

## Risk Factors of Breast Cancer in Kerala, India – A Case Control Study

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### Abstract

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Breast cancer is the most common malignancy among women in Kerala state of India. This study tried to determine the strength of association of known risk factors of Breast Cancer among women in Kerala. An unmatched Case control study was conducted at Regional Cancer Center, Thiruvananthapuram, among 660 newly detected breast cancer patients admitted for surgery during 2003-2004 and 920 controls selected from the hospital and community. Advancing age, delayed first child birth, nulliparity, history of previous breast biopsies and family history of breast cancer among first degree rela-

tives were found to be associated with increased risk of breast cancer. History of breast feeding was found to reduce the risk. This study concludes that age and parity play a major role in the occurrence of breast cancer in Kerala. It also suggests that past history of breast symptoms requiring biopsy is associated with increased risk of breast cancer. Longer duration of breast feeding was found to be protective against breast cancer.

**Key words:** Breast cancer, Breast cancer risk, Breast feeding, Breast biopsy, Kerala, Crude and adjusted odds ratios, Cancer screening

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### Introduction

Breast cancer incidence and mortality varies from region to region. The age - standardized incidence rate of breast cancer across the globe is 43.3 per 100,000 female population. In India it is found to be 25.8 per 100,000 females.<sup>1,2,3,4</sup> The figures for Kerala state of India is 30.5 in urban areas and 19.8 in rural areas<sup>5</sup>. Initial results from a cluster randomized controlled trial in Kerala on 'Clinical Breast Examination as a Screening Method' revealed that the incidence per 100,000 women ranges from 29.8 in the control group to 38.4 in the intervention group. The age-standardized incidence rates for early-stage (stage IIA or lower) breast cancer were 18.8 and 8.1 per 100,000 women and for advanced-stage (stage IIB or higher) breast cancer were 19.6 and 21.7 per 100,000 women, in the intervention and control groups, respectively.<sup>6</sup> World cancer declaration urges all countries to adopt appropriate evidence-based guidelines for early detection and treatment programs and deliver relevant priority actions tailored to different socioeconomic, cultural and resource settings. National level public and health professional education programs which stress the benefits of early detection should also be given concurrently with these services.<sup>7</sup>

The incidence of breast cancer has been increasing in Kerala in the past two decades and now contributes to nearly a third of all cancers amongst females in the state.<sup>8</sup> The reason for the increasing incidence can be understood only by identifying the predominant risk factors in the state. Numerous studies worldwide have shown reproductive factors like early age of menarche, age at first live birth, nulliparity, avoidance of

breast feeding, family history of breast cancer and number of previous breast biopsies as the major risk factors of breast cancer.<sup>9</sup> There is paucity of data regarding the strength of association of these risk factors of breast cancer in Kerala. A study to assess the strength of association of these risk factors would help in better planning and implementation of prevention programmes in the community. Better perception of individual's risk could be motivation for screening and early case detection.<sup>10,11,12,13</sup> Early detection and proper treatment is crucial to achieving cure and reducing morbidity due to the disease.<sup>14</sup>

### Objective

To determine the strength of association of known risk factors of breast cancer among women admitted for surgery at Regional Cancer Center, Thiruvananthapuram, Kerala.

### Methodology

A case-control study was conducted from June 2003 to March 2005 at Regional Cancer Center Thiruvananthapuram, Kerala, India. The cases (n=660) were incident, newly diagnosed breast cancer patients from all over Kerala, and they were entered into the study if they had a confirmed pathological breast cancer diagnosis and were admitted for breast surgery between 1st of September 2003 and 31st December 2004. The controls were women (n=920) without any history of breast problems or neoplastic disease and were recruited from female bystanders of patients during the same period from the hospital (n=460), and also from the community (n=460),

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identified from 15 clusters selected randomly from the 81 wards of Thiruvananthapuram corporation area. Since age was a risk factor under study, age matching was not done while selecting controls.

Participants were interviewed using a structured questionnaire to obtain demographic and risk factor data, including information on age, educational level, socio economic status, marital status, family history of breast cancer (first-degree relatives), age at menarche, parity, age at first live birth, oral contraceptive use, menopausal status, history of previous breast biopsy and breast feeding history. Women were classified as menopausal if they had not menstruated during the 6 months before the date of interview. First-degree relatives of the breast cancer patients included in the study and persons diagnosed with gynecological malignancy / contra lateral breast cancer were excluded. Based on Socio Economic Status (SES) the participants were grouped into poor, middle and high class.

Continuous variables were summarized as means and standard deviations (SD) and independent sample t-test was done for statistical significance. Categorical variables were summarized as proportions and Pearson Chi square test and Chi square for Linear Trend were used appropriately. Univariate Logistic Regression Analysis was performed to calculate crude Odds Ratios (ORs) with 95% Confidence Intervals (CI) to rule out chance. Multiple Logistic Regression Analysis (Binary Logistic - Enter method) was done to calculate adjusted OR and 95%CI.

Ethical committee approval was obtained from Medical College, Thiruvananthapuram and Regional Cancer Center, Thiruvananthapuram, before starting the study. Written informed consent was obtained from the study participants prior to data collection. Participants were provided with free medical examination and counseling wherever necessary.

## Results

The study participants comprised of cases (n=660) with age ranging from 20 – 85 years and controls (n=920) with age ranging from 19 – 77 years. Univariate logistic regression analysis was used to calculate crude odds ratios for each variable. Those found to be significant were included in the multivariate analysis.

The results of statistical test of significance are shown in **Table 1**. Age, socio economic status, marital status, education, irregular menstrual cycles, history of breast cancer among first degree relatives, previous

Table : 1 Description of Study Variables and Statistical Significance

Variable	Group	Control N=920 n (%)	Case N=660 n (%)	Total N=1580 n (%)	p-value
Age	<=35yrs	194(21.1)	78(11.8)	272(17.2)	<0.001*
	36-45yrs	320(34.8)	214(32.4)	534(33.8)	
	46-55yrs	257(27.9)	218(33)	475(30.1)	
	56-65yrs	115(12.5)	108(16.4)	223(14.1)	
	>65yrs	34(3.7)	42(6.4)	76(4.8)	
Socio economic Status	Poor	629(68.4)	391(59.2)	1020(64.6)	<0.001*
	Middle & High	291(31.6)	269(40.8)	560(35.4)	
Marital status	Ever married	900(97.8)	628(95.2)	1528(96.7)	<0.01*
	Unmarried	20(2.2)	32(4.8)	52(3.3)	
Education	<5 yrs of schooling	70 (7.6)	36 (5.5)	106(6.7)	<0.05*
	5-10 yrs of schooling	218 (23.7)	165 (25.0)	383(24.2)	
	Intermediate	501 (54.5)	337 (51.1)	838(53.0)	
	Graduate	94(10.2)	79(12.0)	173(10.9)	
	PG and above	37(4.0)	43(6.5)	80(5.1)	
Age of Menarche	> 12 yrs	839(91.2)	591(89.5)	1430(90.5)	NS**†
	<= 12 yrs	81(8.8)	69(10.5)	150(9.5)	
Regularity of cycles	Regular	864(93.9)	599(90.8)	1463(92.6)	<0.05**
	Irregular	56 (6.1)	61(9.2)	117(7.4)	
Menstruation status	Premenopause	479(52.1)	324(49.1)	803(50.8)	NS**†
	Post menopause	441(47.9)	336(50.9)	777(49.2)	
First Degree Relatives with Breast Cancer	No	900 (97.8)	629(95.3)	1529(96.8)	<0.005**
	Yes	20(2.2)	31(4.7)	51(3.2)	
History of Breast Biopsy	No	899(97.7)	608(92.1)	1507(95.4)	<0.001**
	Yes	21(2.3)	52(7.9)	73(4.6)	
Oral Contraceptive Pills Use	Never Used	908(98.7)	647(98.0)	1555(98.4)	NS**†
	Ever Used	12(1.3)	13(2.0)	25(1.6)	
Breast Feeding <sup>‡</sup>	No	31(3.5)	68(12.1)	99(6.9)	<0.001**
	Yes	844(96.5)	492(87.9)	1336(93.1)	
Age at first live birth	<=25yrs	719(65.0)	388(35.0)	1107(100.0)	<0.001*
	26-30yrs	131(49.4)	134(50.6)	265(100.0)	
	>=30yrs	22(34.9)	41(65.1)	63(100.0)	
	Nullipara	48(33.1)	97(66.9)	145(100.0)	

\* Chi Square for linear trend,\*\* Pearson Chi square,†Not Significant,‡1435 ladies who had at least one child were included

breast biopsies, and advanced age at first live birth were found to have significant association with breast cancer. Breast feeding was found to be associated with significant reduction in breast cancer risk. Early age of menarche, Post-menopausal status and use of oral contraceptive pills, which are known risk factors of breast cancer were not found to be significant in this study. These variables were nonetheless included in the initial multivariate analysis to look for any confounding effects, and adjusted odds ratios also were not found to be significant.

Urban women had higher odds (Odds Ratio 1.893; 95% CI-1.364 - 2.626) of developing breast cancer compared to rural women. Compared to Hindus, Muslims has a significantly higher odds of developing breast cancer (OR=1.541, 95%CI- 1.125-2.112).

In Multivariate Analysis, Unconditional Logistic Regression (Enter) was used to calculate the adjusted odd ratios because, the study was not an age-matched case-control study and most of the reproductive variables were age dependent. Age, regularity of cycles, age at first live birth, breastfeeding, family history and history of previous biopsy were having significant odds ratio even after adjustment. Post-menopausal women showed a higher risk in univariate analysis which got reversed when adjusted for age.

The mean age of cases and controls were 47.79 (SD -11.1) years and 44.77 (SD -10.93) years respectively. Significant Crude Odds Ratio of 1.025 (95% CI 1.016-1.034), was obtained from univariate analysis using logistic regression. Table 1 shows 4.7% of cases had a positive family history of breast cancer. Those who had a first degree relative with breast cancer had a twofold risk [Crude OR 2.22(95% CI -1.25-3.93) and Adjusted OR of 1.97(95% CI -1.07-3.63)] for developing breast cancer. Participants were asked about history of previous breast biopsy and 7.9% of the cases and 2.3% of the controls had past history of breast biopsy. Crude Odds Ratio was 3.66 (95% CI-2.18 - 6.14) and adjusted odds ratio was 4.04 (95% CI-2.34 - 6.97).

Middle and high socio economic class had higher odds (OR 1.487; 95%CI -1.207-1.832) and married women, were at higher risk for breast cancer (OR=2.29; 95%CI-1.30-4.05) in univariate analysis. After adjustment, odds ratio for marital status reversed and became insignificant (OR=0.76, 95%CI-.37-1.58). Participants were asked about their highest education, and it was found to be significantly different among cases and controls. Women with higher education (Post graduate and above) had a significant two fold risk compared to those who had less than five years of schooling. Only 2 % of the cases and 1.3% of controls had ever used OCPs and no significant risk was noticed.

The mean age of first live birth among cases was 23.99(SD 4.359) and of controls was 22.28(SD 3.78). P-value using t-test was <0.001. Age of First Live Birth was grouped into four categories, with nullipara as the fourth category and odds across the groups were compares. Crude odds ratio was found to be significant at 1.15; (95% CI -1.11-1.19). Women with Age of First live birth 30 years and above had

Table :2 Comparison of Crude and Adjusted Odds Ratios of Significant Risk Factors

Variable	Group	Crude OR	95 % CI	Adjusted OR	95 % CI
Age	<=35yrs	1.00	--	1.032	1.02-1.41
	36-45yrs	1.66	1.21 - 2.28	1.897	1.35-2.66
	46-55yrs	2.11	1.53 - 2.90	2.413	1.70-3.43
	56-65yrs	2.34	1.61 - 3.39	2.828	1.88-4.25
	>65yrs	3.07	1.82 - 5.18	3.75	2.13-6.59
Socioeconomic Status	Poor	1.00	--	1.00	--
	Middle & High	1.49	1.21 - 1.83	1.41	1.10-1.82
Marital status	Ever married	1.00	--	1.00	--
	Unmarried	2.29	1.30 - 4.05	0.76	0.37-1.58
Education	<5 yrs of schooling	1.00	--	1.00	--
	5-10 yrs of schooling	1.47	0.94 - 2.31	1.65	1.02- 2.68
	Intermediate	1.31	0.86 - 2.00	1.43	0.89-2.29
	Graduate	1.63	0.99 - 2.70	1.36	0.76-2.44
	PG and above	2.26	1.25 - 4.10	2.21	1.11-4.39
Regularity of cycles	Regular	1.00	--	1.00	--
	Irregular	1.57	1.08 - 2.29	1.64	1.09-2.46
First Degree Relatives with Breast Cancer	No	1.00	--	1.00	--
	Yes	2.22	1.25 - 3.93	1.97	1.07-3.63
History of Breast Biopsy	No	1.00	--	1.00	--
	Yes	3.66	2.18 - 6.14	4.04	2.34-6.97
Breast Feeding	No	1.00	--	1.00	--
	Yes	0.27	0.17- 0.42	0.49	0.33-0.71
Age at first live birth	<=25yrs	1.00	--	1.00	--
	26-30yrs	1.90	1.45 - 2.49	1.85	1.39-2.47
	>=30yrs	3.45	2.03 - 5.88	2.96	1.70-5.14
	Nullipara	3.75	2.59 - 5.41	4.28	2.66-6.90

an adjusted odds ratio of 2.96 (95%CI 1.70-5.14) and nulliparous women had an adjusted Odds ratio of 4.28 (95%CI 2.66-6.90) for developing breast cancer when compared to women with first child birth before 26 years of age (Table-2).

## Discussion

Advancing age, age at first live birth, nulliparity, history of first degree relatives with breast cancer, and history of previous breast biopsy carry a significant Odds Ratio of 1.5 or more in the present study. The influence of some of the risk factors, such as age at menarche, oral contraceptive use and menstruation status may be limited because of geographic variations. Women who had breast fed their child had significant less risk of developing breast cancer. Sociodemographic variables like urban residence, and higher socioeconomic status also showed significant association in the development of breast cancer.

Increasing age is a known determinant of breast cancer.<sup>15</sup> In this study mean age of breast cancer patients was 47.79 years(SD 11.1) and 44.77 years (SD 10.93) for controls. Crude OR for age was 1.025 (95% CI-1.016-1.034) which means for every year of age, the risk

increases by 2.5%. The commonest age group of incidence was 36–55 years (65%). For every 10 years increase in age above 35 years, the odds of developing breast cancer increases and becomes 3.75 at 65 years and above (Table.2). A study conducted in Delhi by Sunitha Saxena et al had a mean patient age of 47.8yrs and the commonest age group of incidence was 36–54 years (31.8%). Nearly 22% of cases were below 40 years while 16% of cases were above the age of 65 years.<sup>16</sup> Similar hospital based studies carried-out in Jaipur have also reported that the average age of breast cancer cases to be as 46.8 and 47 years.<sup>17</sup> In the United States, the risk of breast cancer is higher among middle-aged and elderly women than among young women.<sup>18</sup> The average age of occurrence of breast cancer amongst US white females has been reported to be 61 years. The average age of occurrence of the breast cancer in India reveals that the disease occurs more than a decade earlier, as compared to western countries.<sup>19,20,21,22</sup> The reason for early age of occurrence amongst Indian women needs to be further studied. A shift of cancer more towards younger women is seen in a study conducted by Borovanova in the Czech population.<sup>23,24</sup>

Urban dwellers had significantly higher odds(1.89) of developing Breast cancer compared to people living in rural areas. This agrees with other studies that Breast cancer is more common in urban areas.<sup>25</sup> High and upper middle class had a significantly higher odds (OR 1.487) of developing breast cancer compared to lower class. According to Gomes et al, women with higher income are at an elevated risk (OR 1.69, 95% CI- 1.18-2.42) compared with women with lower income.<sup>26</sup> Unmarried women had 2.3-fold risk of developing Breast cancer and agrees with findings by Gajalakshmi et al, wherein single women had higher risk than married women.<sup>27</sup> In this study, educated women are having a significant higher risk for developing breast cancer. According to Helmrich et al, 12 or more years of education was independently associated with an increased risk of breast cancer.<sup>28</sup> The risk of breast cancer increased as the level of education increased.

Age of onset of menarche was classified into two groups with 12 as the cutoff age and Odd's Ratio was 1.21(95%CI-0.86-1.70) which was not significant. This is against the common finding that early age at menarche is a risk factor of breast cancer.<sup>29,28,30,31,32</sup> But studies from India has shown that age at menarche have no association with the risk of breast cancer. Gajalakshmy et al analyzed the risk factors for breast cancer separately in premenopausal and postmenopausal groups.<sup>27</sup> In neither group was there significant association between age at menarche and breast cancer risk. According to Helmrich et al, late age at menarche was associated with a lower risk among premenopausal women but not among postmenopausal women.<sup>28</sup>

Menstrual irregularities were present in 9.2% of cases and 6.1% of controls and participants with irregular menstrual

cycles had significantly higher odds (OR-1.64) of developing breast cancer (Table-2). This agrees to the finding by Henderson et al identifying menstrual irregularities as a risk factor for breast cancer.<sup>33,34</sup> In Guptha et al 's study, menstrual irregularities were present in 17.50% of the cases.<sup>35</sup> Contrary to this, a study from Brazil by Gomes et al showed that irregular menstrual cycle (OR = 0.44, 95% CI: 0.25-0.75) had a protective effect on breast cancer.<sup>26</sup>

While exploring menopausal status, it was observed that post-menopausal women were at higher risk (Crude OR=1.126) but was not significant (95%CI-0.922-1.376). But adjusted Odds Ratio was 0.65 (95%CI-0.41-0.83). This shows that post-menopausal women had a significant lower risk for developing breast cancer. The disparity between crude and adjusted OR was obviously due to the confounding effect of age, as this was an age unmatched study. Most of the literature evidence is that breast cancer is more common among post-menopausal women.<sup>27,32,18</sup>

Number of first degree relatives with breast cancer is one of the major known risk factors for breast cancer and is included in the Gail Model breast cancer risk assessment tool.<sup>36,37</sup> In this study those who had a first degree relative with breast cancer had a significant two fold risk for developing breast cancer (Table 2). This finding agrees with many studies, which showed the presence of a first degree relative with breast cancer as risk factor of breast cancer.<sup>38,39,40</sup>

History of biopsies (incision, excision, or fine-needle aspirations, but not cyst aspirations) for benign breast disease are considered as a risk factor for breast cancer and a biopsy showing atypical hyperplasia carries double the risk of a biopsy showing no benign disease.<sup>41,47,48</sup> This association is mainly with biopsy-proven lesions with histologic demonstration of atypia or proliferative lesions (atypical ductal or lobular hyperplasia).<sup>49,50</sup> In this study adjusted odds ratio for history of breast biopsy was 4.04(95% CI-2.34 – 6.97) (Table-2). Literature shows that number of previous breast biopsies is a major risk factor with a relative risk of 1.7 (Clemons M et al)<sup>32</sup> to 1.85 (Tavani A et al).<sup>42</sup> Several studies suggest that the presence (or history) of benign breast disease is associated with an increased risk of breast cancer.<sup>43,44,45,46</sup> While comparing women who never had a breast biopsy, to women who had benign breast disease without hyperplasia, women with hyperplasia without atypia and women with hyperplasia and atypia; the odds to develop breast cancer was 1.5,1.8 and 2.6 consecutively.<sup>51,52</sup> Among women with and without a family history of breast cancer, a history of a single biopsy was a weak risk indicator but with two or more biopsies, the risk was increased. While women without family history, undergoing breast biopsy had a 1.5 fold risk, those with family history had a 5.6 fold excess risk (Brinton et al).<sup>53,54</sup> In this study, Oral Contraceptive Pills (OCP ) use showed no significant risk (Crude Odds Ratio-1.520; 95% C.I.-0.689-3.354)

(Table -2).<sup>29</sup> This is against the common finding that OCP use contributes to breast cancer risk.<sup>55,56</sup>

Participants with at least one child were asked whether they had ever breast-fed their babies; 87.5% of cases and 96.5% of controls had breast fed their babies. 12.1% of the cases had never breast-fed. Crude OR - 2.83 (95% C.I-1.98-4.04 and adjusted OR - 0.463 (95% C.I-0.316-0.680) (Table-2). Compared to those who had never breast fed their children those who breast-fed had significant protection which increased with duration of breast feeding. This agrees with many studies that shows breast-feeding as a protective factor against breast cancer(Nelson et al).<sup>56,57</sup> Similarly, late age of first live birth is another important risk factor with relative risk of breast cancer ranging from 1.9 to 3.5 in studies that compared first child birth after 30 years of age to first child birth before 20 years of age.<sup>58</sup> In this study, the Crude odds ratio was 1.15; (95% C.I.- 1.11-1.19) suggesting that for every year first child birth is delayed, the risk of breast cancer increases by 15%. A study from Jaipur showed that most women (68.50%) had their first live child between 18 and 25 years of age and 13.50% had before 18 years.<sup>35</sup> Late age at first live birth was associated with increased risk of breast cancer among both pre- and post-menopausal women(Gao et al).<sup>30</sup> In this study, women with Age of First live birth 30 years or more had an adjusted odds ratio of 2.96 (95%CI 1.70-5.14) and Nulliparous women had adjusted odds ratio of 4.28 (95%CI 2.66-5.32) for developing breast cancer when compared to women who had first child before 26 years. This agrees with the literature that women who delayed their first childbirth were at elevated risk of developing breast cancer.<sup>59</sup>

This study tried to eliminate most of the potential bias of an unmatched case control study. Attempts were made to identify and tackle different types of Epidemiological Biases. To reduce Selection Bias all incident cases during the study period were taken. Seriously ill and other patients who had their surgery outside RCC were not considered as it could affect the study results. Community controls were included to minimize the bias of choosing only hospital controls. The reason for limiting to Thiruvananthapuram city for control selection was shortage of resources to cover the entire state. Moreover, Thiruvananthapuram being the capital city, people from all parts of the state reside here and a random sample from the city may provide an approximate representation of the state.<sup>60</sup> Information Bias could come in due to misclassification of the exposure status. Care was taken at each state of the interview that the participant understood each question correctly and provided answers after adequate contemplation. The presence and magnitude of Confounding Bias cannot be directly observed. The study of covariates and controlling the effects of the same in multivariate analysis minimizes confounding. Age is identified as a confounder for reproductive factors, especially menopausal status. As the authors wanted to study

age as a risk factor, matching for age was not done. Adjusted odds ratios were calculated to make up for this limitation.

## Conclusion

While many of the risk factor of breast cancer among women in Kerala were found to be consistent with established risk factors, some were not. The factors found to be consistent, in the order of strength of association include, nulliparity, history of previous breast biopsy, advancing age, first child birth after 30 years of age, absence of breast feeding, family history of breast cancer and history of irregular menstrual cycles. Better living conditions, as evidenced by higher education and higher socioeconomic class were found to increase the risk. The factors found to be non-consistent are early age of menarche, use of oral contraceptive pills and post-menopausal status, out of which post-menopausal status could be explained as a design related effect.

In the rapidly changing social order in Kerala, with upwardly mobile women increasingly opting for later marriages and fewer or even no children, many of the risk factors that were hitherto thought to be modifiable, are slowly becoming non-modifiable. In this scenario the best option for intervention would be to increase awareness among women regarding the early diagnosis and treatment of breast cancer. Very high cure rates can be achieved with proper treatment for early breast cancer, while the outcome is still dismal for the late cases, even with improved treatment options. A well planned, individualized management of every patient; rather than hasty decisions including unplanned/unwarranted biopsy should be avoided. For women with very high genetic preponderance, prophylactic measures including medication and skin sparing mastectomy with reconstruction can also be considered.

From a primary prevention point of view, early completion of family with longer duration of breast feeding remains the best option not only for the prevention of breast cancer, but also for the overall health and well-being of the family.

## End Note

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**Conflict of Interest** – None declared

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