Does the Sex of the Firstborn Child Affect the Breast Cancer Risk and Survival: A Systematic Review and Meta-analysis of Over 1 Million Cases

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Background: Reports on the risk and prognosis of breast cancer in relation to the sex of a child have been conflicting. Since medical sciences play an important role in informing sociocultural understandings of health and illness, evidence-based studies have the potential to foster or counter stigma and shape social attitudes toward a newborn's sex.

Aims: To pool all available evidence to provide the highest level of evidence on the association between the sex of the first child and breast cancer risk or prognosis.

Study Design: Systematic review and meta-analyses.

Methods: A comprehensive search using three databases was conducted from inception until May 2020. Titles and abstracts of all papers identified were independently screened by two authors. Data extraction and quality assessment were also performed independently by two researchers. The breast cancer risk was quantified using the odds ratio, and the prognosis (i.e., mortality) was measured using the risk ratio.

Results: In the meta-analysis, 11 studies with more than 1 million participants were included. The pooled estimate from the five studies on risk and the six studies on prognosis were odds ratio 0.99 (95% confidence interval, 0.95-1.03) and risk ratio 1.00 (95% confidence interval, 0.80-1.26), respectively.

Conclusion: When we pooled all available evidence, the sex of the firstborn child was neither associated with risk nor prognosis in breast cancer. Clinically, our findings are reassuring and important, especially in light of previous studies that recommended differential treatment and counseling based on the sex of the first child. Socially, our findings challenge conventional social stereotypes that regard male children as biologically superior to female children.

INTRODUCTION

Reproductive history has been known to affect the risk and prognosis of breast cancer.[1,2] Hormonal or immune mechanisms are suggested as possible pathways for such effects.[3] The fetal antigen hypothesis was proposed to explain the short-term and long-term protective effects of pregnancy on breast cancer risk.[4] In this context, Juret et al.[5] first reported that women with breast cancer whose firstborn child had been a boy experienced better 3- and 5-yr survival rates compared with women whose firstborn child was a girl. They argued that women with male firstborn children were more likely to have no axillary node involvement and postulated that this effect may

be due to differences in the gonadal secretions produced by male fetuses compared with the female fetuses.[5] Such claims, which are supported by scientific authority, have the capacity to substantiate societal preferences for male infants and prompt sex selection framed in pathological terms. Throughout history, the guise of medicine has been used to empower gender hierarchies. Inequity of the sexes are also replicated in medical research, which has been branded as "androcentric" on account of its preoccupation with male health and illness with the exception of women's reproductive health, which receives ample attention.[6] Few studies have addressed the impact of the dissemination of medical research on cultural

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perceptions of health and illness, although many have explored the impact of culture on health behaviors. Lorber and Moore[7] argued that the culture of illness, health, and lay medical knowledge are influenced by medical science and the research results it produces. Laterally, this raises the question of how medical research assessing the association between an infant's sex on mothers' breast health impacts social attitudes and influences reactions to the sex of newborns.Over the last five decades, numerous research papers have evaluated the risk and survival associated with a number of pregnancy and childbirth-related characteristics. These studies found very contradictory findings among women whose firstborn child was a boy; some studies reported a worsened prognosis,[8] while others found no association[9] or better prognosis.[10] Thus, the issue of whether the sex of the firstborn children predicts the risk of developing breast cancer and its prognosis remain unresolved to date.Several cultures evidence a preference for male children owing to a variety of socioeconomic, cultural, and biological factors wherein infanticide has become a method of sex selection.[11-16] With widespread parental preference for a male firstborn child,[17] studies suggesting that female newborns jeopardize maternal health could be readily exploited to legitimize practices, such as female infanticide. This illustrates how biology (sex) contours sociocultural constructs (gender), and it illustrates how our study may debunk sociocultural beliefs pertaining to female inferiority that were previously validated by scientific research. Studies were heterogeneous because there were conflicting findings about risk and survival associated with the sex of the firstborn child, which calls for further investigation to clarify these issues. One reason that might account for these conflicts is the characteristics of the populations studied. For instance, some studies restricted their study population to younger women (<45 yr), while others included broader age groups. Results of such studies may adversely reinforce negative social attitudes toward "geriatric" mothers (age >35) and be detrimental to their self-image and maternal bond to their newborn. McFadyen[18] reported that maternal life-threatening illness negatively affects attachment to newborns, among new mothers. Numerous studies that showed significant association were also small in terms of sample size and possibly subject to random error. Therefore, we conducted a methodological quality adjusted meta-analysis to pool all available evidence and provide the highest level of evidence on the association between the sex of the first child and breast cancer risk or prognosis.

MATERIALS AND METHODS

Findings of this systematic review and meta-analysis are presented according to PRISMA reporting guidelines[19] (Supplementary Material S1).

Search Strategy

A comprehensive search was carried out in three databases: PubMed, Web of Science, and Scopus. The original search strategy was designed to search PubMed. The strategy was then converted and expanded for use in Web of Science and Scopus. Search strategies used in each of these databases are provided in supplementary material (S2).The search included all articles from inception of the databases until May 2020. Search terms related to breast cancer, risk, survival, mortality, child, offspring, and sex were included. The systematic search was supplemented by a forwards and backward citation search as well as retrieving the first 20 similar articles from PubMed for each of the papers included from the initial search to achieve a comprehensive evaluation of the published evidence. In addition, all references from relevant previous systematic reviews were hand searched to identify possible missed studies.

Titles and abstracts of all papers were extracted and uploaded to the Rayyan platform (http://rayyan.qcri.org/), which is a web application developed by Qatar Computing Research Institute (Data Analytics).[20] Two authors (LT and LFK) independently screened the titles and abstracts on the Rayyan platform. The same authors examined the full-text papers for eligibility against the review protocol. Any disagreements were resolved through consensus and the involvement of a third author (SD).

Selection Criteria

Eligible studies were analytical epidemiological studies that reported the risk of women developing breast cancer and/or their prognosis (i.e., survival or mortality) in an extractable format. Studies have to include information on the sex of the women's firstborn child in order to be eligible. Exclusion criteria included studies conducted in animals, conference abstracts or proceedings, book chapters, descriptive studies (e.g., case series/case studies), and ecological studies. No language restrictions were imposed.

Data Extraction and Quality Assessment

Data extraction was performed by two researchers (LT and LFK) using a predefined tool that included (1) authors and year of publication; (2) study population, setting, and study period; (3) source of reproductive, cancer, and mortality data; (4) study design; (5) sample size, number of cases; and (6) effect estimates and its 95% confidence intervals (CIs).The MethodologicAl STandard for Epidemiological Research (MASTER) scale was used to assess the quality of the studies.[21] Studies examining the risk of developing breast cancer were assessed against all 36 bias safeguards of the scale, while studies that examined prognosis were assessed against 29 safeguards (items related to equal prognosis between groups were not applicable).

Statistical Analysis

Two effect measures of interest were examined in relation to the exposure (i.e., firstborn child being a boy compared with being a girl): (1) the risk of development of breast cancer was assessed using the odds ratio (OR) and (2) prognosis (i.e., breast cancer mortality risk) was assessed using the risk ratio (RR). The OR was selected for studies of risk breast cancer development given that cohort as well as case-control studies reported on this association. The RR was selected as the prognostic measure given that only cohort studies examined the prognosis in relation to the sex of the child.

Statistical heterogeneity was defined as tau-squared statistic >0 and quantified as moderate if I^2 > 50%. The quality effects (QE) model,

a bias-adjusted model, was used to pool the study effect sizes.[22] Information obtained from the quality assessment tool (MASTER scale) was used for bias adjustment in this meta-analysis. The presence of publication bias was assessed with the Doi plots and the LFK index.[23] All the analyses were conducted in MetaXL version 5.3 (EpiGear Int Pty Ltd; Sunrise Beach; Australia; http://www.epigear.com).

RESULTS

Studies Identified

The search identified 1,790 publications. After excluding duplicate citations, 1,377 publications remained. After screening the publications by title and abstract, 1,331 were excluded. Full-text screening was carried out in 46 publications, and 13 studies were found to be eligible. There was an overlap in subjects between two sets of publications. Hsieh et al.[24] and Cnattingius et al.[25] used data from the Swedish Birth and Cancer Registries, and Olsen and Storm[26] and Wohlfahrt and Melbye[27] used data from the Danish National Birth and Breast Cancer Registries. The publications with the largest sample size were selected; therefore, Hsieh et al.[24] and Olsen and Storm[26] were excluded from the analysis. Therefore, 11 studies (comprising over 1 million participants) were included in the meta-analysis (Figure 1).

Characteristics of Included Studies

Of the 11 studies included, five reported the risk of developing breast cancer, and six reported on breast cancer mortality. The studies were published between 1978 and 2010, and five were conducted in Europe (Sweden,[9,25] Norway,[28] Denmark,[27] and France[5]), while five were from North America (USA[1,8,10,29] and Canada[30]), and one from Asia (Iran[31]). The most commonly used sources of data were birth registries to identify the sex of the firstborn child, cancer registries for breast cancer ascertainment, and mortality information. A mixture of cohort[25,27,28] and case-control[1,31] studies were found for the risk of developing breast cancer, while only cohort[5,8-10,29,30] studies reported on prognosis. Sample sizes of the studies varied markedly (ranging from 212 to 802269) with four studies each including over 10,000 participants.[1,25,27,28] Two studies included between 1,000 and 10,000 participants,[9,29] and five studies included less than 1,000 participants[5,8,10,30,31] (Table 1).

Among the safeguards that apply to observational studies, the most common deficiencies were observed in equal ascertainment and equal implementation. The proportion of safeguards from the MASTER scale implemented in the various studies ranged between 42% and 79%, and relative ranks based on safeguard counts were used for bias adjustment using the QE model (Supplementary Material S3).

Quantitative Synthesis

There was no association between the sex of the firstborn child and the risk of developing breast cancer in all five studies that examined. The pooled OR was 0.99 (95% CI, 0.95-1.03) for studies that compared male to female firstborn child on the risk of developing breast cancer (Figure 2a). Among the six studies that assessed prognosis, two studies found that women who had a firstborn female child had a worse prognosis, while one study found
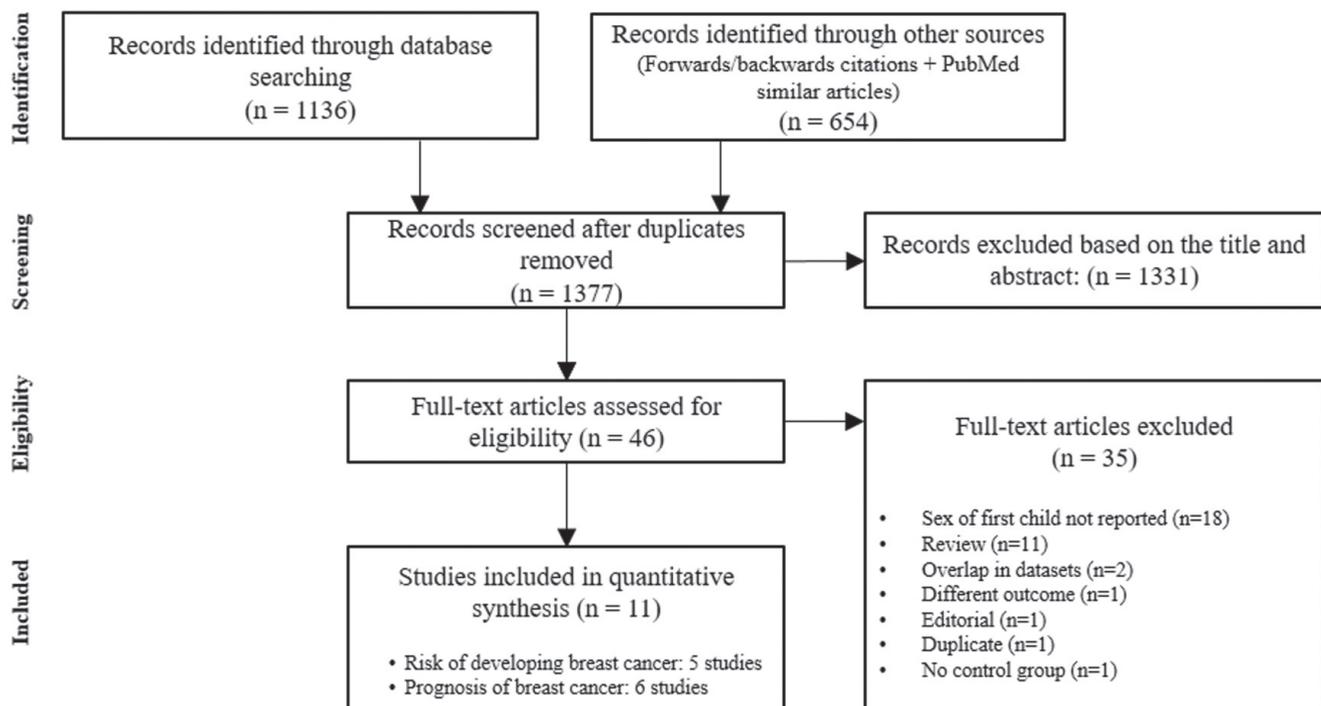

FIG. 1. PRISMA flow diagram of study selection.

TABLE 1. Characteristics of the Studies Included

Author, yr	Study population	Study period	Source of reproductive history data	Source of cancer data	Source of mortality data	Study design	Mean length of follow-up period	Mean age of participants (SD)	Number of participants	Number of women diagnosed with cancer	Number of deaths
Risk of developing breast cancer											
Albrktsen et al.[28]	All parous Norwegian women born between 1935 and 1971	1955-1991	Central Population Registry at the Central Bureau of Statistics	Cancer Registry of Norway and Central Bureau of Statistics	-	Cohort	11.6 yr	20-56 range	802,269	4,782	-
Cnattingius et al.[25]	Primiparous women who delivered singletons between 1982 and 1989	1982-2001	Swedish Birth Registry	Swedish Cancer Registry	-	Cohort	NR	NR	314,019	2,216	-
Innes and Byers[1]	Women who delivered in New York State after 1977	1979-1995	New York State Health Department	New York State Cancer Registry	-	Case-control	NA	37.6 (5.5)	12,574	2,522	-
Saadat[31]	Women with breast cancer attending the Nemazi Hospital (Iran) and healthy women from the general population	NR	Medical records and interview	Medical records and interview	-	Case-control	NA	47.8	745	389	-
Wohlfahrt and Melbye[27]	Women born after 1978 and who delivered in Denmark	1978-1994	National Birth Registry	Danish Breast Cancer Group's Registry	-	Cohort	NR	NR	12.8 million person yr	9,495	-
Prognosis-risk of mortality											
Elwood and Coldman[30]	Women with unilateral breast cancer treated at the A. Maxwell Evans Clinic (Canada)	1969-1978	Social service records	Medical records	Follow-up of the patients	Cohort	NR	NR	226	226	50
Janerich et al.[8]	Women diagnosed with breast cancer in New York State	1970-1976	Birth certificates	New York State Cancer Registry	Death certificates	Cohort	NR	NR	212	212	34
Janerich et al.[29]	Women diagnosed with breast cancer in Utah	1966-1989	Utah family genealogies	Utah Cancer Registry	Utah Cancer Registry	Cohort	NR	64	1,580	1,580	509
Juret et al.[5]	Patients with radical mastectomy operated at the Centre Francois Baclesse (France)	1964-1972	NR	Medical records	NR	Cohort	NR	NR	308	308	37
Olson et al.[10]	Women resident in Maine aged 25-44 when diagnosed with invasive breast cancer	1983-1987	Maine Office of Data, Research, and Vital Statistics	Maine Cancer Registry	Maine Office of Data, Research, and Vital Statistics	Cohort	NR	NR	223	223	106
Thalib and Hall[9]	Women born after 1931 and diagnosed with primary breast cancer	1958-1998	Swedish Generation Registry and the Registry of Population and Population Changes	Swedish Cancer Registry	Cause of Death Registry	Cohort	NR	NR	5,229	5,229	1,168

SD, standard deviation; NR, not reported; NA, not applicable.

Thalib et al. Sex of the First-born Child and Breast Cancer

433

that a firstborn male child was a predictor for poor prognosis. The pooled RR was 1.00 (95% CI, 0.80-1.26) for prognosis comparing male to female firstborn child (Figure 2b).

Publication Bias

There was minor asymmetry in the Doi plot for the risk studies, with an LFK value of -1.45, indicating a potential moderate level publication bias (Figure 3a), however, there was no evidence of publication bias among prognostic studies (Figure 3b).

DISCUSSION

All available evidence published to date that evaluated whether the sex of the firstborn child is associated with the risk of women developing breast cancer or their prognosis was pooled and did not support the proposed hypothesis of differences in the gonadal secretions produced by male and female fetuses. Given that previous studies suggested that women giving birth to a female child were at higher risk for breast cancer and poorer prognosis, our findings are reassuring and demonstrate no statistically nor clinically significant association. Such studies legitimate social devaluation of female newborns, providing scientific rationale that can be harnessed to reinforce gender hierarchies and justify sexual stratification. Our findings counter prevailing stigma associated with having firstborn females.[32] Few studies included in this review did report a significant association between the sex of the first child and breast cancer prognosis, despite the null findings when all the data available were combined. We envisaged that such association might have been due to potential confounders. Most studies did not report any adjusted estimates, and as such, this review was limited to pooling only the crude effects. Lack of adjustment for potential confounders in the studies included in this review may be important as any putative implication of sex of the firstborn
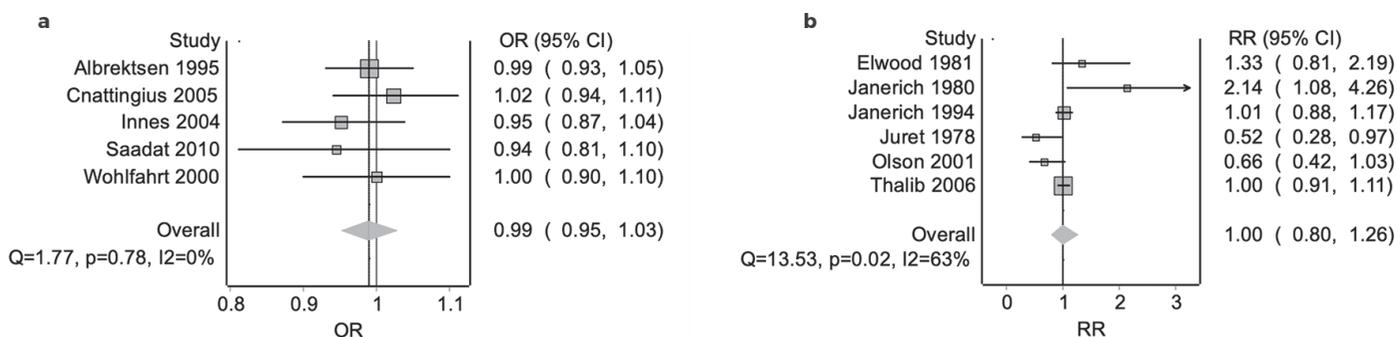

FIG. 2. Forest plots for the a) risk of developing breast cancer and the b) prognosis (mortality) in women whose first child was a male compared with women whose first child was a female.
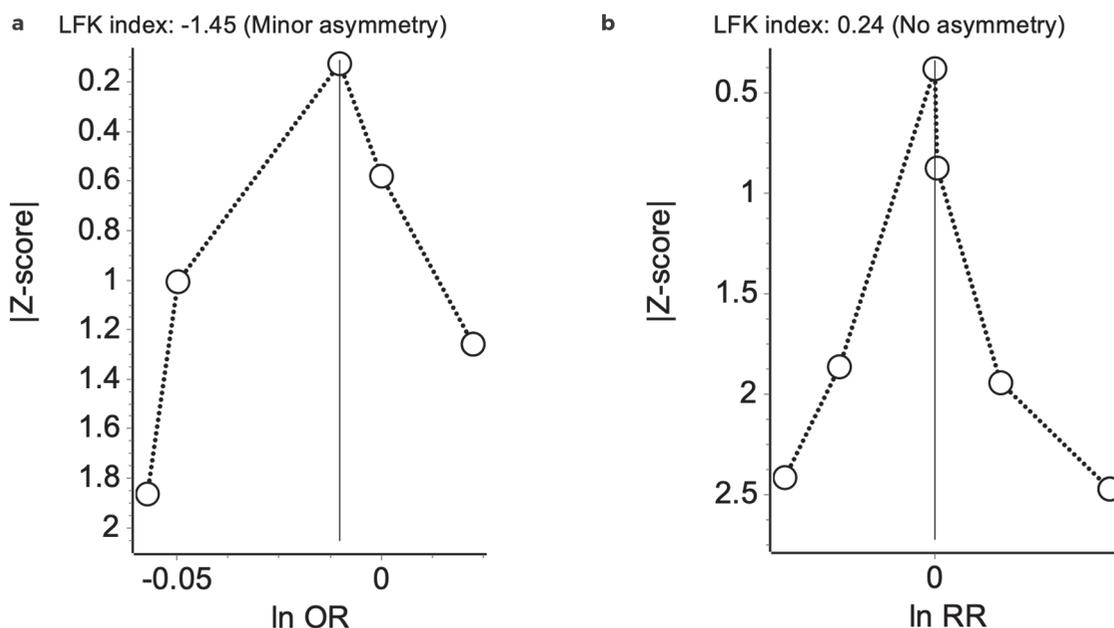

FIG. 3. Assessment of publication bias using the Doi plot and LFK index for a) risk of developing breast cancer and b) prognosis in relation to the sex of their first child.

child in different studies may have been a consequence of variation in factors, such as early age at menarche.[33,34] Some evidence suggests that for every 1-yr delay in the onset of menarche, there is a 5% reduction in breast cancer risk.[34] Another important factor that could vary across studies is later age at menopause, which increases breast cancer risk[34-36] by 1.03% for each year older at menopause, which is also comparable with the increase with the use of menopausal hormone therapy. Finally, parity itself has a dual impact on breast cancer risk. Parous women have an increased risk for developing breast cancer within the first few years of delivery relative to nulliparous women, but parity also confers a protective effect decades after delivery.[37] The effect of parity also differs depending upon the age of first birth and ethnicity. It is known that African American women have a significantly higher number of pregnancies and number of live births, as well as a poor survival with breast cancer.[38] It is clear, therefore, that all these factors associated with pregnancy, may have varied significantly across studies, which explains the variability seen in the association between sex of the first child and the risk of breast cancer or its prognosis. It is more plausible, given our findings, that any effect seen for sex of the firstborn child in the included studies individually were a consequence of random and/or systematic error and this bias-adjusted meta-analysis has addressed this issue by generating a pooled estimate that minimizes such errors. Scientific knowledge, grounded as it is in empirical evidence, can provide an apparent authoritative basis for perspectives, which reflect the specific sociocultural context in which the studies are conducted. Scientific facts can be conveniently adopted by states to justify the privileging of one sex over the other to further their sociopolitical and socioeconomic agendas. While epidemiological research has established associations between a number of reproductive factors and breast cancer risk beyond any doubt, it remains unclear until now if the sex of the firstborn child really indicated any of these influences.In the current study, for the first time, we demonstrate a null effect after pooling all available published evidence between the risk and prognosis of women breast cancer and the sex of their firstborn child. This is clinically important given that previous studies have advocated the use of the sex of the first child to indicate breast cancer risk, and a number of studies have advocated this as a marker of survival among women with breast cancer. Our findings provide reassurance that the sex of the firstborn child does not indicate any change in risk of developing breast cancer nor mortality once breast cancer develops. Socially, the results of this study refute earlier findings that might have be used to propagate notions of male child's biological superiority due to unsubstantiated claims of the protective effect of a male fetus on maternal health. Further, by dispelling an association between an increased risk of breast cancer or poorer prognosis depending on the sex of the firstborn child, these data eliminate a potential biological rationale for sex selection. The findings of this study contravene assumptions about the inherent biological superiority of male fetuses, especially as protective vectors of maternal health in relation to breast cancer, and perhaps additional cancers and other types of genetic diseases.

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