cannot exclude residual or unmeasured confounding by these or other factors.

Biological Plausibility and New Perspectives

These results provide no direct evidence about possible mechanisms underlying the birth size–breast cancer association. Trichopoulos's initial assumption [1] was that birth size was a correlate of foetal oestrogen exposure. Oestriol represents 90% of the oestrogens produced during pregnancy [48]. Birth size indicators have been found to be correlated with maternal oestriol levels [49] but, not with foetal levels [50]. Maternal and/or foetal levels of other growth factors, such as insulin-like growth factors [51,52], leptin and adiponectin [53–55], and alpha-phetoprotein [56] have also been reported to be associated with birth size. The maternal and/or foetal hormonal environment associated with large birth size may alter programming of the breast, making it more susceptible to cancer initiation by endogenous hormone levels and other carcinogens later in life [57]. This altered programming may involve epigenetic changes in the expression of genes linked to cell proliferation, survival, and differentiation; these changes are likely to occur in the foetal mammary stem cells that give rise to all mammary epithelial structures and/or in cells that influence stem cell self-renewal and fate [58]. If pregnancy hormones are the real exposure of interest the use of a surrogate measure, such as birth size, may lead to considerable exposure misclassification with likely attenuation of the true effect. A moderate correlation of birth size with pregnancy hormone levels of about $r = 0.35$, as found with maternal oestriol [49,59], implies that the observed RR of 1.06 per one SD increment in birth weight would correspond to a RR as large as 1.17 for one SD increase in the underlying true exposure (although the corresponding 95% CI would be wider). If, however, the in utero origins of breast cancer result from a complex interplay of several hormonal and nonhormonal processes [60], birth size may, in fact, be a better cumulative summary measure of all relevant exposures than measured levels of any single hormone.

Foetal growth is a predictor of a woman's growth and development during childhood and early adult life, and both age at menarche and adult height [61] are associated with breast cancer risk. Thus, the observed association between foetal growth and breast cancer may be partly mediated through postnatal growth. This pathway would be consistent

with our finding of a stronger association of breast cancer with birth length than birth weight, as birth length for gestational age has been shown to be a stronger predictor of adult height than birth weight for gestational age [62,63]. However the magnitude of the birth size effect was only slightly reduced after adjustment for adulthood height (but on the basis of a small number of cases, Figures 5 and 6), suggesting that the effect of birth size on risk may be only partly mediated through childhood growth [22,23]. Similarly, the woman's BMI in adulthood did not confound the birth size–breast cancer associations. This was true even at premenopausal ages when adult BMI was inversely associated with breast cancer risk and thus any potential confounding by this variable would have lead to an underestimation of the true birth size effects.

Conclusions

This pooled analysis of individual participant data provides a comprehensive and detailed description of the association between birth size and breast cancer risk. Its findings are consistent with positive associations at both pre- and postmenopausal ages, and are largely independent of postnatal risk factors including adult body size. This study is an important addition to previous meta-analyses of published results [34–36] as it offers a comprehensive assessment of possible sources of between-study heterogeneity, and it clarifies the role of several potential confounders, mediators, and effect modifiers. The magnitude of the observed effect, although modest, is similar to those reported for other more established breast cancer risk factors. The RR per one SD increment in birth length of 9% is of similar magnitude to that associated with one SD increase in adult height in our data, and similar to an increase of about 7% for each additional 10 g of alcohol consumed on a daily basis [64]. Assuming causality, we estimated that about 5% of all breast cancers in developed countries could be attributable to high birth size (length $\geq$ 50 cm or weight $\geq$ 3.5 kg). The prevalence of high birth weight has been increasing in many countries [65,66], consequent to rises in maternal prepregnancy BMI and maternal weight gain during pregnancy [67–69], but as this increase appears to reflect mainly rises in PI rather than birth length [70] it may not necessarily translate into an increase in the population attributable fraction. Even if real, the positive association of birth size with breast cancer would have to be interpreted in the context of U-shaped inverse associations of birth size with all-cause mortality [71], particularly mortality from circulatory diseases [71]. Nevertheless, continued investigation of the pathways through which prenatal factors may affect breast cancer risk, and the extent to which their effects may be mediated or modified by later life risk factors, may identify new targets for prevention of this disease in the future.

Supporting Information

Alternative Language Abstract S1. Italian Translation of the Abstract by Bianca De Stavola

Found at doi:10.1371/journal.pmed.0050193.sd001 (25 KB DOC).

Alternative Language Abstract S2. Portuguese Translation of the Abstract by Isabel dos Santos Silva

Found at doi:10.1371/journal.pmed.0050193.sd002 (27 KB DOC).

Figure S1. Minimally Adjusted Pooled Breast Cancer RRs Stratified by Study Type in Relation to Categorical Birth Weight (Singleton Studies Only)

The area of the black squares is inversely proportional to the variance (on the log scale).

Found at doi:10.1371/journal.pmed.0050193.sg001 (51 KB PDF).

Figure S2. Minimally Adjusted Study-Specific and Pooled Breast Cancer RRs Stratified by Study Type in Relation to Continuous Birth Weight (Singleton Studies Only)

The area of the black squares is inversely proportional to the variance (on the log scale).

Found at doi:10.1371/journal.pmed.0050193.sg002 (15 KB PDF).

Figure S3. Minimally Adjusted Study-Specific and Pooled Breast Cancer RRs for Continuous PI (Singleton Studies Only)

The area of the black squares is inversely proportional to the variance (on the log scale).

Found at doi:10.1371/journal.pmed.0050193.sg003 (13 KB PDF).

Figure S4. Minimally Adjusted Study-Specific and Pooled Breast Cancer RRs for Continuous Head Circumference (Singleton Studies Only)

The area of the black squares is inversely proportional to the variance (on the log scale).

Found at doi:10.1371/journal.pmed.0050193.sg004 (13 KB PDF).

Figure S5. Minimally Adjusted Breast Cancer RRs in Relation to Birth Size Variables in the Two Twin Studies and in the Cohort of Premature/Low Birth Weight Babies

Found at doi:10.1371/journal.pmed.0050193.sg005 (12 KB PDF).

Figure S6. Dose-Response Curves of Breast Cancer Risk in Relation to: (a) Birth Weight; (b) Birth Length; and (c) Head Circumference

Analyses restricted to the subset of cohort studies with birth record data: 1,210 cases / 404,970 non-cases (see Table 2). Small circle, estimated category-specific minimally adjusted RRs (reference category: 3.000–3.499 kg for birth weight; 49.0–49.9 cm for birth length; and 33.0–33.9 cm for head circumference); whiskers: 95% CIs for category-specific RRs. Continuous line, estimated linear effect centred on reference category; dotted line, estimated quadratic effect centred on reference category.

Found at doi:10.1371/journal.pmed.0050193.sg006 (32 KB PDF).

Figure S7. Breast Cancer RRs in Relation to Continuous Birth Weight: Minimally Adjusted and Further Adjusted for Various Potential Confounding Factors (Restricted to Singleton Studies Based on Adult Reports)

Adjustments for maternal age (continuous); maternal parity (categorical: 0, 1, 2, $\geq$3); age at menarche (categorical: $<$12 y, 12.0–12.9 y, $\geq$13 y); adult height (continuous); adult BMI (continuous); adult parity (categorical: 0, 1, 2, $\geq$3); age at first birth (categorical: nulliparous, $<$20 y, 20–29 y, $\geq$30 y); adult SES (study-specific categories: adult SES for European Prospective Investigation of Cancer [EPIC]-Norfolk, Nurses' Health Study [NHS] I and II, and Seattle Breast Cancer in Young Women [BCYW], Seattle Breast Cancer in Middle-Aged Women [BCMW], and Seattle Perinatal Factors and Breast Cancer [PFBC]; occupation for Shanghai Breast Cancer Study [SBCS]; and education for UK Women's Cohort Study [UKWCS] and Women's Contraceptive and Reproductive Experiences [CARE] study); oral contraceptive use (categorical: ever, never); and hormone replacement therapy use (categorical: ever, never).

Found at doi:10.1371/journal.pmed.0050193.sg007 (15 KB PDF).

Figure S8. Minimally Adjusted Pooled Breast Cancer RRs in Relation to Categorical Birth Weight, Stratified by Source of Birth Size Data and Age (Singleton Studies Only)

Found at doi:10.1371/journal.pmed.0050193.sg008 (51 KB PDF).

Table S1. Study-Specific Details of the 32 Participating Studies

Found at doi:10.1371/journal.pmed.0050193.st001 (164 KB DOC).

Table S2. Number of Studies (Number of Breast Cancer Cases/Non-Cases) with Information on the Various Birth Size Measures, by Study Design and Birth Size Data Source

Found at doi:10.1371/journal.pmed.0050193.st002 (64 KB DOC).

Table S3. Number of Studies (Number of Breast Cancer Cases/Non-

Cases) with Continuous Birth Weight and Information on Various Potential Confounders, Mediators, and Effect Modifiers, by Study Design and Birth Size Data Source (Singleton Studies Only)

Found at doi:10.1371/journal.pmed.0050193.st003 (96 KB DOC).

Table S4. Study-Specific Breast Cancer RRs by Categories of Birth Weight

Found at doi:10.1371/journal.pmed.0050193.st004 (249 KB DOC).

Table S5. Study-Specific Breast Cancer RRs by Fourths of Birth Length

Found at doi:10.1371/journal.pmed.0050193.st005 (97 KB DOC).

Table S6. Study-Specific Breast Cancer RRs by Fourths of PI

Found at doi:10.1371/journal.pmed.0050193.st006 (97 KB DOC).

Table S7. Study Specific RRs of Breast Cancer by Fourths of Head Circumference

Found at doi:10.1371/journal.pmed.0050193.st007 (68 KB DOC).

Table S8. Study-Specific Breast Cancer RRs by Categories of Age and Birth Weight (Singleton Studies Only)

Found at doi:10.1371/journal.pmed.0050193.st008 (454 KB DOC).

Table S9. Assessment of Publication Bias

Found at doi:10.1371/journal.pmed.0050193.st009 (125 KB DOC).

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Author contributions. IdSS, BDS, and VM designed the study. All members of the Collaborative Group contributed to data acquisition, with final data checking and standardisation by BDS and VM. BDS performed statistical analysis of data. IdSS, BDS, VM, and all members of the Collaborative Group interpreted the findings. IdSS and BDS had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. IdSS prepared the first draft of the manuscript. All authors provided comments in writing the paper.

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Editors' Summary

Background. Last year, more than one million women discovered that they had breast cancer. In the US, nearly 200,000 women will face the same diagnosis this year and 40,000 will die because of breast cancer. Put another way, about one in eight US women will have breast cancer during her lifetime. Like all cancers, breast cancer begins when cells acquire genetic changes that allow them to divide uncontrollably and to move around the body (metastasize). This uncontrolled division leads to the formation of a lump that can be detected by mammography (a breast X-ray) or by manual examination of the breasts. Breast cancer is treated by surgical removal of the lump or, if the cancer has started to spread, by removal of the whole breast (mastectomy). Surgery is usually followed by radiotherapy, chemotherapy, and other treatments designed to kill any remaining cancer cells. Unlike some cancers, the outlook for women with breast cancer is good. In the US, for example, nearly 90% of affected women are still alive five years after their diagnosis.

Why Was This Study Done? Scientists have identified several factors that increase a woman's risk of developing breast cancer by comparing the characteristics of populations of women with and without breast cancer. Well-established risk factors include increasing age, not having children, and having a late menopause, but another potential risk factor for breast cancer is birth size. A baby's weight, length, and head circumference at birth (three related measures of birth size) depend on the levels of hormones (including estrogen, a hormone that often affects breast cancer growth) and other biological factors to which the baby is exposed during pregnancy—its prenatal environment. The idea that prenatal environment might also affect breast cancer risk in later life was first proposed in 1990, but the findings of studies that have tried to investigate this possibility have been inconsistent. Here, the researchers re-analyze individual participant data from a large number of studies into women's health conducted in Europe, Northern America, and China to get more precise information about the association between birth size and breast cancer risk.

What Did the Researchers Do and Find? The researchers identified 32 published and unpublished studies that had collected information on birth size and on the occurrence of breast cancer. They then obtained the individual participant data from these studies, which involved more than 22,000 women who had developed breast cancer and more than 600,000 women who had not. Their analyses of these data show that birth weight was positively associated with breast cancer risk in those studies where this measurement was recorded at birth or based on parental recall during the study participant's childhood (but not in those studies in which birth weight was self-reported or maternally recalled during the participant's adulthood). For example, women with recorded birth weights of more than 4 kg or more had a 12% higher chance of developing breast cancer than women who weighed 3–3.5 kg at birth. Birth length and head circumference were also positively associated with breast cancer risk, but birth length was the strongest single predictor of risk. Finally, the amount by which birth size affected breast cancer risk was not affected by allowing for other established risk factors.

What Do These Findings Mean? These findings provide strong evidence that birth size—in particular, birth length—is a marker of a woman's breast cancer risk in adulthood although the mechanisms underlying this association are unclear. The researchers note that the observed effect of birth size on breast cancer risk is of a similar magnitude to that of other more established risk factors and estimate that 5% of all breast cancers in developed countries could be caused by a high birth size. Because practically all the studies included in this pooled analysis were done in developed countries, these findings may not hold for developing countries. Further investigations into how the prenatal environment may affect breast cancer risk might identify new ways to prevent this increasingly common cancer.

Additional Information. Please access these Web sites via the online version of this summary at http://dx.doi.org/10.1371/journal.pmed.0050193.

- This study is further discussed in a *PLoS Medicine* Perspective by Trichopoulos and Lagiou
- The US National Cancer Institute provides detailed information for patients and health professionals on all aspects of breast cancer, including information on risk factors for breast cancer (in English and Spanish)
- The MedlinePlus Encyclopedia provides information for patients about breast cancer; Medline Plus also provides links to many other breast cancer resources (in English and Spanish)
- The UK charity Cancerbackup also provides detailed information about breast cancer
- Cancer Research UK is the UK's leading charity dedicated to cancer research