SYSTEMATIC REVIEW

Birth-weight and Risk of Breast Cancer: A Systematic Review Study

Stephenson Babatunde Ojeifo, MBBS, MPH; Seun Stephen Anjorin, MPH

1Etsako East Local Government, Edo State Ministry of Health, Benin City, Edo State, Nigeria,
2Women’s Health and Action Research Centre, Benin City, Edo State, Nigeria

Corresponding author email: aosanjorin@gmail.com

ABSTRACT

Introduction: Observational studies have linked the risk of breast cancer to birth weight, however, findings are not consistent. Therefore, the objective of this study was to investigate and quantify the level of risk of breast cancer associated with birth-weight among women.

Methodology: A systematic search of literature was conducted from 1990-2016 using the following databases: PUBMED, DH-Data, EMBASE, MEDLINE, PSYCINFO and GOOGLE SCHOLAR. 13 relevant articles were identified for the systematic review, out of which 5 were suitable for meta-analysis. The computer software Review Manager (RevMan) 5.2 was used for the meta-analysis.

Results: Most of the studies reviewed reported significant increased risk of breast cancer among participants with high birth weight. There were indications that this relationship is more pronounced among premenopausal women. In addition, the meta-analysis further revealed that women with sub-optimum birth-weight (<3,500g) are at lesser risk of breast cancer when compared with optimum birth-weight 3,500g-4,500g (OR= 1.17 (95% CI 0.98, 1.39)); while optimum birth-weight (3,500g-4,500g) women are at lesser risk of breast cancer when compared with women with above-optimum birth-weight (>4,500g) (OR=0.87 (95% CI 0.66, 1.15).

Conclusion and Implications for Translation: This study revealed that the risk of breast cancer increases with increasing high birth weight especially among premenopausal women, thus suggesting early onset of breast cancer in this group. There is a clear relationship between high birth weight and risk of breast cancer; the developmental origin of health and diseases theory as postulated by Baker may be the strongest biological mechanism to explain this finding. Prevention programs through health education and early diagnosis strategies targeted at this group might be promising strategies to tackle global burden of breast cancer.

Key words: Breast cancer • Birth-weight • Level of risk • Developmental origin of disease • Systematic review

Copyright © 2018 Ojeifo and Anjorin. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
1. Introduction
Breast cancer, a non-communicable disease, is the most common cancer in women and the commonest cause of cancer death among women globally. While it is the second cause of cancer death in more developed countries (198,000 death, 15.4% of total), it is the most frequent cause of death in women in less developed countries (324,000 deaths, 14.3% of total). The exact etiology of breast cancer is largely unknown, however, series of studies have linked factors such as age, gender, family history, early menarche, late menopause, oral contraceptives, alcohol consumption, obesity in postmenopausal women, with increased risk of breast cancer.

Meanwhile, there has been increasing evidence about the impact of in utero development on the risk of developing diseases in later life. Studies have shown that birth-weight, a surrogate indicator of in utero development, is closely associated with the risk of developing diseases such as diabetes, cardiovascular diseases, stroke, cancer, infectious diseases and minor illnesses. Barker in 1995 postulated the theory of developmental origin of diseases as the underpinning biological mechanism for these relationships. Recently, there has been an emerging concept that the increased risk of diseases associated with birth-weight in infants, children and adult is in a J-shaped pattern. Therefore, the risk of diseases associated with birth-weight is argued to increase up to 3500g birth-weight, lowest between 3500g-4500g and increases again from 4500g (Spencer, 2003). In relations to breast cancer, findings from research have shown that both low and high birth-weight are also associated with increased risk of developing breast cancer in later life. Generally, this concept is under-researched and there has been conflicting findings from the few studies that has explored it in the literature. Therefore, the aim of this study was to investigate and provide robust evidence on the possibility of a J-Shaped pattern in the risk of breast cancer in association with birth-weight by appraising relevant studies using the systematic review employing meta-analytical method.

2. Methods
This study was carried out using the guideline for conducting and reporting Meta-analysis of Observational Studies in Epidemiology (MOOSE).

2.1. Literature search
A thorough systematic literature search was conducted spanning studies from 1990 to 2016 using the following search terms: ‘Birth-Weight’, ‘Low Birth-Weight’, ‘High Birth-Weight’, ‘Breast Malignancy’, ‘Breast Cancer’, ‘Risk Factors’ or ‘Level of Risk’ and ‘Association’ or ‘Relationship between Breast Cancer’, ‘Birth-Weight’ ‘Case-control’ ‘Cohort’ to identify relevant studies. The following databases; PUBMED, DH-DATA, EMBASE, MEDLINE, PSYCINFO, and GOOGLE SCHOLAR, were used to search for original articles that assessed the relationship between birth-weight and breast cancer. Snowballing approach was used to identify relevant studies. The studies generated while searching the databases unavoidably consisted of duplication and irrelevant studies, hence, the advanced search options of the databases were used to narrow the search to more relevant studies (figure 1).

2.2. Studies Selection
The following inclusion criteria defined a priori were used to determine inclusion or exclusion of studies into the systematic review and meta-analysis: original article that have assessed the relationship between birth-weight and risk of breast cancer, observational (cohort or case-control) studies, published and/or grey literature between 1990-2016, studies that reported sufficient statistical information to permit estimation of appropriate effect seize, measured outcome must be diagnosis of breast cancer in women. In order to ensure methodological appraisal, included studies must have documented the diagnosis of breast cancer using standard diagnostic tool. Further quality appraisal was conducted using STROBE Checklist for Cohort, Case-Control and Observational Studies [Strobe Statement]. All the 13 included studies were assessed across the 22 criteria of THE STROBE statement guideline. Each study
was awarded 0 or 1 according if the criterion was not met or if they criterion was met respectively; therefore, the highest obtainable score was 22. A study is graded as low, if score is < 12, medium, if score is between 12-18, and high quality if score is >18. The outcome of the quality appraisal was not used to determine the inclusion criterion in order to capture all the studies that have assessed desired outcomes. However, it was used to interpret findings in this study.

2.3. Data extraction and data-analysis

All the relevant data involved in the systematic review and meta-analysis was abstracted using a standardized form by the Principal Investigator (PI) (O.S). The meta-analytical process involved two groups of dichotomous comparison. Hence, the total number of subjects with suboptimal birth-weight (<3500g), optimal birth-weight (3500g-4500g) and above optimal (>4500g) were extracted from all the included studies. Further, data on the numbers of participants with morbidity.

Figure 1: Flow Diagram of Study Selection According to Prisma Flow Diagram
or mortality due to breast cancer were also extracted according to the birth-weight group stated above. This process was repeated twice by the PI and crossed checked by S.A using the same standardised form; areas of differences were settled. (Supplement 1 for details of information and data extracted). In addition, authors of the articles were contacted via email for clarifications when necessary.

In the qualitative analysis, the data extracted from the included studies were organized emerging themes and manually analyzed using narrative synthetic approach. Mantel-Haenszel method was used to estimate the mean effect estimates across the included studies due to its robustness and higher precision in combination of weighted average.\textsuperscript{28} The random effect model was used because of the expected variations amongst the included studies while the odd ratio was used to interpret and measure the risk estimate across studies. A sub-group analysis was done to access the variability in the included study design. The Chi-Square ($X^2$), P-Value, $I^2$, and the odds ratio (OR) were the appropriate statistical test used in this study. Hence, $X^2$ and $I^2$ was used to assess the heterogeneity between studies. The funnel plot generated from the forest plot was used to assess publication bias. The Review Manager (RevMan) 5.2 from Cochrane Library was used to perform the quantitative analysis (meta-analysis).\textsuperscript{29}

3. Result

The searches generate 3,004 articles; they were screened by their titles; 2109 were determined as irrelevant and 216 duplicates were excluded. In total, 421 articles were screened by their abstracts, 306 were excluded; therefore, 65 full-text relevant articles were retrieved for detailed reading and assessment with the eligibility criteria, 48 articles did not meet at least one of the selection criteria while data could not be extracted from three articles due to incomplete presentation of birth-weight range. Hence, 14 studies were eligible and included in the systematic review study while only 5 of these studies were eligible and included in the meta-analysis.

3.1. Study characteristics

The following information were retrieved from the included articles: Authors’ name, tile of article, publication year, country, study design, measured exposure and outcomes, source of data, follow-up period, study size, major findings and co-founding factors (table 1). All the included studies were recent studies as least year of publication was in year 2000; the studies were all conducted in United States, United Kingdom and other European countries (table 1).

Of these 14 studies, 5 were case-control studies and 8 were cohort studies. However, only 5 out of the 13 included studies were eligible to be used for meta-analysis; these studies collected and presented outcome data and estimates of the association between risk of breast cancer and birth-weight using dichotomous comparisons. The number of the participants in the 5 studies used for meta-analysis varied from as small 363 participants to as large as 106,504 participants. The total numbers of 127,012 participant data was extracted from the 5 studies; 77,394 participants were in the sub-optima birth-weight group; 46,317 participants were in the optimal birth weight group; while 3,301 participants were in the above-optimal birth weight group. The total number of breast cancer cases assessed were 7,239; 4,306 were in sub-optimal group; 2,587 were in optimal group; while 346 were in above-optimal birth-weight group, respectively.

During quality assessment using the STROBE Checklist, 6 of the 14 included studies were evaluated to be of high quality while the remaining 8 studies were adjudged to be of medium quality. Primarily, reasons for lower quality are variables and outcomes not clearly defined, study participants characteristics not provided, and study limitations not explained. The findings from the systematic review are presented under two themes: 1) Risk of breast cancer in suboptimum (<3500g), and 2) Risk of breast cancer in above-optimum birth weight (3500g-4500g) with optimum birth weight as the reference. The results from the meta-analysis were presented under same themes.

3.2. Risk of breast cancer in suboptimum birth-weight

Three (3) out of the 14 included studies documented increased risk of breast cancer among women with
Table 1: List of studies included in the systematic review.

<table>
<thead>
<tr>
<th>Study (Author, Year of Publication, Country)</th>
<th>Study title &amp; Design</th>
<th>Follow-up Period</th>
<th>No. of Breast Cancer Cases</th>
<th>Study Population Source of Birth weight Information</th>
<th>Results/findings</th>
<th>Adjustment for other Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troisi et al., 2006 UK</td>
<td>Birth weight and breast cancer risk Cohort study</td>
<td>1992-2001</td>
<td>97</td>
<td>The NCI DES Combined Cohort Study National Death Index (NDI)-Plus</td>
<td>There was no association between birth weight and breast cancer risk comparing women who weighed  &lt;3000 g (rate ratio (RR) = 0.93) or &gt;43500 g (RR = 1.09) with women who weighed 3000–3499 g at birth (P for trend = 0.69) and there was no obvious pattern in the association of gestational age with breast cancer incidence (P for trend = 0.66).</td>
<td>Mother’s age, and gestational age</td>
</tr>
<tr>
<td>Ahlgren et al., 2004 Denmark</td>
<td>Birth weight and risk of cancer Cohort study</td>
<td>1936-1975</td>
<td>12,540</td>
<td>Danish Cancer Registry</td>
<td>Breast cancers demonstrated a positive linear association with birth weight.</td>
<td>None</td>
</tr>
<tr>
<td>Kaijer et al., 2003 Sweden</td>
<td>Preterm birth, birth weight, and subsequent risk of female breast cancer</td>
<td>1925-1949</td>
<td>1483</td>
<td>Swedish Cancer Register</td>
<td>The overall risk of cancer among the women was not increased. The risk of breast cancer was neither associated with preterm birth nor with low birth weight, but a birth weight of more than 3000 g was associated with an increased risk of breast cancer</td>
<td>Gestational age,n</td>
</tr>
<tr>
<td>Mæhle et al., 2010 Norway</td>
<td>Birth length and weight as predictors of breast cancer prognosis</td>
<td>1910-2003</td>
<td>331</td>
<td>Norwegian Cancer Registry, The Central Person Registry</td>
<td>The results indicate that women who were longer than 52 cm at birth had 92% higher risk (hazard ratio 1.92, 95% confidence interval, 1.09-3.41) of dying from breast cancer compared to patients who were 48 cm or shorter. No clear associations with survival related to birth weight or ponderal index.</td>
<td>Ponderal Index, Gestational age</td>
</tr>
</tbody>
</table>

(Contd...)
<table>
<thead>
<tr>
<th>Study (Author, Year of Publication, Country)</th>
<th>Study title &amp; Design</th>
<th>Follow-up Period</th>
<th>No. of Breast Cancer Cases</th>
<th>Study Population</th>
<th>Source of Birth Weight Information</th>
<th>Results/findings</th>
<th>Adjustment for other Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCormack et al., 2003, Sweden</td>
<td>Fetal growth and subsequent risk of breast cancer: results from long term follow up of Swedish cohort</td>
<td>1915-1970</td>
<td>5358</td>
<td>5358</td>
<td>Swedish Cancer Registry, The Uppsala Birth Cohort</td>
<td>Premenopausal women with a birth weight of &lt;5.5 lbs had a covariate-adjusted hazard ratio (HR) for breast cancer of 0.66 [95% confidence interval (CI) 0.47–0.93] compared with women born at 8.5 lbs or above. Among postmenopausal women, no important association between the birth weight and the incidence of breast cancer was detected (HR comparing women with a birth weight of 5.5 lbs or less with women with a birth weight&gt;8.5 lbs: 0.97; 95% CI 0.80–1.16)</td>
<td>Gestational age, Adult’s height</td>
</tr>
<tr>
<td>Park et al., 2006, Poland</td>
<td>Intrauterine environment and breast cancer risk in a population-based case-control study in Poland</td>
<td>2000-2003</td>
<td>2385</td>
<td>4888</td>
<td>Population-based breast cancer case-control study in Warsaw and Lodz in Poland</td>
<td>Birth weights over 4,000 g were associated with a significantly increased risk compared to weights less than 2,500 g (OR 5 1.54, 95% CI 1.08–2.19).</td>
<td>Maternal smoking and gestational age</td>
</tr>
<tr>
<td>Stavola et al., 2000, UK</td>
<td>Birth weight, childhood growth and risk of breast cancer in a British cohort</td>
<td>1971-1992</td>
<td>37</td>
<td>2548</td>
<td>The Medical Research Council National Survey of Health and Development</td>
<td>There was evidence of greater risk of breast cancer with greater birth weight (rate ratio = 1.76 [95% CI: 0.92, 3.35] for birth weight 3.5 kg vs birth weight &lt; 3.5 kg), which was more marked at pre-menopausal ages (RR = 2.31, 95% CI: 0.93, 5.74).</td>
<td>Age, birth order, adult height, body mass index</td>
</tr>
<tr>
<td>Vatten et al., 2002</td>
<td>Birth weight as a predictor of breast cancer: a case – control study in Norway</td>
<td>1910-1970</td>
<td>719</td>
<td>2876</td>
<td>Norwegian Cancer Registry</td>
<td>Birth weights in the highest quartile (3730 g or more) were associated with 40% higher risk (odds ratio, 1.4, 95% confidence interval, 1.1 – 1.9) of breast cancer compared to birth weights in the lowest quartile (less than 3090 g).</td>
<td>Mother’s socioeconomic status</td>
</tr>
</tbody>
</table>

(Contd...)
Table 1: (Continued)

<table>
<thead>
<tr>
<th>Study (Author, Year of Publication, Country)</th>
<th>Study title &amp; Design</th>
<th>Follow-up Period</th>
<th>No. of Breast Cancer Cases</th>
<th>Study Population</th>
<th>Source of Birth weight Information</th>
<th>Results/findings</th>
<th>Adjustment for other Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michels et al., 2006, USA</td>
<td>Longitudinal study of birth weight and the incidence of breast cancer in adulthood</td>
<td>1976-2001</td>
<td>2969</td>
<td>Health Study (NHS) and the Nurses’ Health Study II (NHS II).</td>
<td>Premenopausal women with a birth weight of &lt;5.5 lbs had a covariate-adjusted hazard ratio (HR) for breast cancer of 0.66 [95% confidence interval (CI) 0.47–0.93] compared with women born at 8.5 lbs or above</td>
<td>As expected, increasing age at first birth was associated with increasing risk of breast cancer, and there was a reduction in risk with increasing parity</td>
<td>Age at menarche, adult height, family history of breast cancer</td>
</tr>
<tr>
<td>Hodgson, 2004, USA</td>
<td>Birth weight, parental age, birth order and breast cancer risk in African-American and white women: a population-based Case-control study.</td>
<td>May 1993 to December 1996</td>
<td>196</td>
<td>Birth records</td>
<td>Findings revealed that there was a weak inverse association between birth weight in the highest tertile and breast cancer overall. Although associations varies by race. As high birth weight was inversely associated with breast cancer among African-American women, and there was no association found with low birth weight.</td>
<td>Adjusted for maternal age, age, race, adult BMI, sampling fraction, and history of previous biopsy.</td>
<td></td>
</tr>
<tr>
<td>Innes, 2004, USA</td>
<td>First pregnancy characteristics and subsequent breast cancer risk among young women. A Case-control study.</td>
<td>1978-1995</td>
<td>2,522</td>
<td>New York State birth and tumour registries</td>
<td>The data assessing birth weight and the risk of breast cancer was statistically significant.</td>
<td>Conditions on extreme prematurity, abruption placenta, preeclampsia, perinatal factors, gestational hormones (particularly oestrogens).</td>
<td>(Contd...)</td>
</tr>
<tr>
<td>Study (Author, Year of Publication, Country)</td>
<td>Study title &amp; Design</td>
<td>Follow-up Period</td>
<td>No. of Breast Cancer Cases</td>
<td>Study Population</td>
<td>Source of Birth weight Information</td>
<td>Results/findings</td>
<td>Adjustment for other Covariates</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>---------------------</td>
<td>-----------------</td>
<td>---------------------------</td>
<td>-----------------</td>
<td>-----------------------------------</td>
<td>-----------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Ahlgren, 2003, Denmark.</td>
<td>Birth weight and risk of breast cancer in a cohort of 106,504 women. A cohort study.</td>
<td>968 to August</td>
<td>2,334</td>
<td>106,405</td>
<td>School health records</td>
<td>There was a significant positive association between birth weight and breast cancer equivalent to a 9% increase in risk per 1,000 g increase in birth weight</td>
<td>Adjusted for age and calendar period additional adjustment for parity and age at first birth did not indicate confounding</td>
</tr>
<tr>
<td>Tius-Ernstoff, 2002, USA.</td>
<td>Early life factor in relation to breast cancer risk in postmenopausal women. A Case-control study</td>
<td>1992 to 1994</td>
<td>1,716</td>
<td>1,886</td>
<td>Telephone interview</td>
<td>A week J-shaped relationship between breast cancer and birth weight was observed; the increased risk was not statistically significant for either lower birth weight or the high birth weight. Overall results are consistent with previous studies and suggest that these early life factors have a modest influence on breast cancer risk in postmenopausal women</td>
<td>Covariates including other available early-life factors, parental smoking, religion, family history of breast cancer, parity, age at first full-term pregnancy, BMI at reference date, and age at menopause considered, but analysis provided no evidence of confounding, so final model adjusted only for age and state.</td>
</tr>
<tr>
<td>Innes, 2000, USA.</td>
<td>Birth characteristics and subsequent risk for breast cancer in very young women. A Case-control study.</td>
<td>1978-1995</td>
<td>484</td>
<td>2,870</td>
<td>New York and New York City birth records</td>
<td>Birth weight showed a J-shaped relation to breast cancer risk, which was said to be more with high birth weight babies. Relatively to babies whose weight at birth range between 2,500-3,499g; those babies of 4,500g and above were over three time as likely to develop breast cancer as a young adult.</td>
<td>Conditions on date of birth and maternal country of residence. Adjusted for gestational age, preeclampsia, abruptio placentae, multifetal gestation, birth rank, maternal age at birth, parental age at birth, and ethnicity.</td>
</tr>
</tbody>
</table>
Birth-weight and Risk of Breast Cancer

suboptimum birth weight (< 3500g). The three studies were part of the five articles included in the meta-analysis, indicating that useful ranges of birth weight data were presented. While the three studies were carried out in the United States, and used the same research design – case-control - two of the studies involved young women while the third one involved postmenopausal women. The three included studies adjusted for various confounders such as maternal age, race, BMI, religion, parental smoking, only one of the studies adjusted for gestational age – the most potent confounder. Only one of the studies reported a weak relationship between LBW and risk of developing cancer, however, this study involves postmenopausal women only. Seven (7) studies reported that risk of breast cancer reduces with lower birth weight.

3.3. Risk of breast cancer in above-optimum birth-weight

Ten (10) out of the fourteen (14) included studies documented increased risk of breast cancer among women with above-optimum birth weight (>3500g). While the ten studies were conducted in the US, UK and other European countries, different research designs – cohort and case-control study design – were used to assess the association. Five (5) out of the 10 studies reported that the association was stronger among premenopausal or young women; one study reported stronger association in postmenopausal women. In addition, all the 10 studies adjusted for potential confounder including gestational age, and two studies documented birth length and/or ponderal index as a better indicator to assess prenatal exposure and risk of developing breast cancer in later life. Interestingly, two out of the 13 studies reviewed reported no significant relationship between birth weight and the risk of developing breast cancer in later life, neither with LBW nor HBW. It must be noted that these two studies were conducted in US and Norway with the same research design – cohort study.

3.4. Meta-analysis of optimum birth weight vs. Sub-optimum birth-weight

Based on the five studies analysed, optimum birth weight (<3500g) was found to be associated with increased risk of breast cancer when compared with sub-optimum birth weight (3500g-4500g) (figure 1). The pooled odd ratio (OR) estimate risk for breast cancer disease was 1.17 (95% CI 0.98, 1.39). However, there was an obvious heterogeneity between the studies included in the meta-analysis (Tau²=0.03, Chi²=28.93, df=4 (P<0.00001); I²=86%), this informed our decision to use the random-effect model to compute the odds ratio. In addition, the forest plot showed that the diamond shape crossed the line of no effect (figure 1) which implies that the sub-optimum birth weight are not totally out of risk of breast cancer as reflected in the confidence interval (95% CI 0.98, 1.39). Finally, the overall effect of birth weight (Z=1.74) on the risk of breast cancer was found to be not-significant (p=0.08).

4. Discussion

This systematic review study has provided a more robust and broader insight into the relationship between birth-weight and risk of breast cancer in later life by highlighting the quality, distribution, and the characteristics of studies few studies found to be eligible according to the eligibility criteria. The findings from the systematic review showed that there is a clear relationship between high birth weight and risk of breast cancer; this relationship was found to be more pronounced among premenopausal women by most of the studies included in the systematic
In addition, the meta-analysis study—based on 127,012 participants drawn from the 5 eligible studies—showed that the risk of breast cancer increases with increased birth weight such that participants with birth-weight >4500g were found to be at greater risk of breast cancer. On the other hand, our findings, both from the systematic review and meta-analysis, showed that participants with optimum birth weight (3500g-4500g) are not less likely at risk of breast cancer as hypothesised, and neither were participants with sub-optimum birth weight (<3500g) at increased risk. Therefore, the hypothesized J-shaped relationship was not observed in this study. In both meta-analysis, significantly high heterogeneity were observed, and this is likely due to the various methodology used by the included studies; however, this was addressed in the analysis by using the random-effect model to estimate the odd ratios\[Higgins et al, 2011\]. In addition, none of the estimated risk were significant (p<0.05), however, findings from the systematic review revealed that risk of breast cancer in association with birth weight is more pronounced in premenopausal women, below 50 years in age. This might have affected the findings in the meta-analyses as the data from the included studies could not be disaggregated by menopausal status or age.

Figure 2: Forest plot on the risk of breast cancer in optimum birth-weight 3,500 g-4,500 g versus sub-optimum birth-weight <3,500 g. Studies were arranged according to their year of publication. The line shows the range of 95% confidence interval (CI) for each study. Odds ratios (ORs) estimate for each study risk of breast cancer was indicated by the black square and the size of the square shows the statistical weight that each study contributes to the overall estimates of the square.

Figure 3: Forest plot on the risk of breast cancer in optimum birth-weight 3,500 g-4,500 g versus above-optimum birth-weight >4,500 g. Studies were arranged according to their year of publication. The line shows the range of 95% confidence interval (CI) for each study. Odds ratios (ORs) estimate for each study risk of breast cancer was indicated by the black square and the size of the square shows the statistical weight that each study contributed to the overall estimate of the square.
Meanwhile, the findings from this study are consistent with other body of literature— which have indicated that breast cancer risk increases with high birth weight.\textsuperscript{2,18,27,33,36,37,38,39} A large meta-analysis study\textsuperscript{19} involving 2,334 breast cancer cases and 106,504 participants found a significant positive association between birth weight and breast cancer risk such that a 1,000g rise in birth weight was estimated to increase the risk of breast cancer by 9\% [OR=9.95\% CI= 2\% to 17\%]. Another meta-analysis study\textsuperscript{17} pointed that evidence from available data strongly suggest a positive relationship between birth weight >4000g and increased risk of breast cancer in later life.

The biological mechanisms that underpin this relationship have been under investigation, strongest among them is the developmental origin of health and diseases (DOHaD) theory postulated by Baker.\textsuperscript{13,40,41} According to this theory, it is believed that adverse intrauterine exposure of foetus, which is usually have overwhelming impact on birth seize, can result to a permanent change in the physiology and metabolism of the foetus, thus, increases susceptibility to diseases in later life.\textsuperscript{42,43,44} There is a growing body of evidence that the risk of breast cancer in later life is largely influenced by intrauterine exposure—which is usually assessed birth weight as surrogate indicator. In animal experiments,\textsuperscript{34,45,46} exposure to increased maternal oestrogen level- a hormonal exposure that has been linked to birth weight,\textsuperscript{30,47} during foetal and early postnatal development has been found to make marked changes to foetal mammary development which in turn may increase the risk of breast cancer in adulthood. In addition, breast cancer risk in association with high birth weight maybe confined to oestrogen receptor-positive (ER+) tumours and progesterone receptor positive (PR+) tumours; thus stressing on the potential mechanistic role of sex steroid hormonal pathway.

On the other hand, findings from few studies also indicated that there is a weak relationship between birth weight and the risk of breast cancer.\textsuperscript{24,30} A study conducted in Sweden using birth records\textsuperscript{23} reported a positive associated risk of breast cancer in low birth weight and high birth weight participants. The same author\textsuperscript{23} in another study using birth records information in four additional hospitals to that used in their first study could not confirm an association between birth weight and the breast cancer.

4.1. Limitations

There is need to interpret the findings from this systematic review and meta-analysis carefully due to some limitations encountered during the study. There was a significant level heterogeneity among the studies included was observed in the meta-analysis. This was addresses by using a random effect model to compute the odd ratio. In addition, due to the fewer number of studies involved in the meta-analysis, we could not conduct meta-regression and publication bias. Furthermore, only English Language studies were included, the studies included for systematic review and meta-analysis were conducted in Europe and US, hence, affected the generazablity of the study.

5. Conclusion and Implications for Translation

A total of 13 studies for the systematic review and 127,012 of secondary data derived for individual studies included in the meta-analysis provided more robust and clearer evidence on the relationship between birth weight and risk of breast cancer later in life. Using systematic review methodology, which is usually the highest in hierarchy of evidence in medical research, there is a clear relationship between high birth weight and risk of breast cancer; this relationship was found to be more pronounced among premenopausal women.

In the developed countries, which has the highest incidence rate of breast cancer, prevention programs through health education and early diagnosis strategies targeted at this group might be a promising strategy to tackle its associated burden. This is also important in developing countries, where 58\% of breast cancer-associated deaths occur but patients have the lowest survival rate due to late diagnosis of most cases on breast cancer. In addition, further research is needed to understand the underlying factors between risk of breast cancer and high birth weight, especially among premenopausal women.
Compliance with Ethical Standards

Ethics Approval: This study is based on analysis of existing data. Acknowledgment: Dr Denise Bellingham-Young for introducing meta-analysis and providing technical assistance at different stages during the study. Funding: The authors did not receive any funding for this study. Conflict of Interest: There is no conflict of interest in the research paper.

References


