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ORIGINAL ARTICLE Breast Cancers

Reproductive factors and breast cancer risk: A meta-analysis of case–control studies in Indian women

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Abstract

Background/Objective: India is the world's most biodiverse region and is undergoing a period of dramatic social and economic change. Due to population's explosion, climate change and lax implementation of environmental policies, the incidence of breast cancer is increasing. From population-based cancer registry data, breast cancer is the most common cancer in women in urban registries where it constitutes more than 30% of all cancers in females. We conducted a meta-analysis of all breast cancer case–control studies conducted in India during 1991–2018 to find pooled estimates of odds ratio (OR).
Materials and Methods: Eligible studies were identified through a comprehensive literature search of PubMed, EMBASE, and HINARI databases from 1991 to January 2018. This analysis included 24 observational studies out of 34 that reported the case–control distribution of reproductive factors, body mass index (BMI) and type of residence. The analysis was performed using RevMan 5.3 (Review Manager, 2017) applying the random-effects model.
Results: A total of 21,511 patients (9889 cases and 11,622 controls) were analyzed, resulting in statistically significant association between breast cancer and the following reproductive factors: never breastfeed (OR: 3.69; 95% confidence interval [CI]: 1.70, 8.01), menopausal age >50 years (OR: 2.88; 95% CI: 1.85, 3.85), menarche age <13 years (OR: 1.83; 95% CI: 1.34, 2.51), null parity (OR: 1.58; 95% CI: 1.21, 2.06), postmenopause (OR: 1.35; 95% CI: 1.13, 1.62), and age at the 1st pregnancy >25 years (OR: 1.57; 95% CI: 1.37, 1.80). Family history (FH) of breast cancer (OR: 5.33; 95% CI: 2.89, 9.82), obesity (OR: 1.19; 95% CI: 1.00, 1.42), and urban residence (OR: 1.22; 95% CI: 1.03, 1.44) were also found to be significant risk factors.
Conclusion: The results of this meta-analysis are indicative of significant associations between reproductive factors and breast cancer risk, profoundly so among women experiencing menopause after the age of 50, women who never breastfeed and FH of breast cancer.

Key words: Breast cancer, India, meta-analysis, reproductive risk factors

Introduction

Breast cancer is the most common female cancer worldwide, including India (Global cancer statistics, 2012). About 12% of women in the general population will develop breast cancer sometime during their lives.[1] Worldwide, breast cancer is the fifth most common cause of cancer death (after colon cancer, lung cancer, liver cancer, and stomach cancer).[2,3] India is the world's most bio-diverse region and is undergoing a period of dramatic social and economic change. Due to population's explosion, climate change, and lax implementation of environmental policies, the incidence of breast cancer is increasing. From population-based cancer registry data, breast cancer is the most common cancer among women in urban registries where it constitutes more than 30% of all cancers in females. The death rate connected with breast cancer varies in different regions, depending on the stage of diagnosis, treatment quality, prevalence of assorted subtypes, and therapy effectiveness. Breast cancer treatments include surgery, radiation therapy, chemotherapy, hormone therapy, and targeted therapy.[4,5]

By 2020, an estimated 26% increase in breast cancer is projected, predominantly in developing countries, with a rise from 1,00,000 to 1,31,000 new cases annually in the Indian population.[6] It is unfortunate that by 2030, the global incidence of breast cancer will be burgeoning to more than 2 million new cases per year; in India, it will reach up to 2 Lakh/year.[7-9] The American Cancer Society estimates that 1,78,480 new cases of invasive breast cancer were diagnosed in 2007 in the USA and about 2% by 50 years of age, 4% by age 60, 7% by age 70, and 10% by age 80.[10] Previous study among Indian women elucidated that breast cancer incidence is increasing although age-adjusted rates vary with the different regions and cancer registries. Factors potentially associated with breast cancer risk include age, early menarche, childbearing, breastfeeding, use of oral contraceptive, late menopause, hormone replacement therapy, exogenous hormones, previous benign breast disease, breast density, diet, alcohol, smoking, and family history (FH).[11,12-15]

The preceding study has reported the highest increase in breast cancer incidence to be among women in Asian countries. Breast cancer has been found to be the most common cancer type among urban Indian women and the second most common among the rural Indian women.[11] In India, breast cancer incidence rates are approximately 100% higher among urban women than among rural women.[16] Physical activities have been strappingly suggested to reduce breast cancer risk among premenopausal and postmenopausal women independent of its effect on obesity, possibly by reducing estrogens production, and influencing age at menarche and menopause. The high occurrence of breast cancer among urban women can be concurrent with numerous factors, including having late sex, having fewer children, and breastfeeding them for a shorter period compared with rural women. This ultimately increases their exposure to estrogens and thus subsequently, upsurge the risk of developing breast cancer.[17] In addition, urban Indian women also tend to consume a western diet, which leads to obesity and high alcohol intake. All these factors contribute enormously to enhancing the risk of breast cancer. An increase in the number of cases and the net mortality due

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to breast cancer could have resulted from the large population, inadequate screening programs, and lack of proper education.[18]

Except Das *et al*. 2012,[19] all other studies reported that women residence of the urban area are at higher risk of breast cancer.[20-23] Dietary pattern and use of oral contraceptive pills (OCP) were the controversial risk factor of breast cancer.[9,21,24-27] Similarly, Meshram and Kulkarni 2009 and Wirth *et al*. 2014 reported that obese women have lower risk of breast cancer.[28,29] Considering the aforementioned issues, we conducted a meta-analysis of all case–control studies of breast cancer risk conducted in India during 1991–2018 to find pooled estimates of odds ratio (OR) for the corresponding reproductive and other risk factors in Indian women as compared to controls.

Materials and Methods

This study is a quantitative research meta-analysis on Indian women to find reproductive factors as risk factors for breast cancer. Eligible studies were identified through a comprehensive literature search of PubMed, EMBASE, and HINARI databases from 1991 to January 2018. The inclusion criteria were recognized to minimize bias or heterogeneity in the selection of studies [Figure 1]: (i) Full-text articles published between January 1991, and March 2018; (ii) Indian studies with Indian population; (iii) Case–control studies on breast cancer; (iv) original articles containing results related to reproductive factors, body mass index (BMI), and type of residence. Clinical trials, cohort studies, and case–control studies based on genetic polymorphism as the outcome were excluded from the meta-analysis. Search was bounded only for English articles published in journals.

Data synthesis and statistical analysis

The following information was extracted from eligible articles: pre–post menopausal status, age at menarche (<13 years and ≥13 years), age at first pregnancy (<25 years and ≥25 years), breastfeeding (yes/no), parity (multi-parity vs. nulliparity), marital status (unmarried and ever married), age of menopause (<50 years and ≥50 years), BMI (<25 and ≥25), FH of breast cancer (Yes/No), use of OCP (ever used, never used), place of residence (urban/rural), and dietary pattern (vegetarian/nonvegetarian).

The analysis included 24 observational studies out of 49 that reported the case–control distribution of reproductive factors, BMI, FH, and type of residence. Pooled ORs with 95% confidence interval (CIs) were reported with forest plots separately for each factor. The analysis was performed using RevMan 5.3 (Review Manager, 2011) applying Mental Haenszel method by the random-effects model.

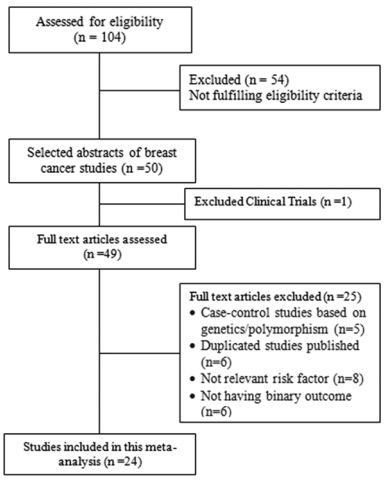

Figure 1: CONSORT diagram

Results

A total of 24 case–control studies were analyzed out of 34 with a sample size of 21,511 (9889 cases and 11,622 controls). A total of 104 articles were identified from database searches. Clinical trials and case–control studies based on genetics/polymorphism were excluded from the meta-analysis. Characteristics of the studies included in the analysis are described in Table 1. Figure 2 depicts the regional distribution of breast cancer cases reported by case–control studies performed in India. Most of the reported studies were done in the Indian states of Kerala, Tamil Nadu, Haryana, Maharashtra, and Northeast, whereas few studies were done in New Delhi, Punjab, and West Bengal.

Modifiable risk factors

Stated modifiable risk factors of breast cancer in selected studies were BMI, age at first pregnancy, breastfeeding, OCP, parity, dietary pattern, residence, and marital status. The highest OR was observed for never breastfeed (pooled OR = 3.69, 95% CI = 1.70–8.01; $P < 0.001$) followed by never married (pooled OR = 2.29, 95% CI = 1.65–3.17; $P < 0.001$), nulli-parity (pooled OR = 1.58, 95% CI = 1.21–2.06; $P < 0.001$), age at first pregnancy (>25 years) (pooled OR = 1.57, 95% CI = 1.37–1.81; $P < 0.001$), urban residence (pooled OR = 1.12, 95% CI = 1.03–1.44; $P = 0.02$), and obese (BMI ≥25) (pooled OR = 1.19, 95% CI = 1.00–1.42; $P = 0.04$) [Figure 3]. Dietary pattern (pooled OR = 1.12, 95% CI = 0.81–1.53; $P = 0.50$) and use of oral contraceptive (pooled OR = 1.65, 95% CI = 0.99–2.73; $P = 0.05$) were not associated with breast cancer risk as pooled ORs are not statistically significant [Figure 3].

Nonmodifiable risk factors

Figure 4 represents forest plots for nonmodifiable risk factors of breast cancer in selected studies, i.e. FH of breast cancer, menopausal status, age at menarche, and age of menopause. The highest OR was recorded in FH (pooled OR = 5.33, 95% CI = 2.89–9.82; $P < 0.001$) followed by menopausal

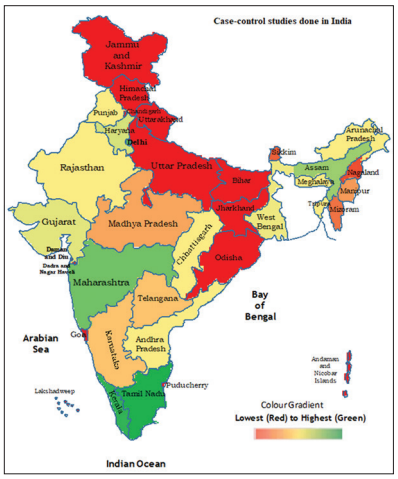

Figure 2: Distribution of breast cancer cases through case–control studies done in India

Table 1: Characteristics of selected studies for meta-analysis

Author	Year	City/place	Cases	Controls	Ratio	Type of control	Center
Asegaonkar *et al.*	2012	Aurangabad (Maharashtra)	50	50	1:1	CC	SC
Babita *et al.*	2014	Rohtak (Haryana)	128	128	1:1	HC	SC
Bhadoria *et al.*	2013	AIIMS (New Delhi)	320	320	1:1	HC	SC
Das *et al.*	2012	Kolkata (West Bengal)	105	105	1:1	HC	SC
Datta *et al.*	2009	Kolkata (West Bengal)	267	267	1:1	HC	SC
Devi *et al.*	2015	Assam, Meghalaya, Tripura, Mizoram, (North East)	462	770	1:2	CC	MC
Dey *et al.*	2009	Trivandrum (Kerala)	900	1208	1:1	HC	SC
Gajalakshmi *et al.*	1991	Chennai (Tamil Nadu)	238	238	1:1	HC	SC
Gajalakshmi *et al.*	2009	Chennai (Tamil Nadu), Trivandrum (Kerala)	1866	1873	1:1	HC	MC
Gathani *et al.*	2017	Jaipur (Rajasthan), Ahmedabad (Gujarat), Vellor and Bangalore (Karnataka), Coimbatore (Tamil Nadu), Trivandrum (Kerala), Silchar (Assam)	2101	2255	1:1	HC	MC
Jayalekshmi *et al.*	2009	Trivandrum (Kerala)	264	792	1:3	CC	PBCR
Kapahi *et al.*	2014	Amritsar (Punjab)	102	102	1:1	HC	SC
Lodha *et al.*	2011	Bhopal (Madhya Pradesh)	215	215	1:1	CC	PBCR
Mathew *et al.*	2009	Chennai (Tamil Nadu), Trivandrum (Kerala)	1866	1873	1:1	HC	MC
Meshram *et al.*	2009	Nagpur (Maharashtra)	105	210	1:2	CC	SC
Mohite *et al.*	2015	Satara (Maharashtra)	217	217	1:1	HC	SC
Parmeshwari *et al.*	2013	Kottayam (Kerala)	20	80	1:4	CC	PBCR
Rao *et al.*	1994	Mumbai (Maharashtra)	689	711	1:1	HC	SC
Sambyal *et al.*	2015	Amritsar (Punjab)	200	200	1:1	HC	SC
Samson *et al.*	2007	Chennai (Tamil Nadu)	250	500	1:2	HC	SC
Saxena *et al.*	2009	AIIMS, New Delhi	413	410	1:1	HC	SC
Singh *et al.*	2011	AIIMS, New Delhi, Ballabhgarh (Haryana)	320	320	1:1	HC	MC
Singh *et al.*	2013	Rohtak (Haryana)	128	128	1:1	HC	SC
Wirth *et al.*	2014	Mumbai (Maharashtra)	255	249	1:1	HC	SC

SC=Single centric, MC=Multi-centric, CC=Community control, HC=Hospital control, PBCR=Population-based cancer registry

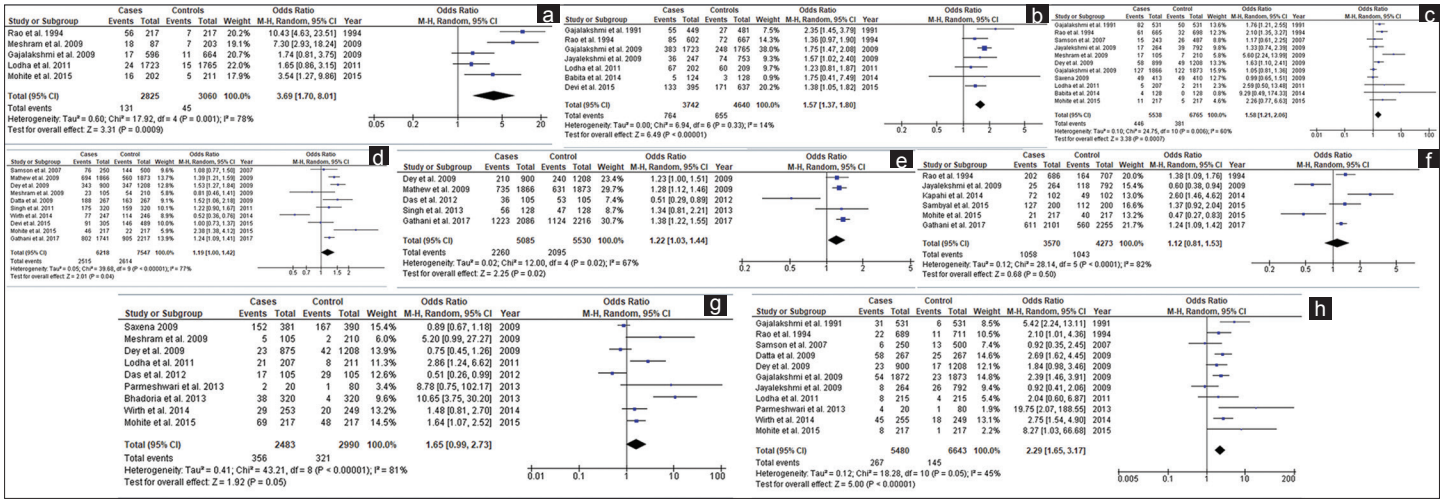

Figure 3: Forest plots of modifiable risk factors of breast cancer. (a) Breastfeeding (never). (b) Age at 1st pregnancy (>25 years). (c) Parity (Nulli). (d) BMI (≥25). (e) Residence (Urban). (f) Dietary Pattern (Veg). (g) OCP (Yes). (h) Marital status (never)

age >50 years (pooled OR = 2.99, 95% CI = 1.90–4.36; $P < 0.001$), menarche onset age <13 years (pooled OR = 1.83, 95% CI = 1.34–2.51; $P < 0.001$), and menopausal status (pooled OR = 1.35, 95% CI = 1.13–1.62; $P < 0.001$).

Publication bias

Funnel plot assumes that observed effect sizes with similar precision (i.e., with similar standard error) should be more or less symmetrically distributed around the combined effect size. Publication biased is assessed by funnel plot [Figure 5]. Although there was no clear asymmetry, however, the plot demonstrates no significant publication bias.

Limitations of the study

This meta-analysis incorporated only published studies and we are conscious of the so-called "file drawer effect problem" whereby statistically non significant studies are hardly published. As such there is the legitimate reason the results presented here may overestimate the true ORs. A comment about the relative quality of the included studies is warranted too. Furthermore, the extensiveness of the search guarantees that important studies were not omitted.

Discussion

The result of the meta-analysis done in this study reveals that modifiable factors such as BMI, age at first pregnancy,

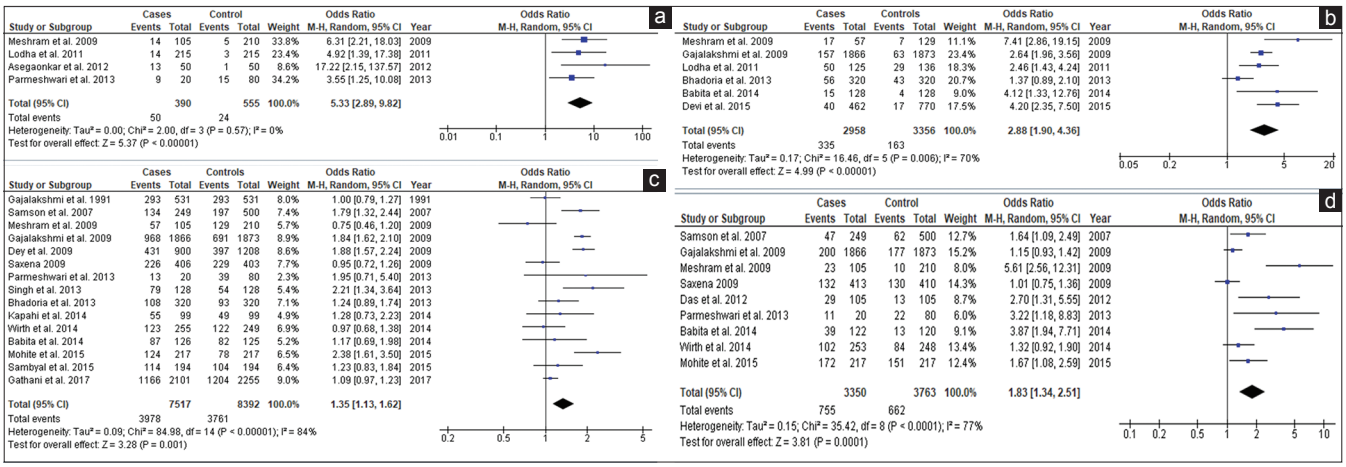

Figure 4: Forest plots of non-modifiable risk factors of breast cancer. (a) Family history (Yes). (b) Menopausal status (post). (c) Age at menopause (>50 years). (d) Age at menarche (<13 years)

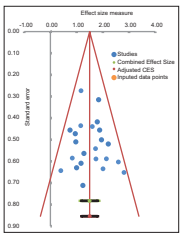

Figure 5: Funnel plot of studies included in the analysis

breastfeeding, OCP use, parity, and marital status are risk factors of breast cancer in addition to nonmodifiable risk factors. Similar findings are given in Datta *et al*., Devi *et al*., Dey *et al*., Gathani *et al*., Mathew *et al*. (2008), Meshram and Kulkarni, Mohite and Mohite, Samson *et al*., Singh and Jangra, Wirth *et al*., Bhadoria *et al*., Parameshwari *et al*., Saxena *et al*., Jayalekshmi *et al*., Rao *et al*., and Babita *et al*.[9,10,12,17,20-24,26,28-33] and others. Marital status and urban residence are not independent factors as they are associated with sedentary lifestyle and dietary pattern. The statement "use of oral contraceptive is a risk factor of breast cancer" is always contradictory in literature.

Women with nulli-parity and women with first pregnancy after 25 years have 58% and 57% breast cancer risks, respectively, as compared to women with parity and pregnancy before 25 years. In this study, the investigating team also confirms the findings in Babita *et al*., Dey *et al*. Lodha *et al*., Meshram and Kulkarni Gajalakshmi *et al*. Gajalakshmi *et al*., Mohite and Mohite, Rao *et al*., Saxena *et al*., Samson *et al*., and Jayalekshmi *et al*.[[9,20,24,26,28,30,32-36] and others in this regard. Women with menopause after 50 years are almost three times more likely to have breast cancer as compared to women with menopause before 50 years.[12,17,28,30,35,36]

There is 35% higher risk of breast cancer to women with post-menopausal status as compared to post-menopausal status. However, it is directly linked with age at menopause. For more information, the reader is referred to Gajalakshmi *et al*. Gajalakshmi *et al*.Samson *et al*., Meshram and Kulkarni Dey *et al*. (2009), Saxena *et al*., Parameshwari *et al*., Singh and Jangra, Bhadoriya *et al*., Kapahi *et al*., Wirth *et al*., Babita *et al*. Mohite and Mohite, Sambyal *et al*. and Gathani *et al*.[9,17,20,21,23,25,27-35] and others. Women with <13 years onset age of menarche are at 85% higher risk of breast cancer.[9,19,28-33,35]

From the findings of this study, FH of breast cancer is a risk factor of breast cancer confirming the findings of Asegaonkar *et al*., Lodha *et al*., Parameshwari *et al*. and Meshram and Kulkarni[11,28,31,36] and others. Our results show that women with FH are 5.3 times more likely to have breast cancer risk as compared to women without any history of breast cancer.

Conclusion

This meta-analysis comprises studies from almost all the Indian regions. It confirms the results that the FH of breast cancer, never breastfeeding, nulli-parity, age at menarche (<13 years), age at menopause >50 years, first pregnancy age >25 years, BMI more than 25 years, post-menopausal status and never married are risk factors of breast cancer for women in India.

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Conflicts of interest

There are no conflicts of interest.

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