## The parity paradox: how number of children influences breast cancer mortality across age groups

**Abstract**

While parity has been extensively studied in relation to breast cancer risk, its age-specific impact on breast cancer mortality remains unclear. We examined how the relationship between parity and breast cancer mortality rates varies across different age groups. This retrospective cohort study included 894,608 Israeli women born between 1940 and 1960 and who were followed for 31 years (1990–2020). We employed an age-stratified approach (30–49, 50–64, and 65–80 years) and used Cox regression to examine associations between number of children (0, 1–2, and ≥ 3) and breast cancer mortality rates, adjusting for sociodemographic variables and calendar year of entry into each age group. Among women aged 30–49 years, those with 1–2 children (hazard ratio [HR] = 1.656; 99% confidence interval [CI] 1.349–2.033) or ≥ 3 children (HR = 1.551; 99% CI 1.271–1.893) had a greater breast cancer mortality risk than childless women. In women aged 50–64 years, these differences disappeared after adjustment (HR = 1.071; 99% CI 0.949–1.209 and HR = 0.935; 99% CI 0.830–1.054, respectively). In women aged 65–80 years, women with 1–2 children continued to exhibit an elevated risk (HR = 1.237; 99% CI 1.045–1.466), while no significant difference existed between women with ≥ 3 children and childless women (HR = 0.989; 99% CI 0.834–1.173). We thus revealed an age-dependent relationship between parity and breast cancer mortality. These findings highlight the need for age-tailored approaches to breast cancer risk assessment and prevention.

**Keywords:** breast cancer, parity, mortality, age-stratified analysis, cohort study

**Background**

Breast cancer is the most commonly diagnosed malignancy among women worldwide and remains a leading cause of cancer-related mortality. Despite advances in screening and treatment methods, projections indicate that by 2050, breast cancer incidence and mortality rates will increase considerably, underscoring the urgent need for further investigation into modifiable risk factors [1].

Breast cancer risk is influenced by a combination of genetic, environmental, and lifestyle factors. Obesity increases the risk of breast cancer in women who are menopausal or postmenopausal but may offer a protective effect in women who are premenopausal. Regular physical activity and weight management provide protective benefits [2]. Women who are postmenopausal face increased risk due to changes in estrogen metabolism, body composition, and immune function [3].

Reproductive history affects breast cancer risk. A meta-analysis found that early menstruation (age < 13 years), nulliparity, and hormonal contraceptive use are predictors of breast cancer in women of reproductive age [4]. Studies into infertility and breast cancer risk remain inconclusive, with a modest association with postmenopausal breast cancer, particularly among women with early infertility [5].

**Pregnancy-associated breast cancer**

Pregnancy-associated breast cancer occurs during pregnancy or after delivery and is characterized by more aggressive tumors, delayed diagnosis, and worse outcomes. Post-delivery diagnosis increases the risk of metastasis, likely due to immune suppression enabling tumor spread [6]. Pregnancy can promote short-term breast cancer risk while reducing lifetime risk [7].

**Breastfeeding and hormonal contraceptives**

Breastfeeding provides considerable protection against breast cancer, particularly for hormone receptor-negative subtypes. It lowers estrogen levels and helps eliminate damaged epithelial cells, with longer duration of breastfeeding providing greater protection [8]. Conversely, hormonal contraceptives increase breast cancer risk through sustained estrogen–progesterone stimulation of breast cells, although this risk decreases following discontinuation of these contraceptives [4].

**Risk factors during and after menopause**

The menopausal transition represents a critical period for breast cancer risk. Women experiencing menopause at a later age remain exposed to endogenous estrogen for longer, increasing the risk of hormone receptor-positive breast cancers [9]. Hormone replacement therapy (HRT), particularly combined estrogen–progesterone therapy, is associated with increased breast cancer risk, especially with long-term use [10, 11].

High-density breast tissue complicates early tumor detection, while postmenopausal genetic changes may contribute to cancer development [12, 13]. Obesity increases the risk of breast cancer in women who are menopausal or postmenopausal, highlighting complex hormonal interactions across different life stages [2].

Women who are postmenopausal face an increased risk of breast cancer due to changes in estrogen metabolism, inflammation, and immune function. [3] Estrogen receptor-positive cancers are particularly influenced by endogenous hormones, with the risk decreasing shortly after menopause due to reduced estrogen levels [14].

Additionally, obesity characteristic of women after multiple births [15], which may increase breast cancer risk and reduce survival rates in women who are postmenopausal [3, 16].

**Number of children as a risk or protective factor**

Parity (number of births) has been identified as a key modifier of breast cancer risk, although its impact on long-term survival outcomes remains unclear [9]. A study that analyzed data from 385,816 married women in Norway found a significant decrease in breast cancer incidence with each additional pregnancy, with a 10.5% reduction per additional child in cases of high parity [17].

Regarding the relationship between parity and breast cancer survival, a study of 1,485 African women diagnosed with breast cancer found that each pregnancy increased mortality risk by 5%. Premenopausal women who gave birth within the three years prior to their diagnosis exhibited a 52% lower survival rate [18]. Another study found that younger women (aged < 40 years) face a higher risk of breast cancer mortality, particularly in hormone receptor-positive subtypes [19].

Early studies found there was a higher risk of developing breast cancer among nulliparous women, especially compared with those who had their first child before the age of 20 years, which was suggested to reduce lifetime risk by up to 50% [20]. However, more recent research indicates that the protective effect of parity varies across breast cancer subtypes, with no consistent association found between parity and HER2-positive or triple-negative breast cancer [21, 22].

**Fertility in Israel and identified risk factors**

Israeli society is characterized by relatively high fertility rates compared with other Western countries, particularly within the Arab and ultra-Orthodox Jewish communities. In Israel, hormonal contraceptive use is relatively uncommon while fertility treatments are widely used [23, 24].

Previous studies conducted in this cohort have reported notable differences in breast cancer mortality rates, with higher mortality rates among Jewish women than Muslim women [25], lower mortality rates among Haredi Jewish women than non-Haredi Jewish women [26], and higher mortality rates among women living in urban areas than among those living in rural localities [27].

**Study objective**

In this study, we examined the age-dependent relationship between parity and breast cancer mortality in a large cohort of 894,608 Israeli women who were followed for 31 years. Through an innovative age-stratified approach examining three distinct life stages, we aimed to determine whether the association between the number of children and breast cancer mortality varies across a woman’s life course and persists after adjusting for sociodemographic variables.

The potential confounding variables in this study (ethnicity, ultra-Orthodox identity, residential locality size, socioeconomic status, and country of origin) were selected based on previous findings from this cohort that demonstrated their importance in breast cancer mortality patterns.

**Methods**

**Study design and population**

This retrospective cohort study included 894,608 Israeli women born between 1940 and 1960, who were followed up for a period of 31 years, from January 1, 1990, to December 31, 2020. The women were aged 30–50 years at entry and 60–80 years at conclusion. We used a unique age-stratified approach to examine breast cancer mortality rates among these women.

Individual-level data were obtained from various official sources, including the Population Authority, the Tax Authority, the Education Ministry, the Central Bureau of Statistics (CBS), and the Ministry of Health. Each individual was assigned a fictitious ID number that was used consistently across all databases, enabling comprehensive data integration while maintaining the confidentiality of the women.

The study received ethical approval from the Ethics Committees of the Tax Authority, the Population Registry, and the CBS. All data processing and analysis were conducted in the CBS Research Room after obtaining ethical approval.

**Study variables**

Sociodemographic variables collected from the Population Registry included sex, year of birth, religion, ethnicity, size of locality of residence, and country of origin. These were constructed as potential confounding variables.

Education level was categorized into three groups using data from the Education Registry (managed by the CBS): high (≥ 13 years of education), intermediate (8–12 years of education), and low (up to 8 years of education). Individuals with missing education data were classified as low, according to CBS standard procedures. All variables were examined as potential confounders based on a literature review and previous cohort findings.

The primary exposure variable was the number of children per woman, categorized as no children (women who were childless), 1–2 children, and ≥ 3 children.

The outcome variable was breast cancer mortality, determined from death certificates obtained from the Ministry of Health.

**Method used for age-based follow-up period division**

A key methodological feature of this study was the use of an age-stratified analysis approach within a single cohort. To examine age-specific impacts on breast cancer mortality rates, each woman contributed to relevant age groups based on the number of years lived within that specific interval. Only survivors from each age group who remained in Israel were included in subsequent age groups. Mortality rates were calculated based on the number of person-years. In the 30–49 years age range, 866,160 women participated, contributing 9,780,823 person-years; in the 50–64 years age range, 857,104 women participated, contributing 12,179,461 person-years; and in the 65–80 years age range, 752,958 women participated, contributing 3,853,657 person-years.

This approach created a situation where women born in 1940 who entered the cohort at age 50 years did not contribute to the 30–49 years age range, while women born in 1960 who were aged 60 years at the end of follow up did not contribute to the 65–80 years age range.

To prevent bias from improvements in breast cancer survival rates over time, statistical models across age ranges were adjusted for the calendar year of entry into each specific age range.

**Statistical analysis**

We examined the distribution of various baseline characteristics, including age at study entry, level of education, ethno-religious group (non-Haredi Jewish, Haredi Jewish, or Arab), country of origin, and size of locality of residence. Chi-square tests were used to compare frequency distributions of categorical variables, while *t*-tests were used for age comparisons (Table 1).

Breast cancer mortality rates per 10,000 women during the entire study period were stratified by education, ethno-religious group, country of origin, and size of locality of residence. Adjusted hazard ratios (AHRs) for breast cancer mortality were calculated, adjusting for age at the time of study entry. Using Cox regression and adjusted Kaplan–Meier analysis, we calculated relationships between study variables and breast cancer mortality, controlling for entry age. Effect estimates are presented as hazard ratios (HRs) with 99% confidence intervals (CIs) (Table 2).

Breast cancer mortality rates per 10,000 women and per 100,000 person-years by number of children were examined for the overall population throughout the entire follow-up period and by age-based follow-up period (30–49, 50–64, and 65–80 years). We used Cox regression and adjusted Kaplan–Meier analysis to evaluate relationships between the number of children and breast cancer mortality, controlling for age at the time of study entry (Table 3).

Additional Cox regression models and adjusted Kaplan–Meier curves were constructed to evaluate relationships between the number of children and breast cancer mortality while controlling for multiple factors. These factors included age at study entry or entry year in the age-based follow-up period, level of education, ethno-religious group, country of origin, and size of locality of residence. Likelihood ratio tests were used to compare models. Effect estimates are presented as HRs and 99% CIs. All analyses were conducted for the total population and by age-based follow-up periods.

Women who emigrated from Israel during the study period and did not return were considered censored, contributing to the number at risk in survival analyses until their year of departure.

All statistical analyses were performed using SPSS software (version 29).

**Results**

**Study design and population**

This cohort study followed 894,608 Israeli women born between 1940 and 1960 over a 31-year period (1990–2020). The study design included an initial analysis of the entire cohort, followed by stratification into age-based follow-up groups. Only individuals who entered each age period while still alive were included in the respective analyses, ensuring accurate mortality tracking over time

**Distribution of study variables**

The mean age at study entry was highest among women who were childless (39.95 years, SD = 5.65), while in women with 1–2 children, it was 38.63 years (SD = 5.42), and in those with ≥ 3 children it was 38.70 years (SD = 5.95; *P* < 0.001). Significant differences were observed in ethno-religious composition, level of education, country of origin, and size of locality of residence, with women who were childless being more educated and more represented among European- and American-born groups.

**Breast cancer mortality by number of children in the entire follow-up period**

The overall breast cancer mortality rate during the study period was 86.61 per 10,000 women. A significant association was found between the number of children and breast cancer mortality risk (*P* < 0.001). Women with 1–2 children or ≥ 3 children had a higher risk of breast cancer mortality compared with women who were childless (HR = 1.375; 99% CI 1.270–1.487 and HR = 1.213; 99% CI 1.125–1.308, respectively).

After adjusting for age at study entry, level of education, ethno-religious group, country of origin, and size of locality of residence, women with 1–2 children continued to exhibit a higher risk of breast cancer mortality compared with women who were childless (HR = 1.216; 99% CI 1.117–1.324), while there was no significant difference between women with ≥ 3 children and women who were childless (HR = 1.056; 99% CI 0.970–1.149).

**Breast cancer mortality by number of children in our age-based follow-up analysis**

**Aged 30–49 years follow-up period**

Among women aged 30–49 years, those with 1–2 children and those with ≥ 3 children exhibited higher breast cancer mortality rates compared with women who were childless (HR = 1.195; 99% CI 1.092–1.307 and HR = 1.140; 99% CI 1.140–1.166, respectively).

After adjusting for entry year in this age period, level of education, ethno-religious group, country of origin, and size of locality of residence, the association strengthened. Women with 1–2 children (HR = 1.656; 99% CI 1.349–2.033) and those with ≥ 3 children (HR = 1.551; 99% CI 1.271–1.893) continued to exhibit higher breast cancer mortality rates compared with women who were childless. No significant differences in mortality were observed between women with 1–2 children and those with ≥ 3 children.

**Aged 50–64 years follow-up period**

Among women aged 50–64 years, those with 1–2 children and those with ≥ 3 children exhibited higher breast cancer mortality rates compared with women who were childless (HR = 1.273; 99% CI 1.140–1.421 and HR = 1.141; 99% CI 1.027–1.267, respectively).

However, after adjusting for entry year in this age period, level of education, ethno-religious group, country of origin, and size of locality of residence, no significant differences in breast cancer mortality rates remained between women with 1–2 children (HR = 1.071; 99% CI 0.949–1.209) or women with ≥ 3 children (HR = 0.935; 99% CI 0.830–1.054) compared with women who were childless.

**Aged 65–80 years follow-up period**

Among women aged 65–80 years, those with 1–2 children exhibited higher breast cancer mortality rates compared with women who were childless (HR = 1.351; 99% CI 1.155–1.581), while no significant difference existed between women with ≥ 3 children and women who were childless (HR = 1.082; 99% CI 0.931–1.258).

After adjusting for entry year in this age period, level of education, ethno-religious group, country of origin, and size of locality of residence, women with 1–2 children continued to exhibit higher breast cancer mortality rates compared with women who were childless (HR = 1.237; 99% CI 1.045–1.466), while no significant difference remained between women with ≥ 3 children and women who were childless (HR = 0.989; 99% CI 0.834–1.173).

**Summary of findings**

Our study revealed an age-dependent relationship between parity and breast cancer mortality rates. In younger women (aged 30–49 years), motherhood was associated with increased mortality risk due to breast cancer, while this effect weakened in women of middle age (aged 50–64 years) and varied in older women (aged 65–80 years). These findings highlight the need for age-stratified approaches to breast cancer risk assessment and prevention.

**Discussion**

In this study, we employed a unique methodological approach involving an age-stratified analysis within a single cohort, enabling precise calculations of mortality rates. The strengths of our study include its complete population coverage, extended follow-up period, adjustment for sociodemographic variables, and implementation within a universal healthcare system.

Our findings revealed a significant age-dependent relationship between parity and breast cancer mortality rates. While previous studies have suggested that childbirth is protective against breast cancer, our results highlight a more complex association, particularly regarding mortality rates. Although women who give birth at a young age or have multiple children tend to have a lower risk of developing breast cancer than women who are childless, this effect pertains to disease incidence rather than mortality risk [20, 21]. Differences in breast cancer subtypes must also be considered, as nulliparous women face an increased risk for certain subtypes of breast cancer, such as luminal A and B cancers, whereas no consistent association has been found for HER2-positive or triple-negative cancers [21, 22].

Women aged 30–49 years who had children exhibited higher breast cancer mortality than women who were childless, even after adjusting for confounders. This may be due to pregnancy-associated breast cancer, which tends to be more aggressive and diagnosed at later stages [4, 6]. Additionally, mothers may have limited time for self-care and attending breast cancer screening appointments. The absence of significant differences between women with 1–2 children and those with ≥ 3 children suggests competing factors may be at play, such as an increased risk from pregnancy-related hormonal changes versus potential long-term hormonal protection from multiple pregnancies [7].

The association between parity and breast cancer mortality rates weakened in women aged 50–64 years and disappeared after adjustment for confounders. This may be attributed to menopause-related hormonal changes affecting all women similarly, regardless of reproductive history. Additionally, widespread mammography screening in Israel likely contributed to improved early detection and survival in this age group [28].

Among women aged 65–80 years, only those with 1–2 children had a higher breast cancer mortality risk compared with women who were childless, while no significant difference was found between those with ≥ 3 children and women who were childless. This finding aligns with previous research indicating that high parity may provide long-term protection, potentially due to cumulative hormonal exposure and epigenetic changes that influence cancer risk [22]. The biological response to multiple pregnancies and the declining immune function in older age may further impact breast cancer outcomes.

The unexpected finding that childlessness serves as a protective factor may be unique to Israel, where fertility rates and societal emphasis on parenthood are high [29](Debowy et al., 2024). Childlessness is often involuntary, unlike in Western countries where contraception or abortion are more commonly used to prevent pregnancy [24, 30]. Fertility treatments are also widespread in Israel, and women with 1–2 children may have undergone such treatments, potentially increasing their risk of breast cancer morbidity and mortality [23].

Another factor influencing mortality risk is obesity, which is more prevalent among women who have given birth multiple times. Obesity is linked to both increased breast cancer risk and poorer survival outcomes, potentially narrowing the gap between nulliparous and parous women [3, 15, 16].

Despite its strengths, our study had some limitations. It relied on administrative data, lacking details about morbidity, breastfeeding, age at first birth, fertility treatments, and contraceptive use. Furthermore, numbers of pregnancies could not be accurately measured, particularly for immigrants with no data relating to any deceased children. Additionally, methodological constraints included varying follow-up periods across age groups (30–49 years, 1990–2009; 50–64 years, 1990–2020; 65–80 years, 2005–2020). Although we adjusted for entry year, this limitation should be considered. Finally, Israel’s unique childbirth patterns and demographic characteristics may limit the generalizability of these findings to other populations [23, 29]. Further research in diverse settings is necessary to assess the applicability of these results.

**Conclusions**

Our study demonstrates that the impact of childbearing on breast cancer mortality risk evolves across the lifespan, with biological and social factors shaping complex age-specific patterns. In younger women (30–49 years), motherhood increased their breast cancer mortality risk compared with the risk in women who were childless, an effect that weakened in middle age (50–64 years) and partially persisted in older women (65–80 years) but only for those with 1–2 children.

Our age-stratified approach challenges traditional views of parity as being protective against breast cancer mortality, revealing an age-dependent relationship between parity and breast cancer mortality that conventional analyses might overlook. Future research should investigate the underlying mechanisms of these associations through prospective cohort studies that incorporate detailed reproductive histories, parity–cancer subtype relationships, and cross-cultural analyses. These insights could inform more nuanced, age-specific risk assessment strategies for breast cancer, tailored to reproductive history and life stage.

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