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Medicine and Health Sciences | Other Medicine and Health Sciences | Women's Health

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Original Article

Birth Weight as a Risk Factor for Breast Cancer: A Meta-Analysis of 18 Epidemiological Studies

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Abstract

Background: Birth weight has been identified as a birth-related factor associated with the risk of breast cancer. However, the evidence is inconsistent.

Methods: To investigate the association between birth weight and breast cancer, we conducted a meta-analysis of published studies between 1996 and 2008. Eighteen studies encompassing 16,424 breast cancer cases were included in the meta-analysis. Data were combined using a fixed-effect or random-effect model depending on the heterogeneity across studies.

Results: Women with their own birth weight >4000 g or 8.5 lb had a higher risk for developing breast cancer than those with birth weight <2500 g or 3000 g (OR = 1.20, 95% CI 1.08, 1.34). Findings were also consistent with a dose-response pattern effect. The summary effect estimate for breast cancer risk per 1 kg increase in birth weight was statistically significant (random effects OR = 1.07, 95% CI 1.02, 1.12).

Conclusions: Although these results provided no evidence indicating whether birth weight is more strongly related to early-onset than to later-onset breast cancer, our findings suggest an association between birth weight and breast cancer. The underlying biological mechanism relating to this phenomenon needs additional study.

Introduction

Breast cancer is the most commonly diagnosed malignant neoplasm among females in the United States, accounting for one of every three cancer diagnoses, with the highest incidence among women >age 50.[1] In 2007, over 40,000 women died of breast cancer in the United States. Although the incidence of breast cancer has decreased slightly in recent years, an estimated 178,480 new invasive cases of breast cancer, including 62,030 new cases of *in situ* breast cancer, were expected to occur annually among women.[1,2] Epidemiological, clinical, and genetic studies have identified a number of biological and social traits as risk factors of breast cancer. These factors include familial history of breast cancer, age, higher socioeconomic status, ionizing radiation, tallness in adult life, alcohol consumption, susceptibility genes of breast cancer 1 (BRCA1) and breast cancer 2 (BRCA2), and a variety of hormonal and metabolic factors.[3] However, these well-established risk factors for female breast cancer do not sufficiently elucidate the incidence pattern of this cancer, and additional risk factors have to be considered to advance our understanding of breast carcinogenesis and suggest future intervention strategies.

Evidence has suggested that the prenatal period may be particularly relevant for the development of future adult breast cancer. Results from animal experiments and migrant population studies support the potential influence of prenatal life exposures on subsequent breast cancer development.[4–7] Trichopoulos[8] hypothesized that prenatal factors, such as elevated hormone concentrations *in utero*, may increase subsequent breast cancer risk. There are methodological and theoretical challenges that these studies face, however, including the long induction period between exposure and disease as well as lack of assurance about the critical time window of exposure. Several epidemiological studies have since linked birth weight as a marker of *in utero* environment with breast cancer risk. Some studies have reported high birth weight as a breast cancer risk factor,[9–17] although other studies have not supported this relationship.[18–24]

Despite the relatively large number of studies, the evidence of an association between birth weight and breast cancer is inconclusive. Thus, combining data across these studies is

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useful to determine the overall statistical pattern of evidence. Three previous meta-analyses have been conducted to evaluate the association between birth weight and breast cancer.[25–27] However, these studies inadequately addressed the dose-responselike relationship between birth weight and breast cancer (i.e., risk of breast cancer per 1 kg increase in birth weight), and there are also concerns about heterogeneity across studies that were not accounted for. A pooled analysis of individual participant data was published in 2008,[28] and although the results of this study are important, the pooled analysis method limited the number of studies that could he used to conduct a trend analysis based on continuous data. The World Cancer Research Fund (WCRF) report, launched in November 2007, examined breast cancer risk per 1 kg increase in birth weight but included only six cohort studies.[29] In addition, although the meta-analysis conducted by Michels and Xue[27] included analysis of potential effect modification by menopausal status, there were a few questions about the selection of studies, compatible birth weight category, and the analytical methods related to this analysis.

This meta-analysis provides new information on the dose-responselike relationship between birth weight and breast cancer risk while also examining effect modification by menopausal status in detail. The primary aims of this meta-analysis were (1) to determine the overall risk for breast cancer of the highest birth weight (≥4000 g or ≥8.5 lb) compared with the lowest birth weight (<2500 g or 3000 g), (2) to assess whether the association followed a dose-responselike pattern, and (3) to determine if the association could be discerned separately for women with breast cancer diagnosed at premenopausal or postmenopausal status.

Materials and Methods

Study identification

We performed a systematic literature search of PUBMED, EMBASE, and GOOGLE SCHOLAR Search Engine (*scholar.google.com*) through 2008 to identify epidemiological studies of the association between birth weight and breast cancer. We used the index terms birth weight, breast cancer, risk factors, and epidemiology in various combinations. A manual review of references from primary or review articles was performed to identify any additional relevant studies. The studies included in the meta-analysis were systematically selected based on the following criteria: (1) studies were peer-reviewed and published in English, (2) studies provided measures of odds ratios (OR) or relative risk (RR) (e.g., unadjusted or adjusted ORs) for breast cancer or the number of individuals (both cases and controls or both cases and person-years) in different birth weight strata as well as an indication of the uncertainty of the central estimate (e.g., 95% confidence interval [CI]) corresponding to birth weight strata, and (3) studies with more comprehensive covariate adjustment, focused on breast cancer, or with compatible categorization of birth weight were preferred.

From a review of abstracts identified in the database search, 32 articles were selected for a full review after excluding review articles, studies of other risk factors, and commentary. We further excluded 14 studies of the total of 32 studies. Two studies did not provide adequate information for either dichotomous comparisons or trend analysis,[21,30] 2 twins studies were excluded because we were concerned with differences between twins and general birth populations, particularly with regard to birth weight,[31,32] and 10 other studies were excluded because their results were included in other detailed publications that provided more comprehensive results or adequate information.[10,16,17,19,20,22,33–36] Thus, the present meta-analysis includes 18 unique studies: 11 case-control studies,[9,13,18,23,37–43] and 7 cohort studies[11,12,14,15,24,44,45] (Tables 1 and 2).

Data were extracted using standardized data extraction forms. For each study, extracted information included study country and year, study design, population characteristics (country and age), source of birth weight information, number of cases, sample size, unadjusted or adjusted ORs, and 95% Cl in different birth weight strata. In addition, matching factors for cases and controls and factors for which statistical adjustment was performed were extracted.

Statistical analysis

Dichotomous comparisons. To obtain the association between high birth weight (i.e., ≥4,000 g or ≥8.5 lb) and risk of breast cancer across studies, we used the lowest birth weight stratum as the reference group, a standard that most of the studies applied. A majority of the included studies used a birth weight cutoff of <2500 g or <5.5 lb as the lowest birth weight stratum. Only a few studies used a birth weight cutoff of <3000 g as the lowest birth weight stratum.[12,14,37,45] For the statistical synthesis, the covariate adjusted ORs or RRs were used if they were provided. If not, we used the raw data to calculate the unadjusted OR or RR for the studies that used a reference other than the lowest birth weight stratum or that had no estimates for all age groups, if appropriate. To assess the effects of birth weight on early-onset and later-onset breast cancer, the dichotomous ORs or RRs were extracted separately for premenopausal and postmenopausal women if the data were available.

Trend analysis for unadjusted or adjusted strength of association. To obtain a uniform measure of the trend, the change in breast cancer risk per 1 kg increase in birth weight was extracted from each study when the information was provided. Otherwise, we used the method of corrected for covariance of log RR described by Greenland and Longnecker[46] to quantify the change in risk per 1 kg increase in birth weight for studies that provided information for three or more birth weight strata. In this method, the regression coefficient and its Cls between the risk of breast cancer on the logit scale and the median of birth weight in each category were obtained. The ORs or RRs for the change in risk per 1 kg increase in birth weight were estimated by exponentiation of the regression coefficient.[47,48]

Meta-analysis: Estimations of summary effects and heterogeneity evaluation. Each study contributed measures of ORs or RRs of breast cancer comparing highest birth weight to lowest birth weight for women of all ages, or separately by menopausal status, or ORs or rate ratios per 1 kg increase in birth weight (separately by menopausal status, if available). As a summary estimate, we used the general variance-based method, which provides an inverse variance weighted average of the study-specific estimates, to calculate the summary effect estimate for either the dichotomous ORs or ORs per 1 kg increase in birth weight. This summary effect estimate represents a weighted average estimate of the effect of birth weight on breast cancer across the studies.

Table 1. Characteristics of Studies Included in the Meta-Analysis

Study/country	Year	Study design	Sources of cases and controls	Birth weight source	Case recruitment period	No. of cases	Sample size	Matching factors	Adjusting factors[a]
Andersson/Sweden[45]	2001	Cohort study	Cancer registry/ population-based cohort	Medical record	Born 1914, 1948, 1922, 1930	62	1,080	NA[a]	GA, BC, MP, BO, P, AM
Ahlgren/Denmark[15]	2004	Cohort study	Cancer registry/ population based cohort	School health records	Born 1930–1975	3,340	3,333,359	NA	APG, AM, H, BMI_14
Ekbom/Sweden[23]	1997	Case-control	Cancer registry/ hospital control	Medical record	Born 1874–1961, Diagnosed 1958–1994	1,068	2,727	Hospital and date of birth	A, MSES, P, TM, NJ, SP, MP
Hilakivi-Clarke/Finland[24]	2001	Cohort study	Hospital born birth cohort	Hospital record	Born 1924–1933	177	3,447	NA	NA
Innes/USA[9]	2000	Case-control	Cancer registry/ population control	Birth record	Diagnosed 1978–1995, age 14–37	484	3,354	Residence	GA, MP, AP, MG, P, MA, PA, R
Lahmann/Sweden[37]	2004	Nested case-control	Cohort case/control	Birth record	Born 1924–1950, age >55 years	89	327	Age	GA, BY, MP, O, BMI_A, EDU
McCormack/Sweden[12]	2003	Cohort study	Cancer registry	Medical record	Born 1915–1929	63	5,062	NA	GA, MS, CH, AFM, EDU, PCP, O
Mellemkjær/Denmark[38]	2003	Case-control	Cancer registry/ population control	Midwives' reports	Diagnosed 1943–1990, age <40	894	4,317	Midwife and time of birth	MS, MA, BO
Michels/USA[11]	2006	Cohort study	NHS cohort	Questionnaire	1992–2002 in NHS and 1991–2001 in NHS II	3,140	136,466	NA	A, AM, BC, P, AFB, BMI, FHBC, HBBD, P, OC, AC, PAC
Park/Poland[13]	2006	Case-control	Hospital records and cancer registry/population-based control	Interview	Diagnosed 2000–2003, age 20–74	2,386	4,888	Frequency match: age and residence	A, EDU, AM, MPS, AMP, AFB, CH, FHBC, MGS, BMI
Sanderson/USA[39]	1996	Case-control	Cancer registry/population control	Questionnaire	Diagnosed 1983–1990	1,147	2,546	Frequency match: age and residence	A, FHBC, MPS, AM, BY, RY, AFB, BMI, IF, OC, MSK, MA, BO
Sanderson/China[18]	2002	Case-control	Cancer registry/population control	Interview	Diagnosed 1996–1998, age 25–64	288	638	Frequency match: age	A, IN, FHBC, HF, AM, P, AFB
dos Santos Silva/UK[14]	2004	Cohort study	Cancer registry/ population-based cohort	Medical record	Born 1946	59	2,176	NA	A
Barba/USA[40]	2006	Case-control	Cancer registry/ population control	Self-reported	Diagnosed 1996–2001, age 35–80	845	2,383	Frequency-matched: age, race, and residence	A, EDU, R, BMI, HBBD, FHBC, AM, AMP, P, L, AFB
Hodgson/USA[41]	2004	Case-control	Cancer registry/population control	Birth record	Born 1949 or later, age 18–74	196	363	Frequency match: age and race	A, R, MA, BMI_A, SF, HB
Troisi/USA[44]	2006	Cohort study	NCI DES cohort	Questionnaire and obstetrical charts	Diagnosed 1978–2001	97	118,985	NA	A, GA
Vatten/Norway[42]	2002	Case-control	Cancer registry/population control	Birth record	Born 1910 and 1970, age 27–83	373	1,523	Year of birth, residency	AFB, P
Titus-Ernstoff[43]	2002	Case-control	Cancer registry/licensed drivers and Medicare beneficiaries	Interview	Diagnosed 1992–1994	1,716	3,602	NA	A, Place

[a]A, age; AC, alcohol consumption; AFB, age at first birth; AFM, age at first marriage; AM, age at menarche; AMP, age at menopause; AP, abruptio placentae; APG, age at peak growth; BC, birth cohort; BMI_A, adult BMI; BMI_14, BMI at 14 years; BO, birth order; BY, birth year; CH, children in the home; EDU, education; FHBC, family history of breast cancer; GA, gestational age; H, height; HB, history of biopsy; HBBD, history of breast benign disease; HF, history of fibroadenoma; IF, infertility; IN, income; L, lactation; MA, maternal age; MG, multifetal gestation; MGS, mammography screening; MP, maternal preeclampsia; MPS, menopausal status; MS, marital status; MSES, maternal socioeconomic status; MSK, maternal smoking; NA, not available; NJ, neonatal jaundice; O, occupation; OC, oral contraceptives; P, parity; PA, paternal age; PAC, physical activity; PCP, personal car possession; R, race; RY, reference year; SF, sampling fractions; SP, severe prematurity; TM, twin membership.

Table 2. Excluded Studies of Birth Weight and Breast Cancer

Study/country	Year	Study design	Sources of cases and controls	Source of birth weight	Case recruitment period	No. of cases	Sample size	Reason for exclusion
Michels/USA[10]	1996	Nested case-control	NHS cohort	Questionnaire	Born 1921–1945 and 1946–1965	582	2,151	Overlap with Michels/USA/2006[11]
Vatten/Norway[33]	2005	Cohort study	Cancer registry/ population-based cohort	Medical record	Born 1920–1958	312	16,016	Overlap with Vatten/Norway/ 2002[42] and no adequate information for either "dichotomous comparisons" or "trend analysis"
Sanderson/USA[20]	1998	Case-control	Cancer registry/ population control	Questionnaire	Diagnosed 1983–1992, age under 45	510	436	Overlap with Sanderson/USA/1996[39]; part of data concerning breast cancer risk and only for premenopausal women
Ekbom/Sweden[22]	1992	Nested case-control	Cancer registry/population control	Medical record	Born 1874–1954	458	1,655	Overlap with Ekbom/Sweden/1997[23]
Ahlgren/Denmark[17]	2003	Cohort study	Cancer registry/ population-based cohort	School health records	Born 1930–1975	2340	3,266,070	Overlap with Ahlgren/Denmark/2004[15]
Ahlgren/Denmark[16]	2006	Cohort study	Cancer registry/ population-based cohort	School health records	Born 1930–1975	3340	3,333,359	A reprint of Ahlgren/Denmark/2004[15]
Ahlgren/Denmark[34]	2007	Cohort study	Cancer registry/ population-based cohort	School health records	Born 1930–1975	12,540	6,975,553	Overlap with Ahlgren/Denmark/2004[15]; no adequate information and evaluate other cancers including breast cancer
McCormack/Sweden[36]	2005	Cohort study	Cancer registry/ population-based cohort	Medical record	Born 1915–1929	2,685	11,529	Duplication of data with McCormack/ Sweden/2003[12] on breast cancer and better controlling for confounding factors
Kaijser/Sweden[35]	2003	Cohort study	Cancer registry/ population-based cohort	Medical record	Born 1925–1949	39	1,483	No adequate information for either "dichotomous comparisons" or "Trend analysis"
Stavola/UK[19]	2000	Cohort study	National survey of Health and Development	Birth records	Born March 3–9,1946	37	2,221	Case-referent and different birth weight categories
Löf/Sweden[21]	2007	Cohort study	National health registers/Women's Lifestyle and Health study	Questionnaire	Diagnosed 1991–2003	657	38,566	No adequate information for either "dichotomous comparisons" or "Trend analysis"
Mogren/Sweden[30]	1999	Cohort study	Cancer registry/ population-based cohort	Birth registry	Born 1955–1990	57	Unavailable	Different birth weight categories and inadequate information
Hubinette/Sweden[32]	2001	Case-control	Cancer registry/ population-based female twins	Twin registry	Born 1886–1956	96	184	Different population (twins)
Kaijser/Sweden[31]	2001	Case-control	Cancer registry/population-based opposite-sexed twins	Twin registry	Born 1926–1967	90	180	Different population (opposite-sexed twins)

For each fixed effects of ORs, we quantified the degree of heterogeneity in the measures across studies with a Q-statistic, which follows the chi-square distribution with degrees of freedom (*df*) equal to the number of included studies minus 1.[49] In this study, if the *p* value of the Q-statistic was <0.1, we considered studies to exhibit significant statistical heterogeneity.[50] In this case, a random-effects OR is reported. The random-effects OR is also a weighted average of study-specific ORs that considers heterogeneity and can be a reasonable summary effect estimate of the effect of birth weight on breast cancer when heterogeneity exists across studies. In addition, we also calculated the I^2-statistic, which is equal to the Q-statistic minus the *df* and then divided by the Q-statistic itself. Its CI was also calculated using the method described by Higgins and Thompson.[51] The I^2-statistic is a quantitative measure of the degree of between-study heterogeneity. Smaller values of the I^2-statistic suggested lower between-study heterogeneity (0 in I^2-statistic suggests no heterogeneity, and larger values indicate increasing heterogeneity).[52]

Publication bias. The funnel plot method was applied to determine if there was publication bias among the included studies.[53] The funnel plot includes the log of the ORs as the x-axis and the standard error (SE) of the log of ORs as the y-axis. If the plot is asymmetrical, it is interpreted to imply that publication bias is present. This method provides a direct visual inspection.

Results

Description of studies

The 18 studies included in the meta-analysis were published between 1996 and 2008. The study populations included participants from the United States,[9,11,39–41,43,44] Europe,[12,15,23,24,37,38,42,45] and China,[18] for a total of 16,424 women with breast cancer. The cases in these studies were primarily obtained from cancer registries, hospital records, or both. Birth weight was ascertained from birth records or interviews and questionnaires (Table 1).

Birth weight and breast cancer

Fifteen studies provided estimates of the association between risk of breast cancer and birth weight using dichotomous comparisons (highest vs. lowest). Among them, 8 studies presented the ORs or RRs for the effect of highest birth weight on breast cancer among all women, regardless of menopausal status. Figure 1 shows the forest plot for the study-specific ORs or RRs of these studies and the summary estimate across them. All 8 studies included in this meta-analysis suggested a positive association between highest birth weight and breast cancer risk, although the association was statistically significant in only 2 of the studies (summary fixed-effect OR 1.20, 95% CI 1.08, 1.34 for highest vs. lowest birth weight). There was little heterogeneity in effect estimates across the reviewed studies (Q-statistic = 4.52, *p* for heterogeneity = 0.72; I^2-statistic = 0, 95% CI 0, 50%).

Figures 2 shows the forest plots of the association estimates of highest birth weight on premenopausal and postmenopausal breast cancer and the summary estimates across them. Altogether, 9 studies provided adequate information to ascertain the association between birth weight and premenopausal breast cancer risk (Fig. 2A). Because of the heterogeneity of the estimates (Q-statistic = 15.89, *p* for heterogeneity<0.05, I^2-statistic = 50%, 95% CI 0, 76.5%), a random-effects summary OR was calculated. The random-effects summary OR

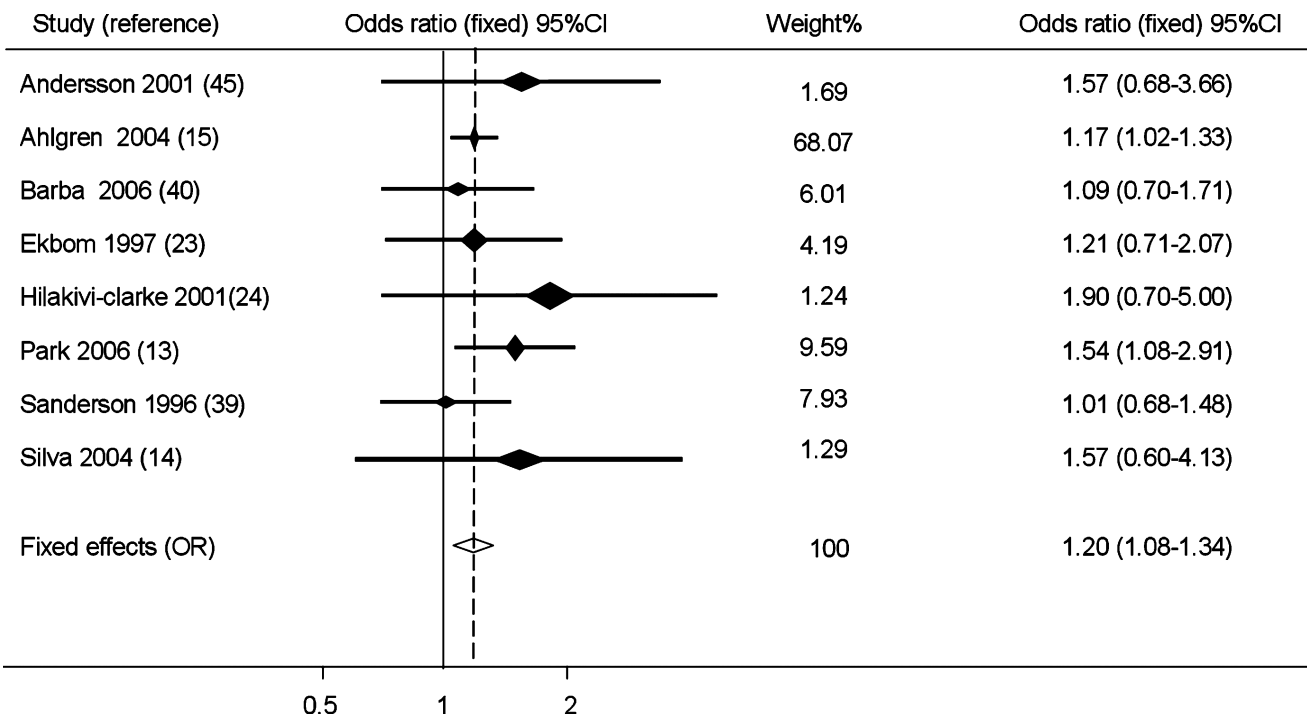

FIG. 1. Odds ratio with corresponding 95% confidence intervals for breast cancer in women of all ages with highest (>4000 g or 8.5 lb) vs. lowest (<2500 g or 3000 g) birth weight. The Q-statistic and I^2-statistic tests indicated no heterogeneity (Q-stastistic = 4.52, *p* for heterogeneity = 0.72, I^2-statistic = 0, 95% CI 0, 50%). The fixed-effects odds ratio is 1.20 (95% CI 1.08, 1.34).

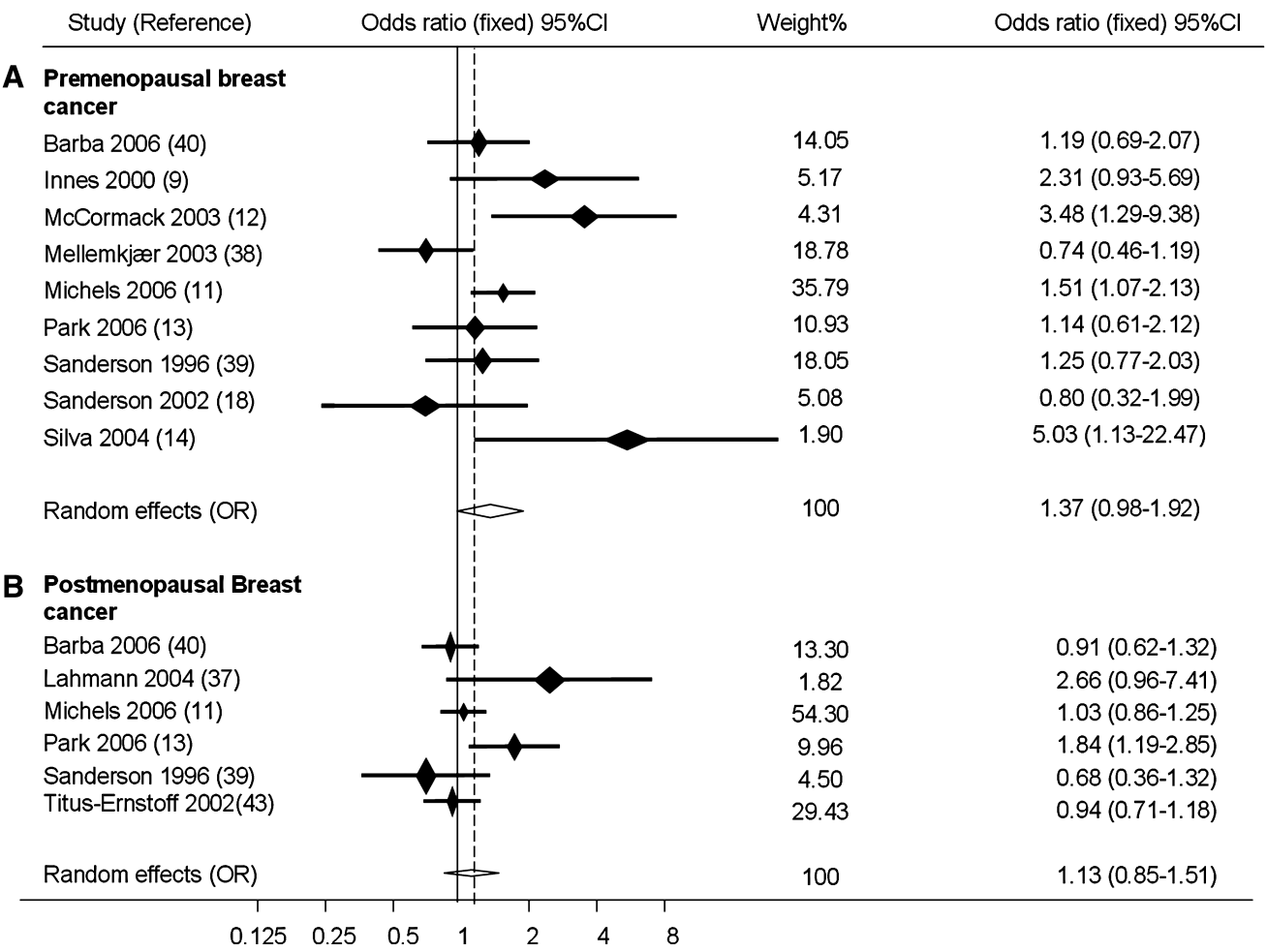

FIG. 2. (**A**) Odds ratio with corresponding 95% confidence intervals for premenopausal breast cancer risk with high (>4000 g or 8.5 lb) vs. lowest (<2500 g or 3000 g) birth weight. The Q-statistic and I^2-statistic tests indicated heterogeneity across studies (Q-statistic = 15.89, p for heterogeneity <0.05, I^2-statistic = 50%, 95%CI 0, 76.5%). The random-effects odds ratio is 1.37 (95% CI 0.98, 1.92). (**B**) Odds ratio with corresponding 95% confidence intervals for postmenopausal breast cancer risk with highest vs. lowest birth weight. The Q-statistic and I^2-statistic tests indicated heterogeneity across studies (Q-statistic = 12.0, p for heterogeneity <0.05, I^2-statistic = 58%, 95%CI 0, 83%). The random-effects odds ratios is 1.13 (95% CI 0.85, 1.51).

was 1.37 (95% CI 0.98, 1.92) for the effect of highest birth weight (≥4,000 g or ≥8.5 lb) compared with the lowest birth weight (<2500 g, <5.5 lb, or <3000 g). Only 6 studies provided adequate information on postmenopausal breast cancer and birth weight to allow the dichotomous comparison (Fig. 2B). The heterogeneity in the association estimates from these 6 studies was also significant (Q-statistic = 12.0, p for heterogeneity <0.05, I^2-statistic = 58%, 95%CI 0, 83%). The random-effects OR was 1.13 (95%CI 0.85, 1.51).

Trend analysis

We conducted a separate meta-analysis to determine if there is a log-linear effect of birth weight on breast cancer risk. This analysis included 16 studies, which met the inclusion criteria for the trend analysis, that is, the effect estimates of breast cancer risk associated with a 1 kg increase in birth weight being presented or estimated using the Greenland and Longnecker method,[46] and provided 19 effect estimates. Figure 3 shows a forest plot of these study-specific effect estimates and the summary estimate across them. Among the 19 effect estimates, a positive association was found in 13 studies, although the association was statistically significant in only 5 of the studies. A negative association was observed in 6 other studies in addition to 1 with a statistically significantly negative association (Fig. 3). There was an overall statistically significant association between breast cancer and each 1 kg increase in birth weight (random-effects OR 1.07, 95% CI 1.02, 1.12). The effect estimates were heterogeneous across studies (Q-statistic = 30.02, p for heterogeneity <0.05, I^2-statistic = 40%, 95% CI 0, 65%). The high heterogeneity among the studies seemed to be a result of the effect among African Americans in the study by Hodgson et al.[41] The overall heterogeneity became nonsignificant (Q-statistic = 24.9, p for heterogeneity >0.10, I^2-statistic = 30%, 95% CI 0, 62%) after excluding the study. However, the exclusion did not substantially change the summary effect estimate (fixed-effects OR = 1.08, 95% CI 1.02, 1.13)

Publication bias

Visual inspection of the funnel plots does not suggest substantial publication bias suggested in this meta-analysis (data not shown).

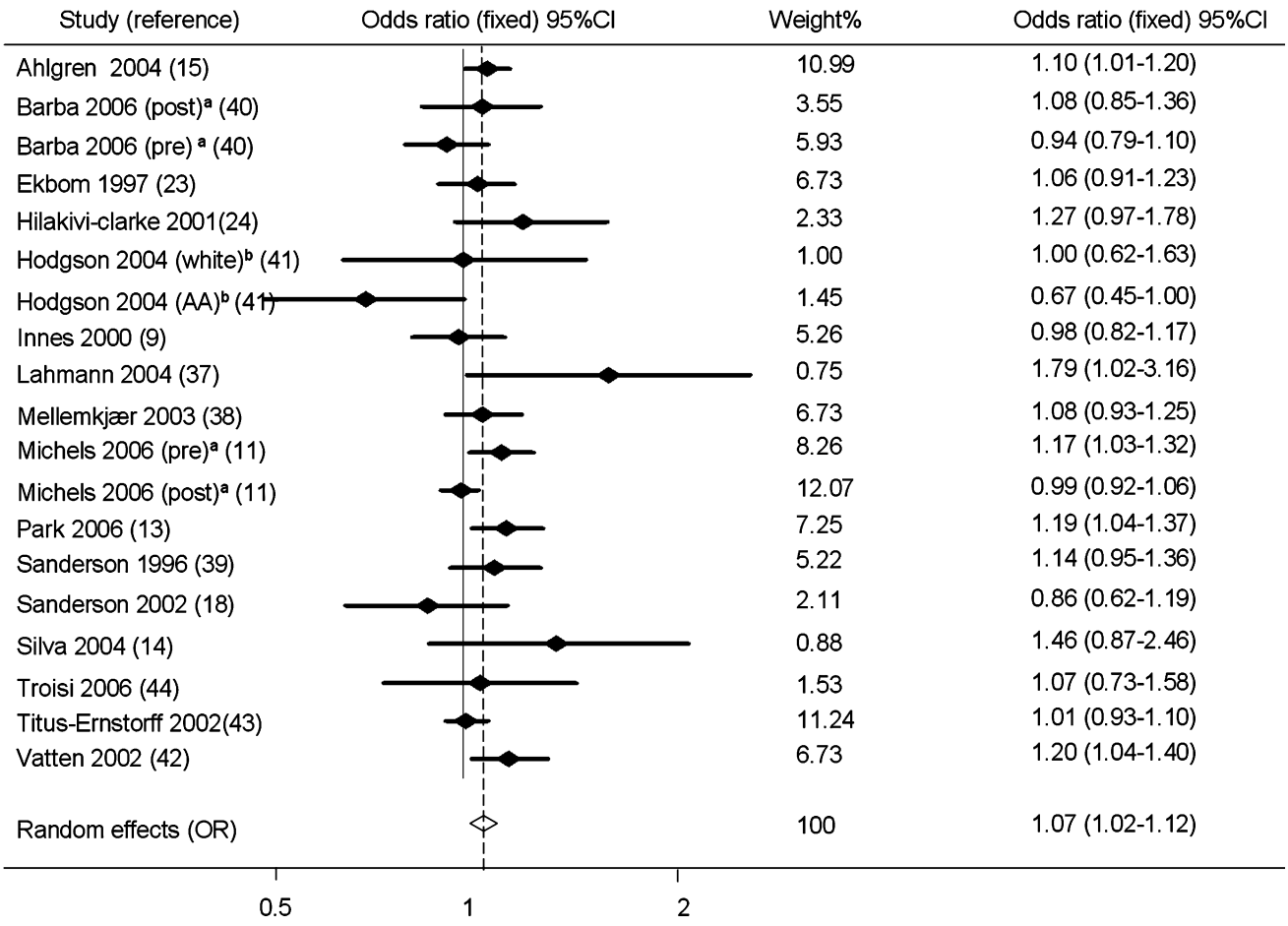

FIG. 3. Study-specific effect estimates for breast cancer risk per 1 kg increase in birth weight. The Q-statistic and I^2-statistic tests indicated the presence of heterogeneity across studies (Q-statistic = 30.02, p for heterogeneity <0.05, I^2-statistic = 40%, 95% CI 0, 65%). The random-effects OR was 1.07 (95% CI 1.02, 1.12) [a]pre, premenopausal women; post, postmenopausal women. [b]Hodgson's 2004 study provided effect estimates for white and African American women, respectively.

Discussion

This meta-analysis of 18 epidemiological studies showed a significant, albeit modest in magnitude, summary effect of breast cancer risk with high birth weight (≥4000 g or 8.5 lb) compared with the lowest category of birth weight (<2500 g or 3000 g) among women of all ages. Our results (OR = 1.37, 95% CI 0.98, 1.92 for premenopausal women; OR = 1.13, 95% CI 0.85, 1.51 for postmenopausal women) differed from the estimates from the meta-analysis conducted by Michels and Xue in 2006[27] (OR = 1.25, 95% CI 1.14, 1.38 for premenopausal women; OR = 1.04, 95% CI 0.91, 1.19 for postmenopausal women), with our estimates higher and approaching significance for premenopausal women. The alternative analytic strategy employed in the study and inclusion of additional studies are the likely reasons behind these difference. In terms of methodological differences, we employed a random-effects model rather than a fixed-effects model to provide a summary estimate accounting for the heterogeneity across the studies. We also used more consistent and clear definitions of highest (birth weight >4000 g)and referent (birth weight<2500 g or <3000 g) categories in our analysis. In addition, we have an alternative approach to Michels and Xue[27] for combining effect estimates based on categorical birth weight together with the effect estimates based on continuous birth weight to generate a single summary estimate. In our analysis, we analyzed both the categorical and continuous measurement, but we did them separately. In addition to these methodological differences, we included 3 publications from 2006[11,13,40] that have become available since the publication of Michels and Xue.[27]

The findings from this meta-analysis demonstrated a clear dose-response relation between birth weight and breast cancer risk after accounting for the heterogeneity across the studies. These results indicated that breast cancer risk increased approximately 7% per 1 kg increase in birth weight. Our results were consistent with the findings of the WCRF report,[29] which indicated that breast cancer risk increased 8% per 1 kg increase in birth weight (based on 6 cohort studies). Another pool analysis[14] indicated that breast cancer risk increased 6% per l SD (0.5 kg) increase in birth weight; our estimate is slightly lower but comparable. Our study adds

additional information that pooled analyses might be unable to quantify. We were able to include additional studies that measured birth weight only in categorical variables by using the Greenland and Longnecker method[46] to estimate the dose-response relationship. In our meta-analysis, although the effect estimate among premenopausal women is larger in magnitude than the effect among postmenopausal women, the association was not statistically significant. Even with the inclusion of additional studies that provided adequate information for stratification by menopausal status and applying the Greenland and Longnecker methods for estimating dose-response relationships incorporating categorical measures, our findings remain consistent with the earlier meta-analyses.

Birth weight as a proxy indicator of intrauterine environment has been linked with several hormone-related cancers, including testicular cancer,[54–56] prostate cancer,[57–59] and breast cancer, and other types of cancers, such as childhood leukemia.[60–62] Although the underlying biological mechanisms that link high birth weight to a higher risk of breast cancer are still ambiguous, the findings from recent animal studies and epidemiological studies might provide clues to elucidate the association. We know that estrogen plays a major role in the etiology of breast cancer.[63,64] Hence, hormonal exposures in early life might have a particularly significant influence on the subsequent breast cancer risk in adult life because the fetus is particularly susceptible to transient hormonal exposure and the change in the hormonal environment of the fetus alters the development of target organs by exerting lifelong effects.[65,66] In animal experiments, exposure to estrogens during fetal or early postnatal development can increase mammary tumorigenesis by changing both proliferation and differentiation of the mammary gland.[67] Several epidemiological studies found that dizygotic twins who were exposed to more estrogens *in utero* because of two placentas have a higher risk of breast cancer than singleton births.[68–70] Pregnancy estrogen levels have been reported positively associated with birth weight.[71–73] Therefore, high birth weight, like twinning, might be a proxy variable of early life exposure to high levels of pregnancy estrogens, as Trichopoulos proposed.[8]

Another potential mechanism is that women with high birth weight may merely have a higher number of mammary gland cells at risk for transformation and, thus, have an increased subsequent breast cancer risk.[74] Findings from the study by Cerhan et al.[75] that birth weight was positively associated with mammographic breast density and dense area among women support the hypothesis because mammographic density is strongly correlated with mammary gland mass, which is also potentially associated with the mammary cells at risk for transformation.[74] However, the specific biological mechanisms remain poorly understood. An important next step is to investigate more thoroughly plausible biological pathways that may explain the relationship between birth weight and breast cancer risk.

Some potential limitations of the meta-analysis should be considered. Publication bias is always a serious concern for meta-analyses; however, visual inspection of the funnel plots did not provide any obvious evidence of publication bias across studies. Many included studies also investigated additional intrauterine environmental factors associated with breast cancer, which could increase the chance of inclusion of studies with a nonsignificant association between birth weight and breast cancer and, consequently, reduce the potential publication bias. Bias within studies, such as information bias or selection bias, could also have influenced the validity of this meta-analysis study. In 7 of the studies we included, birth weight information was obtained from interviews or questionnaires. Recall bias might be a major problem among these studies. However, 1 study indicated that the birth information directly reported from the mother is as precise as the information from medical records.[76] Therefore, the influence of recall bias in these studies could be negligible. Misclassification of cases might stem from the method of ascertaining the outcome through cancer registries as the result of possible incomplete reporting,[77–79] errors in the registry,[80–82] mismatched cases,[83] residential mobility, and subsequent losses to follow-up. Although the potential impact of this problem is difficult to evaluate, there is no reason to believe that the misclassification is differential with regard to the breast cancer outcome among different birth weight categories. Finally, the inconsistent findings across the included studies might result from the differences in sample sizes, study populations, measurement cutoff points of birth weight, or other study design characteristics, such as inclusion of different potential confounding variables.

Overall, the results of this study supported the hypothesis that birth weight plays an important role in determining breast cancer risk in adult life. In particular, our findings indicated that breast cancer risk increased approximately 7% per 1 kg increase in birth weight. These results underscore the importance of conducting additional studies to clarify the underlying biological mechanisms that may further our understanding of the relationship between birth weight and breast cancer. This meta-analysis did not reveal effect modification by menopausal status, and additional studies are warranted because of the limited number of studies that stratified by this factor. In addition, more studies with improved research methods and analytic approaches are warranted to address the question of whether birth weight is more strongly associated with early-onset than with later-onset breast cancer.

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Disclosure statement

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