RESEARCH ARTICLE

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Potential Risk and Protective Factors in High- and Low-incidence Breast Cancer Populations in Northeast India: A Cross-sectional Study

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Abstract

Objective: The case-control study aims to identify the potential risk and protective factors contributing to breast cancer risk in the high-incidence Aizawl population and the low-incidence Agartala population, using age-specific prevalence data of established reproductive factors and body mass index (BMI) among healthy women. **Methods:** A risk profile survey was conducted on asymptomatic women aged 30-64 in Aizawl and Agartala towns. Data was analysed using SPSS software. A descriptive statistical analysis characterised variable distribution, and bivariate inferential analyses of variable differences including birth cohort study across two states were conducted. Logistic regression determined odds ratios of mean values of reproductive factors and BMI. **Results:** The study reports that in Aizawl, a high prevalence of delayed marriages, late pregnancies, postmenopausal obesity and family history are potential risk factors for breast cancer in women, while an elevated mean age at menarche, high parity, and extended breastfeeding are protective factors. Conversely, in Agartala, early marriage, early first childbirth, high parity, prolonged breastfeeding, and healthy BMI are associated with low breast cancer risk in women. The study underscores the potential risk factors of early menarche and an extended reproductive period for women in Agartala. **Conclusion**: The study emphasizes the importance of conducting age-specific prevalence studies in healthy women to identify critical risk and protective factors for breast cancer. Such information is crucial for healthcare professionals to develop prevention strategies, raise public awareness, and facilitate early detection of breast cancer in different populations. The study results will also set the stage for more extensive research on risk and protective factors for breast cancer in the Northeast region of India.

Keywords: Breast cancer risk- reproductive risk factors- BMI

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Introduction

Breast cancer is the most common cancer among Indian women, with 221,757 new cases in 2022. The age-adjusted annual rate (AAR) is 31.2 per 100,000 population, constituting 28.8% of all female cancers [1]. Even though the overall incidence rate of breast cancer in India is lower compared to that in the Western world, it remains a significant public health concern. This is due to a significant increase in its incidence over the last few decades among both urban and rural populations in the country [2, 3].

Breast cancer is a complex disease with multiple risk factors involving interactions among biological, genetic, and lifestyle factors. A variety of modifiable and non-modifiable genetic and lifestyle factors have been linked to the risk of breast cancer [4, 5]. Various reproductive and hormonal factors influence the risk of breast cancer. For example, early menarche, late menopause, and hormone replacement therapy (HRT) are linked to an increased risk [6, 7, 8]. While, modifiable factors such as early marriage and first pregnancy, multiple pregnancies, and breastfeeding are known to reduce the risk of breast cancer [9-12]. Lifestyle choices like smoking, alcohol consumption, physical inactivity and obesity are also known to be independent risk factors [13-15]. Benign breast disease, dense breasts, and race and ethnicity also impact breast cancer globally [4, 16]. Several genetic mutations are known to increase the risk; first-degree relatives having breast cancer have a higher risk of developing breast cancer compared to those not having any family history of the disease. The two most significant genes associated with high penetrance are BRCA1 and BRCA2 [17, 18].

The varying rates of breast cancer among different populations underscore the crucial role of lifestyle, socio-cultural environment, and genetics in influencing cancer risk. Moreover, the prevalence and impact of different

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breast cancer risk factors vary among different human populations, affecting the incidence rates of the disease [19, 20]. Geographical variations in breast cancer risk factors and incidence rates have also been observed across India due to varying lifestyles, food habits and other sociocultural and racial diversity [21, 22]. Breast cancer incidence (AAR) per 100,000 people ranges from 48.0 in Hyderabad to 7.0 in Meghalaya [22]. In the Northeast region of the country, breast cancer shows wide variation due to sociocultural, dietary, and racial factors [23-25]. In the Aizawl district of Mizoram province, the AAR is 30.7, comprising 15.4% of all female cancers. Conversely, the neighbouring Tripura province PBCR shows a low incidence of breast cancer at AAR of 7.9, accounting for 14.4% of female cancers [22].

Currently, there are no explicit methods for primary prevention of breast cancer. Therefore, the best approach for healthy women to minimize their chances of developing the disease is to focus on reducing known risk factors. While reducing modifiable risk factors is crucial for prevention, identifying non-modifiable risk factors in a population facilitates early detection of breast cancer. It is essential, therefore, to identify the risk factors that have a significant influence on breast cancer in a population.

In developed countries, the availability of wide-ranging national surveys or registration databases have been used to accurately identify a population's risk and protective factors for breast cancer through case-control or cohort studies [13, 26, 27]. However, using case-control studies to identify risk factors presents challenges in developing countries like India, lacking national surveys or databases. Factors such as low population and incidence, limited patient numbers, insufficient clinical and diagnostic information, and confounding biases can hinder accurately identifying risk factors [28, 29].

Given these constraints, we used the age-specific prevalence of standard reproductive risk factors and body mass index (BMI) in healthy women to identify the risk and protective factors for breast cancer. For our cross-sectional study, we specifically chose a sample population of healthy women aged 30-64 from high-incidence, Aizawl, and low-incidence breast cancer Agartala towns in Northeast India [22]. Both these towns have population-based cancer registries, but no comprehensive case-control studies for breast cancer are available identifying potential risk factors.

The in-person survey used a pre-tested questionnaire on proven standard breast cancer risk factors and the details of socio-demographic, anthropometric characteristics. The study aims to identify the potential risk factors that may be contributing to the higher incidence of breast cancer in Aizawl and find factors that may offer protection or reduced breast cancer risk to women in Agartala. Additionally, through an age-specific prevalence study of reproductive risk factors in women, we have examined the birth cohort effect in the prevalence of crucial risk factors of breast cancer in the two populations. Furthermore, the study also identifies the potential risk factors in Agartala and protective factors in Aizawl which may necessitate careful attention while planning preventive measures and breast cancer screening for women in the region.

Materials and Methods

Study Setting and Design

A cross-sectional descriptive study using a structured questionnaire in Mizo/English languages was conducted in Aizawl, Mizoram. Two thousand nine (2009) healthy women aged 30-64 from patients' families at the Civil Hospital completed the questionnaire. In Agartala, Tripura, 7,917 healthy women aged 30-64 from the local community completed the questionnaire in Bengali/English. Women in both places were then educated about Breast Self-Examination (BSE) and examined for Clinical Breast Examination (CBE) by qualified medical personnel. According to India Census 2011, the total female population in Aizawl is 5,38,675, and in Tripura, 1,799,541. The study was conducted in accordance with the World Medical Association's Helsinki Declaration of 2013. Clear information about the study's objectives was provided, and verbal consent was obtained from all participants before they were given the survey questionnaire. Participation in the study was voluntary, and strict confidentiality was maintained regarding the data and personal information. The survey was conducted between June 2015 and December 2018.

Study Questionnaire

The questionnaire included six sections [30]. The first part covered the socio-demographic details of the participants, such as their address, age, religion, and current educational status. The second part contained questions about reproductive history, including age at menarche and marital status. The third part included queries about anthropometry, such as height, weight, and waist size. In the fourth section, respondents answered questions about alcohol drinking and other habits. The fifth part consisted of questions assessing their knowledge of cancer in general, as well as breast cancer, its risk factors, symptoms, and whether a close relative in the family is affected by it. The sixth part examined the respondent's knowledge and practice of BSE (Breast Self-Examination).

Statistical Analysis

The data were entered in Microsoft Excel and analysed using the statistical software SPSS (IBM et al., USA) version 21. A probability value of less than or equal to 0.05 was considered significant for all statistical methods. We conducted a descriptive statistical analysis to characterise the variables' distribution comprehensively. This involved examining absolute and percentage frequencies for categorical variables and calculating the mean and 95% confidence interval values for continuous or discrete variables.

Bivariate inferential statistical analyses were conducted to identify differences in proportions or means of variables across two states. The Z-test for proportions compared the observed proportions of each category of variables, such as age at menarche, age at menopause, age at marriage, age at first childbirth, number of children, duration of breastfeeding and BMI between the regions. The chi-square ($\chi 2$) test was used to analyse differences

in categorical variables, such as breastfeeding practices, contraceptive pill usage. Fisher's exact test was used instead of the Chi-square test for the variables where any contingency table cell contains a frequency below five. An independent sample t-test was used to compare the mean values of continuous variables, such as age at menarche, age at menopause, reproductive period, and age at the marriage, age at first childbirth, number of children, duration of breastfeeding and BMI, between the places. Additionally, binary logistic regression was employed to identify the factors associated with breast cancer risk in the two populations. The analysis aimed to determine reproductive and lifestyle factors and BMI contributing to the lower cancer prevalence in Agartala (Tripura) compared to Aizawl (Mizoram). In the regression model, Agartala (Tripura) was used as the reference category for the dependent variable. Crude odds ratios with 95% confidence intervals and corresponding p-values were used to assess the relationship between variables. Selective regression models included age adjustments to account for their impact on certain variables.

Results

Demographic Characteristics
Age and Religion

As shown in Table 1, in Aizawl (Mizoram), the mean age of the respondents was 40.41 years (95% CI, 40.61-41.45). The predominant age group was between 30-39 years 1074 (53.5%), with most of them between 30 and 49 years (1633; 81.3%), and 304 (15.1%) between 50 and 59 and 72 (3.6%) those above 60 years. The respondents were primarily Christians (1990; 99.1%), with 9 Hindus (0.4%), 6 Muslims (0.3%), and four others (0.2%). In Agartala (Tripura), on the other hand, the mean age of respondents was 39.37 years (95% CI, 39.34–39.70). A similar age group distribution was observed as in Aizawl, with the majority falling in the 30 - 39 age range (4598; 58.1%), with 2260 women (28.5%) between 40 – 49 years, with 886 women (11.2%) between 50 and 59, and 173 women (2.2%) aged 60 and above. Of the respondents, 6672 (84.3%) identified as Hindu, 463 (5.8%) as Muslim, and 784 (9.9%) as Christian.

Education of women

Eight hundred fifteen women, or 40.6% of respondents in Aizawl, had a secondary school certificate. College graduates and postgraduates accounted for 22.5% (453) and 4.0% (81) respectively, while illiterates made up only 3.1% (62). In Agartala, most respondents, 6503 (82.1%), were educated to at least primary school level, while 957 (12.1%) had completed secondary school education. College graduates and postgraduates were 1.5% (117) and 0.2% (17) respectively, while only 4.1% (323) were illiterate.

Family Income

As per Table 1, in Aizawl, 773 women (38.5%) had a monthly family income of less than INR 5000. Six hundred eighty-four women (34.0%) were from families with incomes between INR 5001 and 15,000, 240 women (11.9%) had family incomes between INR 15,001 and 25,000, and 312 women (15.5%) came from families with income of INR 25,001 and above per month. In Agartala, 51.1% of women (4042) belonged to families with a monthly income of less than INR 5000, while 3795 (47.9%) had a monthly family income of INR 5,001 – 15,000. Only 61 (0.8%) of women were from families with monthly incomes of INR 15,001 – 25,000, and a mere 19 (0.2%) came from families with monthly incomes above INR 25,000.

Marital Status

In Aizawl, 9.6% (194) of women were unmarried, 1524 (75.9%) reported being in marriage at the time of the survey, while 120 (6.0%) were widows, and 177 (8.8%) were separated from their spouses. In Agartala (Tripura), only 49 women (0.6%) were unmarried, 7401 (93.5%) were married, 415 (5.3%) were widows, and 52 (0.7%) were separated.

Reproductive History and Age-specific (Birth Cohort) data
Age at Menarche

The average age at which women in Aizawl (Mizoram)

Table 1. Socio-demographic Details of Women in Aizawl and Agartala

Demographic characteristics	Aizawl (Mizoram) (2009) N (%)	Agartala (Tripura) (7917) N (%)
Age in Years		
30-39	1074 (53.5)	4598 (58.1)
40-49	559 (27.8)	2260 (28.5)
50-59	304 (15.1)	886 (11.2)
60+	72 (3.6)	173 (2.2)
Mean (95% CI)	40.41 (40.61-41.45)	39.37 (39.34-39.70)
Religion		
Hindu	9 (0.4)	6672 (84.3)
Muslim	6 (0.3)	463 (5.8)
Sikh	0	0
Christian	1990 (99.1)	784 (9.9)
Others	4 (0.2)	0
Education		
Illiterate	62 (3.1)	323 (4.1)
Primary and above	598 (29.8)	6503 (82.1)
Secondary School	815 (40.6)	957 (12.1)
College	453(22.5)	117 (1.5)
PG and above	81 (4.0)	17 (0.2)
Family Income (p.m.)		
< 5,000 Rs	773 (38.5)	4042 (51.1)
5,001 - 15,000 Rs.	684 (34.0)	3795 (47.9)
15,001 - 25,000 Rs.	240 (11.9)	61 (0.8)
>25,000 Rs.	312 (15.5)	19 (0.2)
Marital Status		
Unmarried	194 (9.6)	49 (0.6)
Married	1524 (75.9)	7401 (93.5)
Widow	120 (6.0)	415 (5.3)
Separated	177 (8.8)	52 (0.7)

Table 2. The Standard Reproductive Factors and Family History of Breast Cancer

Reproductive Factors	Aizawl (Mizoram) (2009) n (%)	Agartala (Tripura) (7917) n (%)	Z-test / t-test / $\chi 2$ test (p-value)
Age at Menarche (yrs.)			
< 12	17 (0.8)	142 (1.8)	≤0.05
12	151 (7.5)	2444 (30.8)	≤0.05
13-15	1369 (68.1)	5232 (66.1)	>0.05
>15	472 (23.5)	99 (1.2)	≤0.05
Mean (95% CI)	14.45 (14.43-14.57)	13.03 (13.0-13.04)	40.02 (<0.001)
Age at Menopause (yrs.)			
≤ 39	44 (10.1)	73 (5.1)	≤0.05
40-49	259 (59.1)	1330 (90.5)	≤0.05
50-59	135 (30.8)	65 (4.4)	≤0.05
Mean (95% CI)	46.60 (46.13-47.07)	45.36 (45.19-45.52)	6.10 (<0.001)
Experiencing menstruation	1571	6448	≤0.05
Reproductive period			
Mean (95% CI)	31.71 (31.23-32.0)	32.40 (32.23-32.58)	2.64 (<0.009)
Age at Marriage (yrs.)			
< 18	113 (6.2)	1746 (22.1)	≤0.05
18-25	1240 (68.3)	5736 (72.8)	≤0.05
26-30	305(16.8)	360 (4.6)	≤0.05
>30	157 (8.6)	26 (0.3)	≤0.05
Unmarried	194	49	≤0.05
Mean (95% CI)	23.02 (22.78-23.26)	19.75 (19.67-19.82)	25. 72 (<0.001)
Age at First Child Birth			
< 18	50 (2.9)	592 (7.6)	≤0.05
18 -25	1174 (68.3)	6349 (82.9)	≤0.05
26-30	336 (19.5)	660 (8.6)	≤0.05
>30	158 (9.2)	71 (0.9)	≤0.05
Nulliparous	97	196	
Mean (95% CI)	23.72 (23.49-23.95)	21.46 (21.39-21.53)	8.33 (<0.001)
No. of Children			
1-2	661 (38.5)	5093 (64.7)	≤0.05
3-5	990 (57.6)	2492 (31.7)	≤0.05
>5	67 (3.8)	87 (1.1)	≤0.05
Mean (95% CI)	2.90 (2.84-2.97)	2.28 (2.26-2.31)	18.42 (<0.001)
Breastfeeding			
Up to 12 months	531 (31.2)	90 (1.1)	≤0.05
13-18 m	470 (27.8)	95 (1.2)	≤0.05
19-24 m	575 (33.8)	422 (5.5)	≤0.05
25-30 m	38 (2.2)	245 (3.2)	≤0.05
More than 30 m	85 (5.1)	6820 (88.8)	
Mean (95% CI)	15.39 (14.97-15.81)	48.82 (48.41-49.22)	9.38 (<0.001)
Family history of Breast Cancer			
Yes	230 (11.44)	60 (0.75)	≤0.05

experienced menarche was 14.45 years (95% CI, 14.43-14.57; p<0.001), while in Agartala (Tripura), it was 13.03 years (95% CI, 13.0-13.04; p<0.001). 32.6% of women in Agartala experienced menarche at 12 or before (Table 2). In contrast, in Aizawl, only 8.3% of girls experienced menarche before the age of 12 or before. Additionally, the birth cohort data shows that menarche before age 12 in Aizawl is a newer phenomenon, as evidenced by the absence of women who had menarche before 12 in older age groups (Table 3). This trend continues for those reaching menarche at age 12, with lower prevalence observed in older age groups. Moreover, while the women

Table 3. Age-Specific (Birth Cohort) Distribution of the Prevalence of Reproductive Risk Factors in Women from Aizawl and Agartala

Characters	Aizawl (2009) N (%)				$\chi 2$ (p-value)	Agartala (7917) N (%)				$\chi 2$ (p-value)
Age groups (years)	30-39	40-49	50-59	60+		30-39	40-49	50-59	60+	
Age at menarche (yrs)	1074	559	304	72		4598	2260	886	173	
<12	14 (1.3)	3 (0.5)	-	-	47.418	81 (1.8)	37 (1.6)	15 (1.7)	9 (5.2)	23.02
12	100 (9.3)	38 (6.8)	10 (3.3)	3 (4.2)	(<0.001)	1486 (32.3)	662 (29.3)	243 (27.4)	53 (30.6)	-0.005
13-15	754 (70.2)	380 (68.0)	188 (61.8)	47 (65.3)		2968 (64.5)	1535 (67.9)	619 (69.9)	110 (63.6)	
>15	206 (19.2)	138 (24.7)	106 (34.9)	22 (30.6)		63 (1.4)	26 (1.2)	9 (1.0)	1 (0.6)	
Age at Menopause (yrs)	15	101	253	69		21	489	794	164	
≤ 39	11 (73.3)	19 (18.8)	12 (4.7)	2 (2.9)	130.592	18 (85.7)	50 (10.2)	4 (0.5)	1 (0.6)	244.714
40-49	3 (20.0)	82 (81.2)	139 (45.7)	35 (50.7)	(<0.001)	3 (14.3)	439 (89.8)	752 (94.7)	136 (82.9)	(<0.001)
50-59	1 (6.7)	-	102 (33.6)	32 (46.4)		-	-	38 (4.8)	27 (16.5)	
Age at Marriage (yrs)	909	538	300	68		4561	2251	884	172	
< 18	54 (5.9)	38 (7.1)	15 (5.0)	6 (8.8)	32.25	663 (14.5)	464 (20.6)	491 (55.5)	128 (74.4)	907.493
18-25	622 (68.4)	340 (63.2)	228 (76.0)	50 (73.5)	(<0.001)	3590 (78.7)	1727 (76.7)	379 (42.9)	40 (23.3)	(<0.001)
26-30	171 (18.8)	93 (17.3)	31 (10.3)	10 (14.7)		292 (6.4)	55 (2.4)	10 (1.1)	3 (1.7)	
>30	62 (6.8)	67 (12.5)	26 (8.7)	2 (2.9)		16 (0.4)	5 (0.2)	4 (0.5)	1 (0.6)	
Age at First Child Birth (yrs)	840	493	273	64		4383	2228	875	169	
< 18	24 (2.9)	9 (1.8)	4 (1.5)	2 (3.1)	15.096	196 (4.5)	154 (6.9)	174 (19.9)	57 (33.7)	417.243
18 -25	571 (68.0)	323 (65.5)	203 (74.4)	45 (70.3)	-0.08	3638 (83.0)	1923 (86.3)	678 (77.4)	106 (62.7)	(<0.001)
26-30	174 (20.7)	98 (19.9)	45 (16.5)	14 (21.9)		504 (11.5)	133 (6.0)	17 (2.1)	4 (2.4)	
>30	71 (8.5)	63 (12.8)	21 (7.7)	3 (4.7)		45 (1.0)	18 (0.8)	6 (0.7)	2 (1.2)	
No of Children	860	509	282	65		4392	2234	876	170	
1-2	454 (52.8)	139 (27.3)	56 (19.9)	12 (18.5)	189.053	3796 (86.4)	1118 (50.0)	158 (18.0)	21 (12.4)	2560.935
3-5	395 (45.9)	349 (68.6)	202 (71.6)	43 (66.2)	(<0.001)	587 (13.4)	1100 (49.2)	686 (78.3)	119 (70.0)	(<0.001)
>5	11 (1.3)	21 (4.1)	24 (8.5)	10 (15.4)		9 (0.2)	16 (0.7)	32 (3.7)	30 (17.6)	
Breastfeeding	848	503	278	64		4389	2232	875	170	
Up to 12 m	242 (28.5)	157 (31.2)	103 (37.1)	27 (42.2)	26.59	76 (1.7)	10 (0.4)	3 (0.3)	-	299.989
13-18m	231 (27.2)	151 (30.0)	74 (26.6)	15 (23.4)	-0.008	75 (1.7)	17 (0.8)	2 (0.2)	-	(<0.001)
19-24 m	302 (35.6)	156 (31.0)	95 (34.2)	19 (29.7)		354 (8.1)	58 (2.6)	9 (1.1)	-	
25-30 m	25 (2.9)	10 (2.0)	1 (0.4)	1 (1.6)		200 (4.6)	44 (2.0)	4 (0.5)	1 (0.6)	
More than 30m	48 (5.7)	29 (5.8)	5 (1.8)	2 (3.1)		3684 (83.9)	2103 (94.2)	857 (97.9)	169 (99.4)	

Table 4. Logistic Regression of Mean values of Reproductive Factors and BMI

Independent variables Aizawl	Odds ratio (95% CI)	p-value
Age at Menarche (yrs.)	7.280 (6.387-8.297)	<0.001
Age at Menopause (yrs)	1.104 (1.069-1.141)	<0.001
Reproductive tenure	0.957 (0.932-0.983)	0.001
Age at Marriage (yrs)	1.224 (1,207-1.241)	<0.001
Age at First Child Birth	1.177 (1.160-1.194)	<0.001
No. of Children	1.488 (1.427-1.551)	<0.001
Duration of Br. Feeding	0.859 (0.820-0.899)	<0.001
BMI#	1.210 (1.191-1.229)	<0.001

having menarche between 13 and 15 are equally dispersed, Aizawl had a much higher prevalence of women who had their menarche at 15 (23.5%) than Agartala (1.2%). The logistic regression analysis (Table 4) also shows that the age at menarche was higher in Aizawl (OR = 7.280, 95% CI: 6.387-8.297, p < 0.001) compared to Agartala.

Age at Menopause: In Aizawl, women experience menopause at an average age of 46.60 years, compared to 45.36 years in Agartala (p<0.001). 30.8% of women in Aizawl undergo menopause between the ages of 50 and 59, as against only 4.4% in Agartala. Moreover, nearly twice as many women in Aizawl (10.1%) reach menopause before the age of 39 compared to their counterparts in Agartala (5.0%) (Table 2). The age-specific data in Table 3 show that 31.8% of women in Aizawl experience menopause at or before the age of 39. Among these women, a significant portion belongs to the older age groups of 50-59 and 60+, which suggests that premature menopause in Aizawl has been occurring for a long time in the past. Early menopause is observed only in 5.1% of women in Agartala. Additionally, the average reproductive period, or the time between menarche and menopause, for women in Aizawl was 31.71 years, while for women in Agartala, it was 32.40 years (p<0.001). The logistic regression result of the mean of age at menopause shows a higher age of menopause in Aizawl women (OR = 1.104, 95% CI: 1.069-1.141, p < 0.001). A lower reproductive tenure among Aizawl women was associated with a significant decrease in odds (OR = 0.957, 95% CI: 0.932-0.983, p = 0.001) compared to women in Agartala (Table 4).

Age at Marriage: While most women in both Aizawl and Agartala marry between 18 and 25, there is a notable difference in the age of marriage. In Aizawl, 16.8% of women marry between the ages of 26 and 30, and 8.6% marry after 30, whereas in Agartala, the corresponding percentages are 4.6% and 0.3%. Additionally, more women remain unmarried in Aizawl compared to an abysmally low number in Agartala (Table 2). The age cohort data shows that marriages of women before 18 are more common in Agartala (22.2%) than in Aizawl, especially in the 50-59 and 60+ age groups (Table 3). Marriages between the ages of 26 and 30 are more common in the 30-39 and 40-49 age groups, with Aizawl (16.8%) having a higher prevalence than Agartala (4.5%).

Table 5. Body Mass Index (BMI) in Women from Aizawl and Agartala

Body Mass Index (BMI)	Aizawl (Mizoram) (2009)	Agartala (Tripura) (7917)	Z-test / t-test / $\chi 2$ test (p-value)
BMI for the Sample women			
Underweight (<18)	46 (2.3)	534 (6.7)	≤0.05
Normal weight (18.5 – 24.9)	316 (16.0)	6651 (84.0)	≤0.05
Overweight (25.0 – 29.9)	969 (49.1)	690 (8.7)	≤0.05
Obesity Class I & II (30.0 – 39.0)	513 (26.0)	39 (0.5)	≤0.05
Obesity Class III (>40.0)	131 (6.6)	3 (0.1)	≤0.05
Mean (95% CI)	23.79 (23.67-24.27)	21.57 (21.50-21.62)	15.44 (<0.001)
BMI for Premenopausal Women			
<18	40 (2.6)	450 (7.0)	≤0.05
18.5 – 24.9	258 (16.7)	5437 (84.3)	≤0.05
25.0 – 29.9	784 (49.9)	534 (8.3)	≤0.05
30.0 – 39.0	367 (23.8)	25 (0.4)	≤0.05
>40.0	95 (6.2)	2 (0.0)	≤0.05
Mean (95% CI)	23.54 (23.21-23.87)	21.54 (21.48-21.60)	11.70 (<0.001)
BMI for postmenopausal Women			
<18	6 (1.4)	84 (5.7)	≤0.05
18.5 – 24.9	58 (13.5)	1214 (82.6)	≤0.05
25.0 – 29.9	185 (42.9)	156 (10.6)	≤0.05
30.0 – 39.0	146 (33.9)	14 (1.0)	≤0.05
>40.0	36 (8.4)	1 (0.0)	≤0.05
Mean (95% CI)	24.68 (24.24-25.12)	21.71 (21.57-21.84)	12.61 (<0.001)

The data suggest that the average age of marriage has gradually risen from 18 to between 26 and 30 in both locations. In Aizawl, marriages between the ages of 26 and 30 were common even among the birth cohort 60+, with 73.5% prevalence in this age range compared to 23.3% in Agartala (Table 3). Marriages after age 30 are more common in younger birth cohorts of women than in older age groups, with Aizawl (8.6%) having a higher prevalence than Agartala (0.3%). Logistic regression results (Table 4) show that the age at marriage was 1.224 times higher (OR = 1.224, 95% CI 1.207-1.241; p<0.001) among women in Aizawl compared to Agartala.

Age at First Child: In Aizawl, 92.0% of women were reportedly parous, with the average age at first childbirth being 23.72 years (95% CI, 23.49-23.95; p<0.001). Whereas in Agartala, 97.5% of women had children, with the average age at first childbirth being 21.46 years (95% CI, 21.39-21.53; p<0.001). Women in Aizawl tend to have their first child at a significantly older age compared to women in Agartala, mainly due to a higher prevalence of marriages between 26 and 30 years old and over 30 (Table 2). Notably, 9.2% of women in Aizawl had their first full-live pregnancy after age 30, while only 0.9% of women in Agartala did so (p<0.05). Additionally, 5.3% of married women in Aizawl remained childless compared to 2.4% in Agartala. The data in Table 3 shows that women in Agartala and Aizawl tend to have their first child in relation to the age of their marriage. In Agartala, there is a gradual decrease in the prevalence of first-time births under 18 from the older age group (60+) to younger (30-39) women, corresponding with a high prevalence of marriages under 18 in older cohorts of women. This trend is not as clearly observed among women in Aizawl. However, in Aizawl, the first child is more likely to be born after 30 in the 30-39 age group of women (Table 3) than in older birth cohorts, which explains the frequency data in Table 2. The logistic regression results in Table 4 show that the age at the first childbirth was 1.117 times higher (OR = 1.117, 95% CI 1.160-1.194, p<0.001) among women in Aizawl compared to Agartala.

Number of Children

In Aizawl, the average number of children per woman is significantly higher at 2.90 years (95% CI, 2.84-2.97; p<0.001) compared to Agartala, which is 2.28 years (95% CI, 2.26-2.31; p<0.001). Most women in Agartala (64.7%) had up to 2 children, while in Aizawl, most women (57.6%) had between 3 and 5 children. Additionally, 3.8% of sampled women in Aizawl had more than five children, whereas only 1.1% of women in Agartala fell into this category (Table 2). The birth cohort data shows that the 30–39 age group are more likely to prefer having 1-2 children than women in older age groups in Aizawl and Agartala; 52.8% of the women having 1-2 children in Aizawl and 86.4% in Agartala. Conversely, the older birth cohorts tended to prefer having 3 to 5 or more than five children (Table 3). The logistic regression of the mean number of children shows an OR of 1.488 (95% CI 1.427-1.551; p<0.001) for children in women of Aizawl compared to Agartala (Table 4).

Breastfeeding

Breastfeeding was common among women in both locations (Table 2). However, women in Agartala breastfed their children for an average of 48.82 months (95% CI, 48.41-49.22; p<0.001), whereas women in Aizawl breastfed for an average of 15.39 months (95% CI,14.97-15.81; p<0.001). Interestingly, 92.8% of sampled women from Aizawl breastfed their children for up to 24 months, while 88.8% of women in Agartala breastfed their children for over 30 months. The data from Table 3 indicates that in Aizawl, older women between the ages of 50-59 and 60+ have a higher prevalence of breastfeeding for up to 12 months compared to younger women. Conversely, younger age groups breastfed for more extended periods. However, in Agartala, despite 88.8% of women breastfeeding for more than 30 months, younger women breastfed for shorter periods. The logistic regression analysis (Table 4) shows that the duration of breastfeeding was significantly shorter among women in Aizawl, with lower odds (OR = 0.859, 95% CI: 0.820-0.899, p < 0.001).

Body Mass Index (BMI)

As shown in Table 5, the mean BMI of women in Aizawl was 23.79 Kg/m^2 (95% CI, 23.67-24.27; p<0.001). 2.3% were underweight, 16% were within the normal range of 18.5-24.9 Kg/m^2, 49.1% of women were overweight or obese class I, 26.0% of women had class II obesity, and 131 women (6.6%) had a BMI indicating Class III Obesity having a BMI greater than 40 Kg/m^2. The women in Agartala had an average BMI of 21.57 Kg/m^2 (95% CI, 21.50-21.62; p<0.001). 6.7% were underweight with a BMI <18 Kg/m^2, 84.0% were within the normal range, and 8.7% of women were overweight. Additionally, 0.5% of women had class I or II obesity, and only 0.1% had a Class III Obesity. Table 4 shows that the BMI in Aizawl women was estimated to be 1.210 times higher than in women of Agartala (OR = 1.210, 95% CI, 1.191-1.229; p < 0.001).

BMI of Premenopausal and Postmenopausal Women

Table 5 shows that 2.6% of premenopausal women in Aizawl were underweight, 16.7% were in the normal weight range, and a significant 49.9% were overweight or class I obesity. Notably, 30.0% of women were classified as obese, falling into Class II and Class III. A similar trend in BMI is observed in the postmenopausal women in Aizawl, except that a significantly higher proportion of women (42.3%) were in obesity of Class II and C III.

The BMI data for the women of Agartala exhibited a similar trend in pre- and postmenopausal women. In the premenopausal group, 7.0% of women were underweight, 84.3% were in the normal range, 8.3% were overweight, 0.4% were in Class II obesity, and no one had a BMI greater than 40 Kg/m^2. In the postmenopausal women in Agartala, 5.7% were underweight, 82.6% were in the normal BMI range, 10.6% were overweight, and only 1.0% were in the category of obesity of Class II, and none were in obesity Class III.

Breast Cancer in Family

The family history of breast cancer includes first- or second-degree female relatives from the mother's and father's families. Out of the sampled women in Aizawl, 230 (11.44%) responded, while only 60 (0.75%) women were aware of it in Agartala (Table 2).

Discussion

In this study, we compared the prevalence of established reproductive risk factors and BMI among a sample of healthy, asymptomatic women from the high-incidence area of breast cancer in Aizawl (Mizoram) and the relatively much lower incidence area of Agartala (Tripura). We aimed to identify the differences that may contribute to the variation in the risk of breast cancer in these two populations.

The early onset of menarche (menstruation) and late menopause are two significant non-modifiable factors associated with an increased risk of breast cancer [6, 31]. The average age of menarche in Europe has been decreasing and now seems to have stabilised [32, 33]. As a result, starting menarche before the age of 12 is widely accepted to be associated with a higher risk of breast cancer [34]. On the other hand, studies on the age of menarche in Indian girls have reported a mean age between 13-14, and also demonstrating a continuing decline in the age of menarche, with varying mean ages reported from different regions across the country [35, 36]. At the same time, several case-control studies conducted in India have indicated a higher risk of developing breast cancer for individuals who experience menarche before the age of 13 [10, 37]. On the contrary, our data show that women in Aizawl reach menarche at the mean age of 14.45 years, whereas women in Agartala reach it at 13.03 years old ($p<0.001$). Given that the average age of menarche in the Northeast region is reported to be 12.62 ± 1.27 years [35], we have opted to use 12 years as a benchmark for evaluating the risk of breast cancer. In Agartala, 32.6% of women experienced menarche at 12 or earlier. Whereas, in Aizawl, girls reaching menarche before age 12 are only 8.3%. The logistic regression analysis also shows that the age at menarche was higher in Aizawl (OR = 7.280, 95% CI: 6.387-8.297, $p < 0.001$) compared to Agartala. The data from birth cohorts also indicate that the declining age of menarche in Aizawl seems to be more of a recent trend, as older age groups of women in Aizawl lack this category, unlike Agartala, where this trend is evident even among women aged 60 and above. Thus, the prevalence data on age at menarche show a distinct protective predisposition in Aizawl's women against the risk of breast cancer and a definite caution for women in Agartala.

We find that the average age of menopause in women in Aizawl (46.60 years; $p<0.001$) was significantly higher than in Agartala (45.36 years; $p<0.001$), and 59.1% of women in Aizawl and 90.5% in Agartala had menopause between 40-49 years. These results correspond well with the reported average age of menopause in Indian women between 41.9 and 49.4 years [38, 39]. Additionally, we had two noteworthy observations. Firstly, 30.8% of women sampled in Aizawl went through menopause between 50 and 59, against only 4.4% of women in Agartala. Secondly, 10.1% of women in Aizawl reached menopause before age 39 compared to women in Agartala (5.0%). The logistic regression result show a higher age of menopause in Aizawl women (OR = 1.104, 95% CI: 1.069-1.141, $p < 0.001$). The birth cohort data suggest that women in both places, Aizawl and Agartala, increasingly experience menopause below age 39 in the younger birth cohort. The data also shows that 31.8% of women who experienced menopause at or before 39 years in Aizawl were in the older age groups of 50-59 and 60+, compared to only 6.8% in Agartala, suggesting that not only a higher proportion of women in Aizawl experienced menopause at or before 39, but they had also been experiencing it for a much longer time in the past compared to Agartala. These results are consistent with earlier reports that menopause before age 40 is becoming common in the country [38] and has been confirmed through the Indian National Family Health Surveys (NFHS). The NFHS-5 conducted from 2019 to 2021 also showed that 3.0% of women aged 30 to 34 and 6.7% aged 35 to 39 experienced menopause [40]. The etiological significance of early menopause in breast cancer remains unclear. However, women who experience early menopause are known to be at an increased risk of developing cardiovascular disease and diabetes mellitus [41]. Whereas menopause occurring after the age of 50 is associated with a higher risk of breast cancer [31, 37, 42]. Furthermore, early onset of menstruation and delayed menopause are associated with a higher risk of breast cancer due to increased ovulatory cycles and greater exposure to oestrogen [31]. Hence, the substantial percentage of women (30.8%) undergoing menopause between the ages of 50-59 in Aizawl suggests a higher risk of breast cancer. The variations in menopausal age between the two populations discussed here can be attributed to varying socioeconomic status, nutrition, and other lifestyle factors [43].

It is widely accepted that the increased likelihood of breast cancer in marriages after the age of 20 may reflect the well-established risk associated with late age at first childbirth. However, the issue of whether the age of marriage is an independent risk factor for breast cancer was resolved through a multi-national case-control study showing similar odds ratios ($\geq$ 31 years) seen among married parous and married nulliparous women [44]. Our study found that most women in both places get married between 18 and 25. However, a significant number of women (32.6%) in Aizawl get married between the ages of 26 and 30, after 30, or remain unmarried. On the contrary, marriages of women aged 25 or younger are more common in Agartala (94.5%), and fewer women marry after the age of 25 (4.9%) or remain unmarried (0.6%). Logistic regression results show that the age at marriage was 1.224 times higher (OR = 1.224, 95% CI 1.207-1.241; $p<0.001$) among women in Aizawl compared to Agartala. The birth cohort data shows that marriages of women before 18 are more common in Agartala than in Aizawl, especially in the 50-59 and 60+ age groups. Conversely, marriages between 26 and 30 years and after 30 are more prevalent in Aizawl than in Agartala in the 30-39 and 40-49 age groups compared to older age groups. These findings are

significant considering numerous hospital-based case-control studies and multiple systematic reviews indicating that marriage before age 20 is a protective factor. In contrast, a marriage between 25 and 30 years or beyond is a potential risk for breast cancer [11,37]. Thus, a delayed marriage of a significant number of women in Aizawl and a high prevalence of unmarried women can potentially increase the local population's risk of breast cancer.

The age of a woman's first full-term pregnancy is known to influence the risk of breast cancer in two ways. Pregnancy at a younger age, i.e., in the early 20s, is known to be protective against breast cancer, and the first birth after the age of 30 is known to increase the risk of breast cancer independently [9, 42]. Also, null parity is estimated to have a 30% increase in risk compared with parous women [45]. Against this background, it is significant to note that in Aizawl, 28.7% of women have their first child after age 26, 9.2% of whom have their first pregnancy after age 30. Additionally, 5.3% of married women in Aizawl remained childless. Furthermore, the first child is more likely to be born after age 30 in young women in Aizawl, as evidenced by the higher prevalence in younger birth cohorts than in older ones. This shows that the delayed first pregnancy seems to be due to late marriages common among the younger age groups in Aizawl. On the other hand, in Agartala, most women had their first child before age 25, and a mere 0.9% of women had their first child after age 30, with only 2.4% remaining nulliparous, thereby rendering the women a strong protection against breast cancer. The logistic regression results in Table 4 show that the age at the first childbirth was 1.117 times higher (OR = 1.117, 95% CI 1.160-1.194, p<0.001) among women in Aizawl compared to Agartala.

Parity is known to offer lifelong protection against breast cancer, and this protective effect increases with the number of children [11], while nulliparity is an independent risk factor for breast cancer [5]. Our data shows that the average number of children per woman is significantly higher in Aizawl at 2.90 compared to Agartala, which is 2.28 (p<0.001). Most women in Agartala (64.7%) had up to 2 children, while in Aizawl, most women (57.6%) had between 3 and 5 children. The logistic regression of the mean number of children shows an OR of 1.488 (95% CI 1.427-1.551; p<0.001) for children in women of Aizawl compared to Agartala. Additionally, the age-specific data shows that women in the 30–39 age group are more likely to prefer having 1-2 children than women in older groups in Aizawl and Agartala. Conversely, the older birth cohorts tended to prefer having 3 to 5 or more than five children. Studies have shown that women who have experienced at least one full-term pregnancy have a 25% lower risk of developing breast cancer compared to nulliparous women [45]. In the present survey, women have a significant level of protection for breast cancer, as 94.7% and 97.6% of married women were parous in Aizawl and Agartala, respectively. It may be added here that the protection provided by parity is restricted to hormone receptor-positive tumours (ER+PR+) [31].

In the Western world, limited breastfeeding practices have resulted in breastfeeding not being a robust protective factor against breast cancer. However, in less developed countries like India, where the total duration of breastfeeding can be long, significant protective effects have been observed [46-48]. In the current study, breastfeeding was common among women in both areas. Notably, 92.8% of the women surveyed in Aizawl breastfed their children for up to 24 months, while 88.8% of women in Agartala breastfed their children for over 30 months. The data in Table 3 shows that women in the younger cohort of Agartala tend to breastfeed for a shorter period despite the high percentage (88.8%) of women breastfeeding for more than 30 months. In Aizawl, even high proportions of older age groups preferred breastfeeding for a shorter period. The logistic regression analysis shows that the duration of breastfeeding was significantly shorter among women in Aizawl, with lower odds (OR = 0.859, 95% CI: 0.820-0.899, p < 0.001). Nevertheless, due to the significant proportion of parous breastfeeding women in Aizawl and Agartala, these women have inherent protection against the risk of breast cancer.

Multiple studies have demonstrated that postmenopausal women with a high Body mass index (BMI) are at a significantly elevated risk of developing breast cancer [13, 20, 31, 49, 51]. Notably, in Aizawl, 26.0% of women had class II obesity, with a BMI ranging between 30.0 and 39.0 kg/m², and 6.6% had class III obesity, with a BMI greater than 40 kg/m². On the other hand, only 0.6% of women in Agartala were noted to have Class II and III obesity. The logistic regression analysis confirms that the BMI of women in Aizawl was 1.210 times higher than in Agartala (OR = 1.210, 95% CI, 1.191-1.229; p < 0.001). BMI data was further analysed to identify the trend in obesity among the premenopausal and postmenopausal women in the study. The analysis revealed that a significantly higher proportion of postmenopausal women in Aizawl (42.3%) were affected by class II and III obesity compared to premenopausal women (30.0%). On the other hand, 84.3% of premenopausal and 82.6% of postmenopausal women from Agartala remained in the clinically normal range of BMI. Our findings indicate that a significant number of women in Aizawl have a BMI that falls within the high-risk range. However, data from the birth cohort demonstrates a decreasing trend in younger women compared to older age groups. Thus, a higher percentage of postmenopausal women (42.3%) with class II and III obesity present a significant risk factor for breast cancer in Aizawl. This necessitates meticulous monitoring in any preventive program aimed at controlling breast cancer in Aizawl.

Family history (FH) is a well-known factor that significantly increases the risk of breast cancer [4, 50]. Our data shows that amongst surveyed women in Aizawl, 230 women (11.44%) responded positively compared to 60 (0.75%) women who were aware of anyone having breast cancer in their first-degree relatives in Agartala. In view of our data and a recent report showing a correlation between lymph node status, molecular markers, and FH of a first-degree relative in breast cancer in Mizoram [51, 52], it is essential to have a closer examination to understand the role of FH in Aizawl's high incidence of breast cancer.

In Summary, the study shows that a high prevalence

of delayed marriages, late pregnancies, postmenopausal obesity, and family history are potential risk factors for breast cancer in women, while an elevated mean age at menarche, high parity, and extended breastfeeding were identified as protective factors in Aizawl. Conversely, in Agartala, an early marriage, early first childbirth, high parity, prolonged breastfeeding, and healthy BMI are potential contributors to a low breast cancer risk in women, and a high prevalence of early menarche and an extended reproductive period for women are possible risk factors. The study emphasizes the importance of conducting age-specific prevalence studies in healthy women to identify critical risk and protective factors for breast cancer. Such information is crucial for healthcare professionals to develop prevention strategies, raise public awareness, and facilitate early detection of breast cancer in different populations. The study results will also pave the way for more extensive research on risk and protective factors for breast cancer, thereby contributing significantly to the enhancement of women's health in the Northeast region of India.

Author Contribution Statement

MS designed the data analysis, interpreted the data, and drafted the manuscript. SB developed the survey instrument and oversaw the study's implementation. SC, KB and CL, planned and oversaw the data collection and data entry. AG designed and conducted the statistical analyses. .

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