Breastfeeding and Reduced Risk of Breast Cancer: A Systematic Review and Meta-Analysis

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Background. Evidences which prove relation between breastfeeding women and risk of breast cancer have been limited. Objective. A meta-analysis was carried out on the basis of published literature from clinical trials and studies among different parts of the world. Methods. Studies were analyzed and extracted using PRISMA flowchart. RevMan 5.4.1 was used for analyzing the extracted data. Included studies were fully cited texts with complete information about studies, trials conducted for risk of breast cancer, and breastfeeding correlations. Results. Menarche age, family history, lactation duration, and menopausal status have a strong effect on the risks of breast cancer. Family history studies concluded that for 95% CI, the risk ratio was 2.66 (2.00, 3.52). Conclusion. Findings have suggested that family history and lactation duration affect the risks of breast cancer.

1. Introduction

According to the World Cancer Research Fund and American Institute for Cancer Research report from 2007, women’s health is benefited from breastfeeding (BF). The reduced number of breast cancer (BC) cases (most common type of cancer found in women) is observed because of BF [1]. Breast cancer is one of the second leading causes of cancer deaths in women. Therefore, various studies have been conducted to identify as well as quantify the effects of associated genetic and environmental risk factors. Other risk factors documented are lower age during menstruation, i.e., less than 10 years; delay in maternal age as first full-time pregnancy (around 30-40 years); and limited periods of breastfeeding [2, 3].

These studies suggest a strong link between breastfeeding and breast cancer. The initial frail confirmation of breast cancer incidence is observed by the ecological relationship between the observed trends and the depreciation of breastfeeding among women in different parts of the world. Another indirect trail of science is taken from the early observation of the association between breastfeeding and the delayed return of the period of ovulation throughout the postpartum. This has been reported in the clinical observation and the physiological studies [4, 5].

The risk of breast cancer in women is hypothesized to be reduced by breastfeeding which involves two primary mechanisms: (1) differentiation of breast cells where they are modified to generate milk postpregnancy, thus diminishing the vulnerability of the breast tissues towards carcinogenic effects (estrogens), and (2) breastfeeding causes reduction in the lifetime exposure towards the mitogenic effect of estrogens, thus obstructing the process of ovulation [6]. The secretion of carcinogen from the human milk, as well as the exfoliation of the breast tissues, assists in destroying the damaged DNA cells. This helps in diminishing the responsiveness to mutations [7].

Furthermore, serum concentrations of insulin are also minimized by expressing human milk and breastfeeding. Studies have confirmed that proliferation and antiapoptosis effects in breast tissue are correlated with persistent high serum concentrations of insulin, which can raise serum concentrations of IGF-1 (insulin-like growth factor) [8]. Different studies and meta-analysis have independently documented distinct risk elements of breast cancer. The primary aim of this study presents the ways to perform meta-analysis.
over the association between breastfeeding and breast cancer depending on the published epidemiological literature in multiple studies.

2. Material and Methods

2.1. Search Approach. Our literature search strategy is presented in Figure 1; the studies considered for this meta-analysis was performed considering the observational studies in epidemiology (MOOSE) and preferred items for systematic reviews and meta-analysis (PRISMA). The stages of identifying the related and appropriate studies were done on the case-control studies along with the cohort research studies that have documented the risk elements of breast cancer, including the history of breastfeeding published. The inspection of data was performed using the “National Library of Medicine (MEDLINE)” as well as “Excerpta Medica database (EMBASE)” in the period of 1998-2021. This investigation was performed using the following MeSH keywords: “breastfeeding”, “breast cancer”, “epidemiological diseases”, “pregnancy”, “breastfeeding duration”, “dose-response”, “exclusive breastfeeding”, and “breast tissues”. The additional records from the relevant researches were subsequently hand-searched for further studies. As we had to limit the analysis to the published data, thus, no further attempts were made to recognize any unpublished works.

2.2. Inclusion Criteria. The irregularity associated with the inclusion elements of the published researches was short-listed via discussion. The attempts were made to institute communication with the authors of the respective papers. The full set of published works which were identified to be relevant was finalized according to the following inclusion parameters (hospital or population based): (i) the study under either case-control or prospective cohort study, (ii) data related to the breastfeeding exposure was used in the analysis, (iii) outcomes mentioned as invasive breast cancer with/without carcinoma in situ (CIS) in comparison to the nonbreast cancer, and (iv) distinct odd ratios (OR) calculating the link between breastfeeding and breast cancer.

2.3. Exclusion Criteria. According to the objective of the given study, the focus of data was to be made towards the woman who had breastfed versus the women who had not. Multiple studies with the following category of data were discarded: (i) duplicate data, (ii) reviews or letters or abstracts or case studies or any published data with missing crucial information, (iii) reports that could not assess breastfeeding and breast cancer, (iv) any editorials or letters or commentary with repeated analysis, (v) studies with improper data of duration of breastfeeding, and (vi) studies consisting unilateral vs. bilateral breast cancer risk.

2.4. Data Extraction. The data for the studies was selected by the help of a standardized method of data extraction by the first author whereas the last author was randomly checked. Basic characteristics of the study like age group, study design, duration of study, and menopausal status were extracted for the outcome studies and meta-analysis. The frequencies of outcomes and exposures were collected from all individual studies. The studies included for the analysis are listed in Table 1, and PRISMA for studies included is shown in Figure 1.

2.5. Statistical Analysis. Using the fixed and random effect model, a combined OR (odds ratio) and RR (risk ratio) was obtained [14, 15]. RevMan 5.4.1 software was used for the meta-analysis of the studies.

3. Results

Table 1 provides selected characteristics of the studies included in the analysis. A number of cases of breast cancer were compared against the control group cases as listed in Table 2. Risk difference was found to be -0.21 with 95% C.I as -0.46 and 0.04.

A significant number for risk difference was reported in the case of the control group in comparison to the control group for which the forest plot is shown in Figure 2 and the funnel plot is listed in Figure 3.

3.1. Menarche Age. Menarche age was also a parameter which was studied for its impact on the cases of breast cancer; thus, the studies with menarche age are listed in Table 3.

The forest plot was drawn for menarche age in the case of both case and control groups where risk ratio was found to be 0.94 (95% C.I was 0.83, 1.06) (Figure 4).

The funnel plot is shown in Figure 5. A significant role of menarche age with >13 yr was noted in the case of breast cancer cases where heterogeneity ($I^2$) was found to be 51%.

Menarche age with 14-15 yr was also studied where the forest plot is shown in Figure 6 where risk ratio was found to be 1.20 (95% C.I was 0.95, 1.51). The funnel plot for the same is shown in Figure 7.

Heterogeneity was found to be 85% thereby showing a significant role of menarche age in cases of breast cancer.

Girls with menarche age of 16 years were also studied for both case and control groups. Here, a significant risk ratio of 0.57 was noted with 95% C.I of 0.25 and 1.31. Heterogeneity was found to be 97% as found in the forest plot (Figure 8), and the funnel plot for the same is shown in Figure 9.

Family history of breast cancer was studied as a parameter for finding correlation with the breast cancer cases against the control group. The cases are listed in Table 4. A lot of researches have shown that family history of cancer patients plays a significant role in predicting breast cancer cases.

The risk ratio was found to be 2.66 (95% C.I was 2, 3.52) where the forest plot is shown in Figure 10 and the funnel plot for the same is shown in Figure 11.

Duration of lactation was also studied for studies with ≥24-month duration in both control and case groups as listed in Table 5.

The forest plot for the same is shown in Figure 12 where the risk ratio was found to be 0.71 with 95% C.I as 0.59 and 0.84. A significant effect was noted on months of lactation in case groups which impacts breast cancer (Figure 12).
Related related articles were identified and shortlisted using the following MeSH terms: “breastfeeding” “breast cancer” “epidemiological diseases” “pregnancy” “breastfeeding duration” “dose-response” “exclusive breastfeeding” “breast tissues”, “lactation” using (clinical databases and other databases)

n = 218

Possibly relevant papers searched
n = 222

Relevant to the aim of the paper= 181

Full text titles selected = 6

Studies considered for acceptance which were Systematic Review and Meta-analysis based on inclusion criteria (n = 6)

Final Studies Included
n = 6

Additional records considered via other platforms (n = 4)

Removal of duplicate data = 41

Articles that were taken down as per their exclusion criteria: irrelevant outcomes or results, no clinical characteristics data, failed abstract to comply with retrieval criteria and non-English articles = 175

Figure 1: PRISMA study over the study methods.
Table 1: Characteristics of the studies considered for meta-analysis.

| Characteristics                  | [9]   | [10]  | [11]  | [12]  | [13]  |
|----------------------------------|-------|-------|-------|-------|-------|
| Year of study                    | 2000  | 2010  | 2013  | 2000  | 2003  |
| Type of study                    | Case–control study | Case–control study | Cohort study | Case–control study | Prospective study |
| Total participants               | 808   | 800   | 26680 | 2087  | 110604|
| Breast cancer cases reported     | 404   | 400   | 148   | 706   | 360   |
| Breastfeeding only cases         | N/A   | N/A   | 10336 | 1155  | 57440 |
| Duration of lactation (cases)    |       |       |       |       |       |
| 0 months                         | 32    | 23    | N/A   | 173   | 53164 |
| 1–6 months                       | 58    | 62    | N/A   | 262   | 45591 (1–12 months) |
| 7–12 months                      | 109   | 112   | N/A   | 78    | 45591 (1–12 months) |
| 13–23 months                     | 133   | 122   | N/A   | 30    | 7265  |
| ≥24 months                       | 72    | 81    | N/A   | 10    | 4584  |
| Country                          | China | Tunisia | Japan | Germany | Korea |
| Study area                       |       |       |       |       |       |
| Research based on association between breast cancer and lactation (China Province) |       |       |       |       |       |
| Case-control study on breastfeeding and cancer risk reduction, Tunisia |       |       |       |       |       |
| Lactation pattern and cancer risks due to hormones, Japan |       |       |       |       |       |
| A link between lactation pattern and risk of hormone-related breast cancer was established where lactation reduces chances of breast cancer but the pattern of lactation with duration was important |       |       |       |       |       |
| Reduced risk of breast cancer in breastfeeding women |       |       |       |       |       |
| Lactation leads to decrease in breast cancer in women (premenopausal) |       |       |       |       |       |
| Study outcome                    |       |       |       |       |       |
| The study concluded that prolonged lactation leads to decrease in breast cancer risk |       |       |       |       |       |

Table 2: Breast cancer and control cases in the study.

| Characteristics | [9] | [10] | [11] | [12] | [13] |
|----------------|-----|------|------|------|------|
| Cases          | 404 | 400  | 148  | 706  | 360  |
| Controls       | 404 | 400  | N/A  | 1381 | 57440|
| Total          | 808 | 800  | 26680| 2087 | 110604|

Study or subgroup

| Study or subgroup          | Case Events | Total | Control Events | Total | Risk difference M-H, Random, 95% CI | Risk difference M-H, Random, 95% CI |
|----------------------------|-------------|-------|----------------|-------|-------------------------------------|-------------------------------------|
| Awatef et al., 2010        | 400         | 800   | 400            | 800   | 24.9%                               | 0.00 [-0.05, 0.05]                  |
| Zheng T et al., 2000       | 404         | 800   | 404            | 800   | 24.9%                               | 0.00 [-0.05, 0.05]                  |
| Chang-claude J et al., 2000| 706         | 2087  | 1381           | 2087  | 25.1%                               | -0.32 [-0.35, -0.29]                |
| Lee SY et al., 2003        | 360         | 110604| 57440          | 110604| 25.1%                               | -0.52 [-0.52, -0.51]                |
| Total (95% CI)             | 114291      | 114291100.0% | -0.21 [-0.46, 0.04] |
| Total events               | 1870        | 59625 |                |       |                                     |                                     |

Figure 2: Risk difference of breast cancer and control cases in meta-analysis.
Figure 3: Odds ratio funnel plot of breast cancer and control cases in the study.

Table 3: Menarche age comparison of breast cancer and control cases.

| Characteristics | [9] | [10] | [11] | [12] | [13] |
|-----------------|-----|------|------|------|------|
| Age at menarche (years) — breast cancer cases |
| >13             | 168 | 166  | N/A  | 255  | N/A  |
| 14-15           | 168 | 157  | N/A  | 344  | N/A  |
| ≥16             | 77  | 77   | N/A  | 103  | N/A  |
| N (breast cancer cases) | 404 | 400 | 148  | 706  | 360  |
| Age at menarche (years) — control cases |
| >13             | 191 | 189  | N/A  | 479  | N/A  |
| 14-15           | 122 | 120  | N/A  | 676  | N/A  |
| ≥16             | 91  | 91   | N/A  | 224  | N/A  |
| N (control cases) | 404 | 400 | N/A  | 1381 | 57440 |

Figure 4: Forest plot on menarche age > 13 yr age group of the case and control group.
4. Discussion

Six studies were considered for the study which were analyzed on the basis of menarche, menopause, age of patient, age of control, total participants in study, lactation durations, family history of cancer, incidences of breast cancer in breastfeeding and nonbreastfeeding women, and duration of lactation. Other factors like hormones, number of pregnancies, still births, and complications in pregnancies were also responsible for inducing effect of health. Risk ratios and odds ratios were analyzed by the help of forest and funnel plots. Family history studies concluded that for 95% CI, the risk ratio was 2.66 (2.00, 3.52). A relation was strongly established between the lactation, duration of lactation, menarche age, and family history and risk of breast cancer.
### Table 4: Family history of cancer and correlation with cases and controls.

| Family breast cancer history | [9] | [10] | [11] | [12] | [13] |
|-----------------------------|-----|-----|-----|-----|-----|
| No                          | 388 | 385 | N/A | 619 | N/A |
| Yes                         | 16  | 15  | N/A | 87  | N/A |
| Cases                       | 404 | 400 | 148 | 706 | 360 |
| No                          | 400 | 397 | N/A | 1310| N/A |
| Yes                         | 4   | 3   | N/A | 71  | N/A |
| Controls                    | 404 | 400 | N/A | 1381| 57440|
| Total                       | 808 | 800 | 26680| 2087| 110604|

### Figure 10: Forest plot of risk ratio on family history of breast cancer and participants of the study.
5. Conclusion

The duration of breastfeeding reduces the risk of breast cancer when compared via meta-analysis to the case that did not breastfeed. Thus, it was recommended that researchers must collect information on duration of breastfeeding to potentially reduce breast cancer cases.

Data Availability

The data used to support this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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