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Risk factors according to estrogen receptor status of breast cancer patients in Trivandrum, South India

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Estrogen receptor (ER) status is an important biomarker in defining subtypes of breast cancer differing in antihormonal therapy response, risk factors and prognosis. However, little is known about association of ER status with various risk factors in the developing world. Our case–control study done in Kerala, India looked at the associations of ER status and risk factors of breast cancer. From 2002 to 2005, 1,208 cases and controls were selected at the Regional Cancer Center (RCC), Trivandrum, Kerala, India. Information was collected using a standardized questionnaire, and 3-way analyses compared ER+/ER− cases, ER+ cases/controls and ER− cases/controls using unconditional logistic regression to calculate odds ratios and 95% confidence intervals. The proportion of ER− cases was higher (64.1%) than ER+ cases. Muslim women were more likely to have ER− breast cancer compared to Hindus (OR = 1.48, 95% CI = 1.09, 2.02), an effect limited to premenopausal group (OR = 1.87, 95% CI = 1.26, 2.77). Women with higher socioeconomic status were more likely to have ER+ breast cancer (OR = 1.48, 95% CI = 1.11, 1.98). Increasing BMI increased likelihood of ER− breast cancer in premenopausal women (*p* for trend < 0.001). Increasing age of marriage was positively associated with both ER+ and ER− breast cancer. Increased breastfeeding and physical activity were in general protective for both ER+ and ER− breast cancer. The findings of our study are significant in further understanding the relationship of ER status and risk factors of breast cancer in the context of the Indian subcontinent.
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Key words: estrogen receptor; breast cancer; India

Estrogen receptor (ER) status of breast tumors has been instrumental in defining an important subtype of breast cancer with differences observed in risk factors, treatment and prognosis.[1–7] Numerous studies in the past have looked at differences in etiology and risk factors pertaining to presence or absence of ER-alpha. Most of these studies were conducted in Western populations as early as 1980s.[1–5] Around the same time, it was also discovered that ER+ tumors that lacked progesterone receptor (PR) expression were less responsive to endocrine therapy compared to tumors that expressed PR.[8] This led to studies in the past decade that looked at the link of various risk factors of breast cancer and combined ER/PR information to better explain the underlying differences between the various subtypes of breast cancer.[9–13] Chen and Colditz[14] have emphasized the importance of taking into account the ER/PR status information of breast tumors both for effective treatment as well as risk prediction for instituting prophylactic measures. Although there might be numerous ways to subtype breast cancer, the classification into ER+ and ER− cancer remains a key divider.[14] However, information related to ER status is lacking for populations in developing countries. In fact, in most developing countries, determination of hormone receptor status is not a part of standard protocol for treatment of breast cancer, despite the fact that the Breast Health Global Initiative (BHGI) classified hormone receptor status determination as a basic level therapy in the treatment of breast cancer.[15,16]

India is one such developing country, where breast cancer is the most common cancer among women in most places, mainly in the urban areas.[17] Despite this, there have been very few studies on breast cancer in India. Most studies that have looked at hormone receptor status in the recent past utilized secondary data and explored associations with limited number of clinical variables.[18,19] This has prevented effective extrapolation of those results at the population level. Indeed, there have been hardly any studies in India that have looked at the association of hormone receptor status of breast cancer and the underlying risk factors. In our article, we present the results from a case–control study that was conducted in Trivandrum, Kerala. Our study was done as a part of a multicenter breast cancer study in collaboration with International Agency for Research on Cancer (IARC) in South Asia. The main objective of the study was to look at the urban-rural differences between determinants of breast cancer to gain a broad understanding of breast cancer risk factors in India. We hypothesized that the known relationships of risk factors with ER status must hold true in this region of the world as well because evidence indicates that factors that increase exposure to estrogens increase the propensity of ER+ breast cancer occurrence.[12] We were also in a unique position to explore a few additional risk factors due to the unique composition of the population in our study with presence of various religions and mostly rural subjects.

Material and methods

Study setting, subject recruitment and confounding variables

Between 2002 and 2005, the study was conducted at the Regional Cancer Center (RCC), Trivandrum in the state of Kerala. The cases ($n = 1208$) were women with histologically confirmed incident primary breast cancer who attended the above hospital. All cases with past history of any cancer except nonmelanoma skin cancer were excluded from the study. Twenty cases had incomplete data and were excluded from analyses. In addition, 288 cases did not have ER data and were also excluded for the purposes of our study providing a total of 900 cases. The controls ($n = 1,208$) were subjects who did not have cancer and accompanied cancer patients other than those with breast cancer attending the same hospital during the same time period, and matched to cases by age (±5 years) and residence status (urban/rural). The RCC institutional review board approved the study. Written informed consent was obtained from all participants. The participation rates were more than 90% for both cases and controls.

In-person interview of each case and control was conducted at the above hospital using a pretested structured questionnaire at the time of admission to the study. Information on demographic and socioeconomic variables, reproductive history, time spent in household activities on a normal day, residential history, occupational history,

Abbreviations: BHGI, Breast Health Global Initiative; BMI, body mass index; ER, estrogen receptor; IARC, International Agency for Research on Cancer; IGF, insulin-like growth factor; IGFBP, insulin growth factor binding protein; NFHS, National Family Health Survey; PR, progesterone receptor; RCC, Regional Cancer Center; SES, socioeconomic status; WCRF, World Cancer Research Foundation.

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personal and family medical history, tobacco and alcohol habits and diet history was collected by trained interviewers. Anthropometric measurements were taken at the end of interview. Hormone receptor status was obtained from the medical records. All subjects were asked to list all places of residence where they had lived for at least 1 year, starting with the place of birth. Urban/rural residence status was collected according to the definition of national census. If the subject lived in a "Panchayat," residence status is defined as "rural" and all other areas such as "municipality" and "corporation" are defined as "urban."

Socioeconomic status (SES) was assessed using independent scores given to 'yes' and 'no' questions related to home ownership, availability of toilet and running water as well as possession of comfort/luxury items, such as electrical/gas stove, refrigerator, TV, air conditioner, car, motorcycle/scooter, bicycle and computer owned by the subjects. These scores were summed up to create a SES score, which was proxy for the income level of the women.

Anthropometric measurements

The height (in cm) and weight (in kg) of each case and control were measured using standard equipment. All subjects were asked to remove their shoes before measurements were taken. In addition to this, weight was measured with light clothing. All measurements were done twice in succession and averaged for a final value. Body mass index (BMI: kg/m^2) was computed as weight in kilogram divided by height in meters squared. Three mutually exclusive BMI groups were created based on the tertile distribution of BMI of all subjects because there were very few obese subjects in our study (BMI $\geq$ 30).

ER status determination process

Representative section of formalin-fixed paraffin-embedded tumor tissue was stained immunohistochemically using ER (Clone 1D5-Dakocytomation). Both the intensity and extent of staining (as denoted by brown staining of nuclei) were determined and scored 0 (negative), 1+ (weak), 2+ (moderate) and 3+ (strong) positivity.

Data analyses

All statistical analyses were performed using SAS 9.1.3 (SAS Institute, Cary, NC). To estimate the association of various risk factors and the ER status of breast cancer, we used unconditional logistic regression. Three-way analyses were conducted: case–case analysis comparing ER+ and ER− cases, ER+ cases and controls and ER− cases and controls. The case–case analysis points towards presence of heterogeneity between the 2 case subgroups, whereas the comparison between each case subgroup and controls allows for deriving risk estimates for determinants of breast cancer.[12] We also further extended our analyses by stratifying it based on menopausal status of subjects because most of the previous studies have suggested that risk profiles for breast cancer differ between pre- and postmenopausal women. Odds ratios (ORs) and 95% confidence intervals (CIs) were derived from the fitted models to reflect risk factor–ER status associations.

The following reproductive, demographic and lifestyle factors were used for analyses: urban or rural status–self-reported, age (in years) divided into 3 categories (<35, 35–50, >50), religion (Hindu, Christian or Muslim), marital status (married *versus* unmarried, divorced or separated), education (college or higher education *versus* less than college education), SES score (low or high), BMI (1st tertile $\leq$21.4, 2nd tertile >21.4 to $\leq$25.1 and 3rd tertile >25.1), age at menarche (<13, 13–16 and >16), parity (nulliparous, 1–4 children and 5 or more children), age of marriage (<18, 18–21, 21–24 and >24), total duration of breast feeding (<36, 36–54, 54–78 and >78 months) and total amount of physical activity per day (<3, 3–4, 5–6 and >6 hr). SES score was dichotomized using the median value, and the categories for the last 3 variables were determined by dividing their distributions into quartiles followed by comparison of the higher 3 categories with the lowest quartile. We also looked at a number of other variables in our models during the preliminary analysis, which included marital status, use of oral contraceptive pills or hormone replacement therapy, family history of breast cancer, smoking and alcohol intake. However, these factors did not affect the associations in the underlying model, and the results that have been presented here are for variables defined by using the fewest categories having relevant associations.

Results

Characteristics of the study population

Among the cases (n = 1,188), ER status information was not available for 288 cases and these were excluded from analysis. Among the 900 cases that were included in our analysis, 323 cases were ER+ and 577 cases were ER−. We compared the baseline factors for excluded and included cases and found the distribution of these factors to be similar in the 2 groups. Overall, it can be inferred from the distribution among the controls that the study population was predominantly rural (80.1%), Hindu (65.9%), with less than college education (87.5%), low SES score (72.1%) and was married (86.6%) with 1 to 4 children (84.7%) (Table I). Most of the population was premenopausal (67.1%) and had got married between 18 and 24 years (61.7%) having breastfed for a total of 78 months or less (73.4%). Most women were also quite active throughout the day for 5 hr or more (72.8%) and had low prevalence of using oral contraceptive pills (3.4%) (Table I).

Risk factor association outcomes based on ER status

Case–case analysis showed appreciable results for 2 variables (Table II). ER+ status of breast cancer was negatively associated with Muslim religion when compared to Hindus (OR = 0.59, 95% CI = 0.37, 0.93), and breastfeeding for 54–78 months was negatively associated with ER+ breast cancer (OR = 0.61, 95% CI = 0.39, 0.94). On comparing with controls, these associations became more prominent with Muslim women having positive association with ER− breast cancer (OR = 1.49, 95% CI = 1.09, 2.03) and increased duration of breastfeeding being protective for ER+ and ER− breast cancer with a stronger protective effect seen for ER+ breast cancer (p for trend = 0.004). Women with higher SES score had a positive association with both ER+ and ER− breast cancer when compared to controls but positive associations with ER+ breast cancer were stronger (OR = 1.43, 95% CI = 1.07, 1.92). Case–case analysis also showed an inverse association of ER+ breast cancer with increasing BMI, an effect which can be seen prominently in the positive association seen in comparison of ER− cases with controls (p for trend < 0.001) (Table II). Increasing age of marriage increased the probability of having both ER+ and ER− breast cancer with significant p-values of trend for both. However, the positive association of age of marriage more than 24 years was higher for ER− breast cancer (OR = 2.01, 95% CI = 1.42, 2.87). Increased duration of physical activity was protective for both ER+ and ER− breast cancer (p for trend for both < 0.0001) (Table II).

On stratifying by menopausal status, the negative association of Muslim religion with ER+ breast cancer was prominently limited to premenopause as was seen from the effects in case/case analysis (OR = 0.45, 95% CI = 0.23, 0.89) and ER−/control analysis (OR = 1.87, 95% CI = 1.27, 2.79) (Table III). Women with higher SES score had a positive association with having ER+ breast cancer mainly in postmenopausal women (OR = 1.60, 95% CI = 1.03, 2.47). The positive relationship of ER− breast cancer with increasing BMI was seen clearly only in premenopausal women (p for trend < 0.001). Increasing age of marriage increased the odds of having both ER+ and ER− breast cancer in both premenopausal women and postmenopausal women, although in both groups this association was stronger for ER− breast cancer with

TABLE I – DISTRIBUTION OF CHARACTERISTICS FOR WOMEN IN THE CASE–CONTROL STUDY, KERALA, INDIA

	Cases (n = 900)								
	ER+ (n = 323)		ER− (n = 577)		ER+ case/ER− case	Controls (n = 1,208)		ER+ case/controls	ER− case/controls
	No.	%	No.	%	OR (95% CI)[1]	No.	%	OR (95% CI)[1]	OR (95% CI)[1]
Urban-rural status									
Rural	243	75.23	447	77.47	1.00	968	80.13	1.00	1.00
Urban	80	24.77	130	22.53	1.13 (0.82, 1.56)	240	19.87	1.33 (0.99, 1.77)	1.17 (0.92, 1.49)
Age (years)									
<35	36	11.15	69	11.96	1.00	265	21.94	1.00	1.00
35–50	159	49.23	314	54.42	0.97 (0.62, 1.52)	705	58.36	1.66 (1.13, 2.45)	1.71 (1.27, 2.30)
>50	128	39.63	194	33.62	1.27 (0.80, 2.01)	238	19.70	3.96 (2.63, 5.96)	3.13 (2.26, 4.34)
Religion									
Hindu	225	69.66	360	62.39	1.00	797	65.98	1.00	1.00
Muslim	32	9.91	92	15.94	0.56 (0.36, 0.86)	161	13.33	0.93 (0.69, 1.27)	1.27 (0.95, 1.68)
Christian	66	20.43	125	21.66	0.85 (0.60, 1.19)	250	20.70	0.70 (0.47, 1.06)	1.11 (0.86, 1.42)
Education									
Less than college	259	80.19	490	84.92	1.00	1,058	87.58	1.00	1.00
College or higher	64	19.81	87	15.08	1.39 (0.98, 1.99)	150	12.42	1.74 (1.26, 2.41)	1.25 (0.94, 1.67)
SES score									
Low	185	57.28	366	63.43	1.00	872	72.19	1.00	1.00
High	138	42.72	211	36.57	1.29 (0.98, 1.71)	336	27.81	1.94 (1.50, 2.50)	1.50 (1.21, 1.85)
Marital status									
Unmarried	12	3.72	11	1.91	1.00	17	1.41	1.00	1.00
Married	249	77.09	458	79.38	0.50 (0.22, 1.15)	1,047	86.67	0.34 (0.16, 0.72)	0.68 (0.31, 1.46)
Others (divorced, separated)	62	19.20	108	18.72	0.53 (0.22, 1.26)	144	11.92	0.61 (0.28, 1.35)	1.16 (0.52, 2.58)
BMI									
1st tertile (≤21.4)	91	28.17	144	24.96	1.00	466	38.58	1.00	1.00
2nd tertile (>21.4 to ≤25.1)	122	37.77	200	34.66	0.97 (0.68, 1.36)	395	32.70	1.58 (1.17, 2.14)	1.64 (1.27, 2.11)
3rd tertile (>25.1)	110	34.06	233	40.38	0.75 (0.53, 1.06)	347	28.73	1.62 (1.19, 2.21)	2.17 (1.69, 2.79)
Age of menarche									
≤13	93	28.79	184	31.89	1.00	365	30.22	1.00	1.00
>13	230	71.21	393	28.79	0.86 (0.64, 1.16)	843	69.78	0.93 (0.71, 1.22)	1.08 (0.87, 1.34)
Menstrual status									
Premenopausal	153	47.37	316	54.77	1.00	811	67.14	1.00	1.00
Postmenopausal	170	52.63	261	45.23	1.35 (1.02, 1.77)	397	32.86	2.27 (1.77, 2.91)	1.69 (1.38, 2.07)
Parity									
>4 children	39	12.07	70	12.15	1.00	135	11.18	1.00	1.00
1–4 children	258	79.88	474	82.29	0.99 (0.65, 1.51)	1,024	84.77	0.87 (0.60, 1.28)	0.88 (0.65, 1.20)
Nulliparous	26	8.05	32	5.56	1.48 (0.77, 2.83)	49	4.06	1.84 (1.01, 3.33)	1.24 (0.73, 2.11)
Age of marriage									
<18 years	39	12.54	71	12.54	1.00	200	16.79	1.00	1.00
18–21 years	84	27.01	171	30.21	0.79 (0.51, 1.22)	455	38.20	0.79 (0.54, 1.15)	0.99 (0.73, 1.36)
21–24 years	84	27.01	143	25.27	0.94 (0.61, 1.47)	280	23.51	1.28 (0.86, 1.89)	1.35 (0.98, 1.87)
>24 years	104	33.44	181	31.98	0.92 (0.60, 1.41)	256	21.49	1.73 (1.81, 2.53)	1.87 (1.36, 2.57)
Total duration of breastfeeding									
<36 months	105	32.51	145	25.13	1.00	239	19.78	1.00	1.00
36–54 months	71	21.98	139	24.09	0.71 (0.48, 1.03)	313	25.91	0.52 (0.37, 0.73)	0.73 (0.55, 0.98)
54–78 months	64	19.81	156	27.04	0.57 (0.39, 0.83)	335	27.73	0.44 (0.31, 0.62)	0.77 (0.58, 1.02)
>78 months	83	25.70	137	23.74	0.84 (0.58, 1.21)	321	26.57	0.59 (0.42, 0.82)	0.70 (0.53, 0.94)
Physical activity per day									
<3 hr	81	26.64	116	22.31	1.00	128	11.91	1.00	1.00
3–4 hr	69	22.70	97	18.65	1.23 (0.83, 1.83)	164	15.26	1.10 (0.76, 1.58)	0.89 (0.65, 1.22)
5–6 hr	96	31.58	206	39.62	0.81 (0.57, 1.14)	507	47.16	0.49 (0.36, 0.68)	0.61 (0.48, 0.79)
>6 hr	58	19.08	101	19.42	0.99 (0.66, 1.49)	276	25.67	0.55 (0.38, 0.79)	0.55 (0.41, 0.74)
Oral contraceptive pill usage									
No	317	98.14	558	97.04	1.00	1,166	96.52	1.00	1.00
Yes	6	1.86	17	2.96	0.62 (0.24, 1.59)	42	3.48	0.53 (0.22, 1.25)	0.85 (0.48, 1.50)

[1]Unadjusted odds ratios and 95% confidence intervals.

strongest association seen with ER− breast cancer in premenopausal women married above 24 years of age (OR = 2.50, 95% CI = 1.49, 4.10) (Table III). Breastfeeding appeared protective for ER+ breast cancer in both pre- and postmenopausal women and ER− breast cancer only among premenopausal women. Increasing physical activity was protective for both ER+ and ER− breast cancer among both pre- and postmenopausal women. This protection was seen maximally for postmenopausal women who were active for more than 4 hours per day, mainly for ER+ breast cancer with appreciable results seen for physical activity of 5–6 hr (OR = 0.60, 95% CI = 0.36, 0.98) (Table III).

Discussion

In our study on breast cancer conducted in South India among mostly rural women, we found a high proportion of ER− cases. Muslim women had a higher likelihood of developing ER− breast

TABLE II – ADJUSTED[1] ODDS RATIOS AND 95% CONFIDENCE INTERVALS (CI) FOR THE ASSOCIATION BETWEEN POTENTIAL RISK FACTORS AND BREAST CANCER CHARACTERIZED BY ESTROGEN RECEPTOR (ER) STATUS FOR WOMEN IN THE CASE–CONTROL STUDY, KERALA, INDIA

	ER+ case/ER− case (n = 323/577)		ER+ case/controls (n = 323/1,208)		ER− case/controls (n = 577/1,208)	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Age						
<35	1.00		1.00		1.00	
35–50	1.11	(0.69, 1.83)	1.66	(1.08, 2.56)	1.62	(1.17, 2.25)
>50	1.16	(0.62, 2.18)	3.07	(1.73, 5.45)	3.07	(1.95, 4.83)
Religion						
Hindu	1.00		1.00		1.00	
Muslim	0.59	(0.37, 0.93)	0.92	(0.66, 1.28)	1.49	(1.09, 2.03)
Christian	0.80	(0.56, 1.14)	0.83	(0.53, 1.28)	1.08	(0.82, 1.40)
Education						
Less than college	1.00		1.00		1.00	
College or higher	1.36	(0.90, 2.07)	1.41	(0.96, 2.08)	1.13	(0.81, 1.57)
SES score						
Low	1.00		1.00		1.00	
High	1.24	(0.90, 1.70)	1.43	(1.07, 1.92)	1.11	(0.88, 1.41)
BMI						
1st tertile (≤21.4)	1.00		1.00		1.00	
2nd tertile (>21.4 to ≤25.1)	0.89	(0.62, 1.28)	1.29	(0.94, 1.79)	1.46	(1.12, 1.90)
3rd tertile (>25.1)	0.72	(0.50, 1.04)	1.27	(0.91, 1.79)	1.87	(1.43, 2.44)
	p for trend = 0.087		p for trend = 0.17		p for trend < 0.0001	
Age of menarche						
≤13	1.00		1.00		1.00	
>13	0.86	(0.63, 1.17)	1.07	(0.80, 1.43)	1.17	(0.93, 1.47)
Menstrual status						
Premenopausal	1.00		1.00		1.00	
Postmenopausal	1.27	(0.85, 1.88)	1.42	(0.98, 2.06)	1.06	(0.79, 1.42)
Parity						
Having children	1.00		1.00		1.00	
Nulliparous	1.09	(0.58, 2.06)	1.42	(0.78, 2.59)	1.21	(0.70, 2.08)
Age of marriage						
<18 years	1.00		1.00		1.00	
18–21 years	0.89	(0.56, 1.42)	0.98	(0.65, 1.48)	1.12	(0.81, 1.56)
21–24 years	0.99	(0.61, 1.61)	1.55	(1.01, 2.39)	1.53	(1.08, 2.18)
>24 years	0.81	(0.50, 1.31)	1.60	(1.04, 2.48)	2.01	(1.42, 2.87)
	p for trend = 0.59		p for trend < 0.001		p for trend < 0.0001	
Total duration of breastfeeding						
<36 months	1.00		1.00		1.00	
36–54 months	0.75	(0.50, 1.15)	0.66	(0.44, 0.97)	0.83	(0.60, 1.15)
54–78 months	0.61	(0.39, 0.94)	0.52	(0.34, 0.77)	0.80	(0.58, 1.11)
>78 months	0.85	(0.54, 1.32)	0.58	(0.38, 0.87)	0.67	(0.47, 0.95)
	p for trend = 0.30		p for trend = 0.004		p for trend = 0.03	
Physical activity per day						
<3 hr	1.00		1.00		1.00	
3–4 hr	1.23	(0.82, 1.85)	1.06	(0.72, 1.56)	0.91	(0.66, 1.28)
5–6 hr	0.86	(0.60, 1.23)	0.56	(0.40, 0.78)	0.68	(0.52, 0.88)
>6 hr	1.13	(0.73, 1.75)	0.72	(0.49, 1.07)	0.67	(0.49, 0.93)
	p for trend = 0.30		p for trend < 0.0001		p for trend < 0.0001	

[1]Adjusted for all the variables in this table.

cancer, an effect most clearly observed in premenopausal period. Women with higher SES had greater likelihood of developing ER+ breast cancer. Increasing BMI increased the likelihood of ER− breast cancer mainly in premenopausal women. Age of marriage was positively associated with both ER+ and ER− breast cancer, although the effects were stronger for ER− breast cancer among premenopausal women. Increased breastfeeding and physical activity were in general protective for both ER+ and ER− breast cancer. However, protective effects for breastfeeding were stronger for ER+ breast cancer premenopausally, whereas protective effects of physical activity were stronger for ER+ breast cancer postmenopausally.

The results of our study differ from those of other similar studies from European and North American populations because the majority of cases in our study were ER− when compared to breast cancer cases reported in western parts of the world where the majority of cases are ER+. This is consistent with the findings from previous studies done in India, which also found a very high proportion of ER− cases.[19] Similar results have also been seen from other countries in Asia, such as Pakistan,[20] China[21] and Japan.[22] One of the reasons put forth earlier for this observation has been younger age at presentation among Indian women,[19] although this may not be the only factor responsible. Another factor that might be affecting this shift in proportion of cases is perhaps a reduced exposure to exogenous estrogens, such as hormone replacement therapy and oral contraceptive pills, which leads to a higher occurrence of ER− tumors when compared to ER+ tumors.[23] It has been seen that Indian women prefer long-term methods of contraception such as tubal ligation rather than oral contraception.[24] According to the Indian National Family Health Survey (NFHS), the oral contraceptive pill usage among rural women in Kerala is only 0.6%.[25] The NFHS also shows that reproductive factors in rural Indian women still favor a reduced exposure to endogenous estrogens, which will further keep the proportion of ER+ tumors low.[25]

India is a secular country and different religions have varying lifestyles, customs and traditions. One of the most interesting findings of our study is that ER− status of breast cancer was associated with being a Muslim compared to a Hindu. Redkar *et al.*[18] looked at religious differences in ER status of breast cancer in the

TABLE III – ADJUSTED[1] ODDS RATIOS AND 95% CONFIDENCE INTERVALS (CI) FOR THE ASSOCIATION BETWEEN POTENTIAL RISK FACTORS AND BREAST CANCER CHARACTERIZED BY ESTROGEN RECEPTOR (ER) STATUS AMONG POST AND PRE-/PERIMENOPAUSAL WOMEN IN THE CASE–CONTROL STUDY, KERALA, INDIA

	OR (95% CI)					
	Postmenopausal			Premenopausal		
	ER+ case/ER− case (n = 170/261)	ER+ case/controls (n = 170/397)	ER− case/controls (n = 261/397)	ER+ case/ER− case (n = 153/316)	ER+ case/controls (n = 153/811)	ER− case/controls (n = 316/811)
Age (years)[2]	1.01 (0.98, 1.04)	1.06 (1.03, 1.09)	1.06 (1.03, 1.09)	1.02 (0.98, 1.06)	1.07 (1.04, 1.10)	1.05 (1.03, 1.08)
Religion						
Hindu	1.00	1.00	1.00	1.00	1.00	1.00
Muslim	0.78 (0.39, 1.51)	0.90 (0.47, 1.72)	1.20 (0.71, 2.02)	0.45 (0.23, 0.89)	0.81 (0.43, 1.51)	1.87 (1.27, 2.79)
Christian	0.75 (0.45, 1.24)	0.88 (0.53, 1.45)	1.28 (0.85, 1.92)	0.90 (0.54, 1.50)	0.93 (0.59, 1.46)	0.93 (0.65, 1.33)
Education						
Less than college	1.00	1.00	1.00	1.00	1.00	1.00
College or higher	1.35 (0.65, 2.81)	1.26 (0.58, 2.73)	1.27 (0.62, 2.60)	1.40 (0.83, 2.36)	1.57 (0.98, 2.51)	1.18 (0.80, 1.72)
SES score						
Low	1.00	1.00	1.00	1.00	1.00	1.00
High	1.12 (0.72, 1.75)	1.60 (1.03, 2.47)	1.30 (0.90, 1.89)	1.40 (0.87, 2.24)	1.27 (0.83, 1.93)	0.93 (0.67, 1.28)
BMI						
1st tertile (≤21.4)	1.00	1.00	1.00	1.00	1.00	1.00
2nd tertile (>21.4 to ≤25.1)	1.16 (0.69, 1.95)	1.72 (1.04, 2.84)	1.35 (0.88, 2.07)	0.72 (0.44, 1.20)	1.04 (0.66, 1.62)	1.53 (1.08, 2.16)
3rd tertile (>25.1)	0.95 (0.56, 1.62)	1.34 (0.81, 2.23)	1.51 (0.98, 2.30)	0.54 (0.32, 0.92)	1.29 (0.80, 2.08)	2.21 (1.54, 3.16)
	p for trend = 0.78	p for trend = 0.32	p for trend = 0.07	p for trend = 0.24	p for trend = 0.30	p for trend < 0.0001
Age of menarche						
≤13	1.00	1.00	1.00	1.00	1.00	1.00
>13	0.72 (0.45, 1.15)	0.93 (0.59, 1.48)	1.19 (0.81, 1.73)	1.02 (0.67, 1.56)	1.27 (0.86, 1.87)	1.21 (0.90, 1.63)
Parity						
Having children	1.00	1.00	1.00	1.00	1.00	1.00
Nulliparous	0.73 (0.29, 1.86)	1.12 (0.41, 3.07)	1.54 (0.62, 3.84)	1.56 (0.62, 3.88)	1.75 (0.81, 3.79)	1.07 (0.53, 2.18)
Age of marriage						
<18 years	1.00	1.00	1.00	1.00	1.00	1.00
18–21 years	1.03 (0.56, 1.88)	1.11 (0.64, 1.95)	1.15 (0.72, 1.84)	0.75 (0.35, 1.61)	0.89 (0.46, 1.70)	1.16 (0.72, 1.87)
21–24 years	0.93 (0.49, 1.77)	1.61 (0.87, 2.95)	1.54 (0.91, 2.61)	0.93 (0.43, 2.02)	1.58 (0.83, 3.00)	1.65 (1.00, 2.73)
>24 years	0.89 (0.47, 1.68)	1.34 (0.73, 2.49)	1.51 (0.89, 2.56)	0.65 (0.30, 1.42)	1.71 (0.89, 3.28)	2.50 (1.49, 4.10)
	p for trend = 0.88	p for trend = 0.08	p for trend = 0.05	p for trend = 0.35	p for trend = 0.005	p for trend < 0.0001
Total duration of breastfeeding						
<36 months	1.00	1.00	1.00	1.00	1.00	1.00
36–54 months	0.68 (0.35, 1.34)	0.52 (0.26, 1.02)	0.85 (0.46, 1.57)	0.84 (0.48, 1.46)	0.75 (0.46, 1.23)	0.81 (0.55, 1.20)
54–78 months	0.47 (0.24, 0.91)	0.44 (0.23, 0.85)	0.93 (0.52, 1.67)	0.75 (0.42, 1.35)	0.55 (0.32, 0.93)	0.70 (0.47, 1.04)
>78 months	0.72 (0.38, 1.33)	0.47 (0.25, 0.88)	0.61 (0.34, 1.10)	0.92 (0.44, 1.90)	0.50 (0.27, 0.95)	0.63 (0.40, 1.01)
	p for trend = 0.31	p for trend = 0.03	p for trend = 0.07	p for trend = 0.52	p for trend = 0.009	p for trend = 0.03
Physical activity per day						
< 3 hr	1.00	1.00	1.00	1.00	1.00	1.00
3–4 hr	1.40 (0.82, 2.41)	1.37 (0.81, 2.33)	0.92 (0.57, 1.50)	1.05 (0.54, 2.03)	1.01 (0.55, 1.86)	1.05 (0.66, 1.67)
5–6 hr	0.83 (0.50, 1.38)	0.60 (0.36, 0.98)	0.70 (0.46, 1.05)	0.90 (0.53, 1.55)	0.62 (0.38, 1.01)	0.74 (0.51, 1.06)
>6 hr	0.93 (0.46, 1.86)	0.56 (0.29, 1.09)	0.60 (0.35, 1.03)	1.39 (0.75, 2.60)	1.00 (0.59, 1.71)	0.78 (0.52, 1.19)
	p for trend = 0.38	p for trend = 0.003	p for trend = 0.009	p for trend = 0.84	p for trend = 0.05	p for trend = 0.02

[1]Adjusted for all the variables in this table.–[2]Age has been used as a continuous variable.

past and reported that Muslims had the lowest proportion of ER+ breast cancer when compared to other religions. However, in that study, they had not controlled for any of the confounders and could not clearly explain their finding. It is known from previous studies that breast cancer due to causes that act through mechanisms that are independent of hormonal exposures tends to be ER−.[12] Among genetic risk factors, BRCA1 tumors tend to be more likely ER− than ER+.[26] Muslims all over the world including India are known to favor consanguineous marriages. Among Indian Muslims hailing from Kerala, the prevalence of consanguinity is quite low (9.4%) when compared to other parts of India but this remains higher than other communities. For Indian Muslims overall, the prevalence of consanguinity is as high as 22%.[27] Studies done in other parts of the Indian subcontinent, mainly Pakistan, have shown that consanguinity is a risk factor for breast cancer because of the inheritance of breast cancer susceptibility genes.[28] Liede *et al.*[29] found significant associations of consanguinity with early-onset breast cancer in the Pakistani population and have proposed that recessive genes might play a role in the etiology of breast cancer. The association of genetic risk factors of breast cancer with ER− tumors might explain the high proportion of ER− tumors among Muslim women in India as well. However, it is imperative that this finding be explored further in populations from other parts of India. ER− tumors are more aggressive, nonresponsive to endocrine therapy and have a higher tendency to relapse early, and Muslim women in India might bear a disproportionately high burden of disease because of this.

Our study found a positive association of ER+ status of breast cancer and higher SES score mainly in postmenopausal women. These findings are consistent with findings in numerous previous studies that have looked at SES as a risk factor and have found higher risk of breast cancer with higher SES.[30–34] It has been speculated that higher SES is related to and may be a proxy for other factors related to nutrition and physical activity,[32] which change the internal hormonal milieu and increase a woman's lifetime exposure to estrogen which translates into increased occurrence of ER+ breast cancer mainly in the postmenopausal period.

The positive association of increasing BMI with ER− breast cancer, mainly observed among premenopausal women, was peculiar and interesting. In the past, most studies in Asian as well as Western populations have found a positive association of BMI with risk of ER+ status of breast cancer among postmenopausal women.[9,35] Among premenopausal women, positive association,[30] no association[36–39] or inverse association[40–42] has been seen for breast cancer risk and increasing BMI. However, the most recent WCRF report[43] suggests that body fatness is protective for breast cancer in premenopausal women. It is quite possible that the factors that lead to an inverse risk of breast cancer in premenopausal women might be related to the positive association between ER− breast cancer and increasing BMI among premenopausal women who develop breast cancer. Obesity can result in decreased circulatory estrogen levels causing anovulatory cycles.[44,45] In addition, obesity also leads to a state of relative insulin resistance, chronic hyperinsulinemia and an increase in IGF-1 bioactivity because of insulin-mediated decreases in IGF-binding protein 1 (IGFBP-1) and IGFBP-2. Insulin has been shown to be a growth factor for breast cancer cells and level of C-peptide, a marker of hyperinsulinemia and insulin resistance predicted breast cancer risk.[46] Meta-analysis of prospective studies for IGF-1 found a positive association with risk for premenopausal, but not postmenopausal, breast cancer.[47] Thus, breast cancer in premenopausal women is most likely caused by nonestrogenic influences, which results in ER− breast cancer.

Marriage in this population of predominantly rural women was closely associated to having children and breastfeeding, which get postponed because of a later age of marriage. This was clear from the correlation observed between age of first childbirth and age of marriage. Both pregnancy and breastfeeding have long-term protective effects against breast cancer because of the increased differentiation of breast tissue under the effect of female hormones—mainly progesterone.[48–51] Increased age of marriage leads to a lack of differentiation in the breast tissue making it more susceptible to harmful effects of nonestrogenic mutagens as well as genotoxic effects of estrogen, which has been known to cause ER− breast cancers as well.[52,53] Moreover, being married and having children might also reduce the level of circulating hormones or increase the levels of sex hormone-binding globulin.[54–56] This result is consistent with the results of Lord *et al.* who also found an increased risk of ER/PR-breast cancer with late age at first birth.[57]

In this population where the frequency of breastfeeding was high, cumulative breastfeeding was seen to provide protection for ER+ breast cancer for all women and ER− breast cancer only in premenopausal women. Evidence of protective effects of breastfeeding is inconsistent in studies in western populations probably because of low prevalence of breastfeeding.[58] Increased breastfeeding has been speculated to protect the breast against cancer through a number of mechanisms, which more prominently include excretion of carcinogens in breast milk and increased differentiation of breast tissue.[58] Breast milk has been known to carry a number of lipid soluble chemicals that can act as mammary carcinogens.[59–61] Also, increased breastfeeding leads to increased differentiation of breast tissue,[62] and both these mechanisms might be playing a big role in protecting the breast from both ER+ and ER− breast cancers.

More than 80 studies looking at the association of physical activity and breast cancer have found physical activity to have a protective effect.[43,63] This protective effect is due to a multitude of factors which include reduction in circulating levels of and cumulative exposure to sex steroid hormones, changes to insulin-related factors and adipocytokines, modulation of inflammation and immune system and hormonal and cellular metabolism pathways.[63] In our study, this protection was seen most prominently if a woman is active for 5 hours or more per day and was almost similar for both ER+ and ER− breast cancer. In comparison of pre- and postmenopausal women, stronger dose-response was seen in postmenopausal women for both ER+ and ER− breast cancer, a finding consistent with the WCRF report.[43] Also, Enger *et al.* found similar results showing decreased breast cancer risk with increased physical activity across all ER/PR categories for both pre- and postmenopausal women.[64]

Although the aforementioned study had a large number of participants which made the estimates in our study quite powerful, there might have been a few sources of bias. One of them could have arisen from the differences between participants and nonparticipants in the study. However, response rates were high (90%) and it is unlikely that participants and nonparticipants would have differed significantly. Among the participants, only 900 cases were chosen for analysis because ER status information was lacking for rest of the 288 cases. Both the included and excluded cases had similar distributions of baseline factors, and thus it is unlikely it would have biased our results. Also, our study was a hospital-based case–control study, which might generate different forms of bias arising from controls being similar to cases, and recall bias. However, we ensured that none of the controls were relatives of breast cancer patients. In addition, most of the items in the questionnaire included questions on lifestyle and reproductive factors, which were not difficult to recall. Thus, any bias arising because of a hospital-based design seems to be minimal.

One of the main strengths of our study was the ability to disentangle the effect of ER status from that of menopause on breast cancer. The results might suggest independent effects of ER status and menopausal status on the association between breast cancer and the various risk factors (BMI, parity, *etc.*). However, one of the most important things that was lacking in our study was the lack of information on PR status of breast tumors. Given the increasing emphasis on better classification of breast tumors on joint hormone receptor status, the presence of this information might have made the findings of our study more meaningful. Nevertheless, PR expression depends on ER expression and as such ER status of tumors is good predictor of PR status. Overall, the findings of our study are quite significant in better understanding of breast cancer in the context of India and other developing countries. It is also essential that hormone receptor status determination be made a routine part of the breast cancer treatment in developing countries because it would optimize the use of endocrine therapy and chemoprevention agents by improving their cost/benefit ratio. This would reduce the economic burden of breast cancer in developing countries quite effectively.

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