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Case-Control Study of Breast Cancer in India: Role of *PERIOD3* Clock Gene Length Polymorphism and Chronotype

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Abstract

Background—This study examined a *PERIOD3 (PER3)* gene variable number tandem repeat polymorphism and chronotype as potential BrCA risk factors among Indian women.

Methods—This case-control study included sporadic, histologically confirmed BrCA cases (n=255) and controls (n=249) from India with data collection from 2010–2012.

Results—Women with the 4/5 or 5/5 *PER3* genotype had a non-statistically significant 33% increased odds of BrCA. BrCA cases were more likely to have a morning (OR=2.43, 95% CI=1.23–4.81) or evening (OR=2.55, 95% CI=1.19–5.47) chronotype.

Conclusions—Findings are consistent with the possibility that extremes in chronotype may elicit circadian desynchronization, resulting in adverse health outcomes.

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Declaration of Interest

The authors have no other conflicts of interest to declare.

Introduction

Breast cancer (BrCA) is the most common cancer among urban Indian women (1). The estimated range of age-adjusted BrCA incidence in urban areas is ~25–33 per 100,000 (~33% of the United States [US] rate), and ~9 per 100,000 in rural areas (1,2). The Mumbai population increased from 3 to 12 million from 1950 to 2000, and age-adjusted BrCA incidence increased from 14 to 21 per 100,000 (3). Factors related to the demographic and epidemiologic transition currently occurring in India may have contributed to these increases, particularly in urban areas. The Breast Cancer Genetics, Environment, and Lifestyle (BRCAGEL) study was implemented to examine behavioral and genetic BrCA risk factors in the Mumbai region.

Clock genes maintain reciprocal transcriptional-translational feedback loops that drive the molecular clock in the body's master circadian pacemaker (suprachiasmatic nuclei [SCN]), and in most peripheral tissues (4,5). The SCN transduces ambient light into neuroendocrine and autonomic signals that synchronize physiological timekeeping in most major organs (4,5). Clock gene variation or dysregulation can impact the cardiovascular, digestive, endocrine, and central nervous systems, sleep-wake cycles, and cellular processes considered hallmarks of carcinogenesis (e.g., cell proliferation, DNA damage response, apoptosis) (5,6). For example, clock gene polymorphisms have been associated with sleep disorders, mood disturbances, chronotype and increased cancer risk in some studies (4,5,7–10). Tumors among breast and other cancer patients have reduced *PERIOD* clock gene expression relative to adjacent normal tissue (5,11–14). This and other evidence suggests that *PERIOD* clock genes exert a tumor suppressor function (14–16). The *PER3* variable number tandem repeat (VNTR, rs57875989) length polymorphism contains four or five copies of a 54-bp sequence encoding 18 amino acids (4,17). The 5-repeat sequence adds several potential phosphorylation sites, and *PER3*'s interaction with circadian processes may be enhanced among those with the 5/5 compared to the 4/4 genotype (9,18). This may render 5/5 variants more susceptible to changes in sleep schedule or exposure to light-at-night (9,18). The 5/5 genotype has been associated with morningness (19–21) and with increased premenopausal BrCA risk (7). However, not all studies have been consistent (22–24), and the functional consequences of this polymorphism await further characterization.

Chronotype refers to an inherent, self-reported morning or evening preference (25,26). This trait has a 25–50% inheritance pattern (22,27,28), and it predicts intrinsic circadian period (29) sleep-wake timing, and other diurnal psychophysiological processes (5,25). Extremes in chronotype may elicit chronic sleep loss and circadian desynchronization, although few have investigated the potential health-related consequences. Impacts associated with eveningness tend to be more common, including associations with poor sleep, fatigue, depression, hypertension, and type II diabetes (30–32). However, morningness has been linked with sleep disruption, fatigue, lipid dysregulation and weight gain (32–39). Chronotype may also enhance cancer risk associated with shiftwork (40–42). Morning types tend to be less tolerant of shiftwork (43), and BrCA risks among morning types working nights (odds ratio [OR]=3.9, 95% confidence interval [CI]=1.6–9.5) were almost double those observed among evening types working nights (OR=2.0, 95% CI=0.7–5.8) (44). Others have reported no associations between BrCA and extreme chronotype, or with chronotype in combination

with shiftwork or sleep disruption, indicating a need for more research (45,46). Disparities between chronotype and social schedules can induce ‘social jetlag’ due to chronically desynchronized sleep-wake timing, even among non-shiftworkers (47). Such impacts have been associated with depressive symptoms and weight gain (47,48). Similarly, factors reducing psychosocial adaptability have been associated with a poor BrCA prognosis, although they have not been closely examined as potential cancer risk factors (49,50). Chronotype and the *PER3* VNTR both have behavioral, physiological and genetic underpinnings that may foster circadian rhythm disruption and cancer susceptibility. This exploratory analysis tested the hypotheses that: woman with either the 4/5 or 5/5 *PER3* genotype, or women with a morning or evening preference, have an increased BrCA risk compared to women with a 4/4 genotype, or women with no circadian preference, respectively.

Methods and Materials

Women attending the Tata Memorial Hospital (TMH), which houses the largest oncology clinic in India, were recruited from TMH by the Advanced Center for Treatment, Research and Education in Cancer (ACTREC) staff, who also processed biospecimens and performed genotyping after receiving Institutional Review Board approval. Eligible cases included women <80 years old with histopathologically confirmed primary BrCA among patients undergoing treatment or within one year of post-treatment follow-up at the TMH. Patients were ineligible if they had: a previous cancer diagnosis (other than non-melanoma skin cancer), a concurrent cancer diagnosis at another anatomic site, or ductal carcinoma in situ. Control recruitment was conducted at TMH and was restricted to healthy women with no previous cancer diagnosis or active illness, including: non-blood relatives or spouses of male cancer patients, unrelated visitors of cancer patients, or women without BrCA signs or symptoms attending the Preventive Oncology unit for general cancer screening. Controls were frequency matched to cases on age (±5 years), geographic region, and menopausal status.

Participants provided informed consent, completed a detailed interview using a standardized questionnaire, and donated an oral mouthwash specimen or peripheral blood for DNA recovery via standardized phenol chloroform precipitation procedures (51). Trained interviewers ascertained sociodemographic (e.g., age, income, education, occupation, marital status, religion, residential and medical history) and known or potential BrCA risk factors (e.g., family cancer history, contraceptive use, pregnancies, live births, breast-feeding duration and frequency, age of menarche and menopause, pesticide or household chemical use, ionizing radiation exposure, physical activity, diet, tobacco use, sleep behavior (52)). Body mass index (kg/m2) and waist-to-hip ratio (WHR) were obtained from clinic measurements. Cases and controls were recruited and interviewed at the same time of day. Chronotype and occupational items were adapted from the Standard Shiftwork Index (53). Less than 3% had ever worked nights; thus shiftwork was not evaluated. Items used to characterize chronotype included: ‘Some are morning types and some are evening types. What would you consider yourself to be?’ (responses: ‘Definitely a morning type’ [n=286, 57%], ‘Rather more a morning type than an evening type’ [n=23, 5%], ‘Similar throughout the day’ [n=58, 12%], ‘Rather more an evening type than a morning type’ [n=80, 16%], and

'Definitely an evening type' [n=55, 11%]). The 'Rather morning' and 'Definitely morning' categories were combined due to sparse data. To be consistent, the 'Rather evening' and 'Definitely evening' groups also were combined. The other chronotype question was: 'at what time of day do you usually feel your best?' Responses to both questions were highly correlated and results in relation to BrCA status were similar; results using the first question are presented below.

The *PER3* gene was amplified using previously described forward (5′-TGGCAGTGAGAGCAGTCCT-3′) and reverse (5′-AGTGGCAGTAGGATGGGATG-3′) primers, and genotypes were established by sizing of polymerase chain reaction (PCR) products using gel electrophoresis (12% polyacrylamide) with ethidium bromide staining (7). The PCR conditions were: Cycle one, 95°C for 5 minutes; Cycle two (95°C for 45 seconds, 58.8°C for 45 seconds, 72°C for 45 seconds) was repeated for 35 cycles. Reactions were then extended for 10 minutes at 72°C and terminated at 4°C. The 4- and 5-repeat sequences were recorded at 197bp and 257bp, respectively. Laboratory personnel were blinded to the identity and characteristics of the participants and each genotype was reviewed by two individuals with 100% concordance. The 4- and 5-repeat fragments were confirmed via sequencing, and quality control re-analysis yielded 100% concordance of genotype among 10% of the samples.

Data analyses were performed using the statistical analysis software package (SAS, version 9.2, Cary, NC). Potential confounding factors were identified univariately ($p \leq 0.15$) and added to a 'full' model for further examination as confounders. Final models, which were derived from 'full' models, included age and all other variables that, when removed from the model, resulted in a 10% change in the OR for the primary exposure of interest, plus covariates that were statistically significant ($p \leq 0.05$). Unconditional fixed-effects logistic regression was used to calculate adjusted ORs among all women and in subgroups stratified by menopausal status, defined as those who reported no regular menses in at least 12 months. Participants with the 4/5 (58%) or 5/5 (5%) genotype were combined for comparison with the 4/4 (38%) *PER3* homozygotes (7,18,24). Ancillary analyses evaluated the relationship between *PER3* genotype and BrCA status separately among women stratified by estrogen and progesterone receptor (ER, PR) status. In a previous study, women with ER/PR negative BrCA were more likely to have the 5-repeat *PER3* genotype (24), thus similar analyses were performed in the current study, along with an assessment of ErbB2 receptor status, and triple negative status (ER-, PR-, and ErbB2-). Since chronotype and the *PER3* VNTR may both render individuals susceptible to circadian rhythm disruption or clock gene dysregulation, stratified analyses were also performed to examine the combined effects of *PER3* genotype and chronotype.

Results

The study population consisted of 255 BrCA cases (recruitment rate: 77%) and 249 controls (recruitment rate: 73%). Most women had less than a high school education (80%), were married (88%), and refrained from tobacco use (89%). Their average age, income, and BMI were 46±10 years, 123±212 thousand rupees and 24.3±4.7 kg/m^2, respectively. Controls

were more likely than cases to: be married, have an elevated income, refrain from tobacco use, and have a BMI >30 kg/m^2 (Table 1).

The *PER3* VNTR was characterized among 229 cases and 212 controls. Participants without *PER3* genotype (n=64, 13%) were more likely to: live in a flat or house compared to a chawl (small apartment with shared bathrooms, OR=3.57, 95% CI=1.25–10.21), speak Hindi compared to Marathi (local Maharashtra language, OR=3.25, 95% CI=1.62–6.54), live in South or West India compared to Maharashtra (OR=2.24, 95% CI=1.23–4.10), and to have breastfed longer (OR=1.07, 95%CI=1.01–1.13) compared to those with *PER3* VNTR data (n=441, 87%). Adjustment for these factors did not change the interpretation of the results presented below. *PER3* VNTR frequencies (4/4: 38%, 4/5: 58%, 5/5: 5%) were not in Hardy–Weinberg equilibrium (HWE) among all participants (χ^2=38.3, p<0.01) or among controls only (χ^2=16.0, p<0.01). The observed frequencies were generally consistent with those reported previously (4/4: 35–74%, 4/5: 25–46%, 5/5: 2–18%) (7,24,54,55). BrCA cases were ~30–40% more likely to have the 4/5 or 5/5 genotype relative to controls, although the differences were not statistically significant (all women OR=1.33, 95%CI=0.83–2.14; premenopausal OR=1.43, 95% CI=0.73–2.81; postmenopausal OR=1.31, 95%CI=0.63–2.73, Table 2). When stratified by ER/PR status, there were no notable differences in the relationship between *PER3* genotype and BrCA odds among women with either ER/PR negative (OR=1.33, 95% CI=0.73–2.45) or ER/PR positive (OR=1.20, 95% CI=0.64–2.23) BrCA status. Additionally, the relationship between *PER3* genotype and BrCA did not differ among strata of ErbB2 or triple negative receptor status (data not shown).

Among all women, BrCA cases were more likely to have a morning (OR=2.43, 95% CI=1.23–4.81) or evening (OR=2.55, 95% CI=1.19–5.47, Table 2) chronotype compared to controls. This association was more predominant among post-menopausal relative to pre-menopausal women (Table 2). To examine a potential dose-response for the evening group, the ‘Rather evening’ and ‘Definitely evening’ groups were examined separately. Risk estimates for ‘Definitely evening’ types (OR=3.18, 95% CI=1.25–8.07) were higher than ‘Rather evening’ types (OR=2.24, 95% CI=0.97–5.16, Table 2). When stratified by *PER3* VNTR status, an association between BrCA risk and either morning (OR=3.83, 95% CI=1.50–9.81) or evening chronotype (OR=6.35, 95% CI=2.14–18.84) was observed among women with the 4/5 or 5/5 genotype. However, no statistically significant association was observed among those with the 4/4 genotype (morning OR=1.31, 95% CI=0.34–5.04; evening OR=0.67, 95% CI=0.16–2.80, Table 3).

Discussion

India has traditionally had some of the lowest cancer rates globally but it is undergoing rapid modernization with increasing BrCA incidence in urban areas. These transitions bring lifestyle changes that may influence BrCA risk (e.g., light-at-night exposures, altered sleep-wake timing) (5,56). Polymorphic variation in clock genes may contribute to these impacts (4,5,7–10). In this exploratory analysis, the association between *PER3* VNTR genotype and BrCA risk was generally consistent with risk estimates reported among women in the US (7) and China (24), where no statistically significant increased BrCA risks were observed

among pre- and post-menopausal women combined. In the US, the 5-repeat *PER3* genotype was more common among premenopausal BrCA cases relative to controls (OR=1.7, 95% CI=1.0–3.0) (7), whereas the 43% increased odds of a 5-repeat genotype among premenopausal BrCA cases in the present study did not achieve statistical significance (Table 2).

BrCA cases in the present study were more likely to have a morning or evening chronotype relative to controls. Chronotype may influence circadian biological processes relevant to BrCA in a manner similar to what occurs among shiftworkers (40–42). By analogy, endogenous sleep-wake timing among those with extreme chronotype can be desynchronized with social or environmental cues, resulting in inappropriately timed light exposures, clock gene dysregulation, sleep loss, fatigue, and endocrine or immune system perturbations similar to those encountered among shiftworkers. Disruption of these processes may facilitate carcinogenesis. Shiftwork has been associated with several cancers including BrCA (44,57–65), and the relationship may be modified by chronotype (40–42,44). The potential health-related impacts associated with eveningness are generally considered more severe relative to morningness (e.g., sleep loss, fatigue, depression, hypertension, type 2 diabetes) (30–32). However, morningness has been associated with: sleep disruption, physical inactivity, fatigue, lipid dysregulation, weight gain, and shiftwork intolerance (32–39,43,56). A recent study found that morning types who worked nights had BrCA risk estimates that were almost double those observed among evening types working nights (44). Others have found no associations between BrCA and extreme chronotype, or chronotype combined with shiftwork or sleep duration (45,46). Discrepancies among these studies may stem from the timing or type of chronotype assessment used, unexplored chronotype characteristics (e.g., bimodal chronotypes), or mediating factors (e.g., chronotype adaptation strategies). Both chronotype extremes have established differences in intrinsic circadian period length and other diurnal physiological processes (5,25,29). Urban environments may foster social jetlag or other perturbations among those with extreme chronotype as individuals transition between weekdays and weekends (66). Additional research is needed to examine the extent to which chronotype, possibly in combination with social desynchronization, may contribute to carcinogenesis.

Several strengths and limitations of this study are noteworthy. It is possible that psychological or physiological side effects of a cancer diagnosis may have altered cancer patient's self-identification with chronotype, thus resulting in exposure misclassification. To reduce potential recall bias, the interview targeted the year prior to diagnosis as the reporting timeframe. There were no differences in chronotype among BrCA cases with differing levels of disease severity (e.g., tumor grade, nodal involvement) or by time between diagnosis and recruitment, which suggests that BrCA diagnosis did not impact chronotype reporting. Chronotype was assessed using only two questions. These items were internally consistent; morning types woke earlier (5:34AM±55 minutes vs. 6:04AM±70 minutes, respectively, $p<0.01$) and went to bed earlier compared to evening types (10:45PM±62 minutes vs. 11:08PM±64 minutes, respectively, $p<0.01$), and the results in relation to BrCA were similar using either item. Single questions assessing diurnal preference have been well-correlated with more comprehensive scales (25,26,42). The *PER3* VNTR was not in HWE, thus

limiting generalizability of findings. However, the frequencies were similar to those observed in previous studies, and quality control for the genotyping was acceptable. Interpretation of the results is limited by the sample sizes among morning types or within strata of menopausal status. Nonetheless, evidence for dose-response was observed among women with increasing degrees of evening preference. The analysis accounted for most known or suspected BrCA risk factors and factors that differed between cases and controls.

When combined with the 4/5 or 5/5 *PER3* genotype, extremes in chronotype were 3.8–6.4 times more likely to be associated with BrCA risk, whereas no statistically significant associations were observed among those with the 4/4 genotype. These observations are consistent with the possibility that chronotype and BrCA susceptibility may arise from one or more common genetic traits. The 4/4 and 5/5 *PER3* genotypes have been previously associated with eveningness and morningness, respectively (19–21), although others have found no association (22,23), consistent with the current analysis. The *PER3* VNTR does not necessarily ‘re-create’ the complexity of chronotype (19), and other polymorphisms also have been associated with this trait (4). Thus, the heritable component of chronotype may be polygenic and several gene variants may be needed for its full phenotypic expression (22,67). The 5/5 *PER3* VNTR may be more strongly coupled to circadian processes than the 4/4 genotype (18,68). If so, 5-repeat variants may be more susceptible to factors that elicit circadian disruption or clock gene dysregulation, such as altered sleep-wake timing, an inherent aspect of chronotype. The 5-repeat sequence adds several potential phosphorylation motifs to the *PER3* gene. Modification of phosphorylation sites in *PER* genes can alter sleep homeostasis or circadian hormone secretion (9,18), and may also increase cancer susceptibility. For example, a mutated *PER*2 phosphorylation site is linked with familial advanced sleep phase syndrome (FASPS) (69), an extreme form of morningness (70). Transgenic insertion of this mutation into mice recapitulated a morningness (advanced phase) phenotype, and elicited cancer-prone characteristics, including reduced apoptosis and survival following gamma-irradiation *in vivo* (71), and increases in tumor foci *in vitro* (72). The *PER3* gene exhibits tumor suppressor properties; its expression is reduced in breast tumors relative to normal tissue (11–13), and its deletion from breast tumors predicts BrCA recurrence and reduced survival (16). In mice, Per3 deletion increases mammary tumor susceptibility (16).

In conclusion, results from this study suggest a relationship between chronotype and BrCA; an association that is enhanced among women with the 5-repeat *PER*3 genotype. There are some inconsistencies among studies conducted to date, and the underlying mechanism awaits further characterization. Thus, cautious interpretation of this exploratory study is advised pending additional research. The National Center of Sleep Disorders Research has expressed a need for surrogate measures of sleep and circadian physiology that can be readily implemented in population-based studies of chronic disease (73). Chronotype is a simple, reliable and valid measure that may help elucidate the potential relationship between circadian rhythm disruption and BrCA risk in areas where recent modernization may facilitate increased BrCA risk, such as India, or in populations with racial cancer disparities and inherent differences in endogenous circadian timing (74,75).

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Table 1

Population Characteristics by Menopausal Status, BRCA GEL Study, Mumbai, India, 2010–2012

Characteristic	All Women		Premenopausal		Postmenopausal	
	Case (n=255)	Control (n=249)	Case (n=132)	Control (n=127)	Case (n=123)	Control (n=122)
Age (years)						
≤ 35[a]	46 (18%)	37 (15%)	46 (35%)	34 (27%)	0 (0%)	3 (2%)
36 – 45	78 (31%)	93 (37%)	62 (47%)	73 (57%)	16 (13%)	20 (16%)
46 – 55	86 (34%)	73 (29%)	24 (18%)	19 (15%)	62 (50%)	54 (44%)
55+	45 (18%)	46 (18%)	0 (0%)	1 (1%)	45 (37%)	45 (37%)
Annual Income (Rupees in Thousands)						
≤ 40	109 (43%)	63 (25%)*	61 (46%)	32 (25%)	48 (40%)	31 (26%)
41 – 100	85 (34%)	88 (35%)	40 (31%)	52 (41%)*	45 (37%)	36 (30%)*
> 100[a]	58 (23%)	97 (39%)	30 (23%)	43 (34%)	28 (23%)	54 (45%)*
Education Status						
Illiterate	54 (21%)	31 (12%)*	26 (20%)	11 (9%)*	28 (23%)	20 (16%)
Less than 8th Grade	63 (25%)	65 (26%)	25 (19%)	26 (20%)	38 (31%)	39 (32%)
8th to 12th Grade	91 (37%)	99 (40%)	48 (36%)	55 (43%)	43 (35%)	44 (36%)
High school Graduation and Above[a]	47 (18%)	54 (22%)	33 (25%)	35 (28%)	14 (11%)	19 (16%)
Marital Status						
Not Married	45 (18%)	18 (7%)*	14 (11%)	5 (4%)*	31 (25%)	13 (11%)*
Married	210 (82%)	231 (93%)	118 (89%)	122 (96%)	92 (75%)	109 (89%)
Practice of Consanguinity in the Family						
Yes	60 (24%)	68 (28%)	26 (20%)	37 (30%)	34 (28%)	31 (26%)
No	188 (76%)	173 (72%)	101 (80%)	86 (70%)	87 (72%)	87 (74%)
Region						
North or East India	58 (23%)	40 (16%)*	33 (25%)	25 (20%)	25 (20%)	15 (12%)*
Maharashtra[a]	120 (47%)	155 (62%)	53 (40%)	70 (55%)	67 (54%)	85 (70%)
South and West India	77 (30%)	54 (22%)*	46 (35%)	32 (25%)*	31 (25%)	22 (18%)
BMI (kg/m^2)						

Characteristic	All Women		Premenopausal		Postmenopausal	
	Case (n=255)	Control (n=249)	Case (n=132)	Control (n=127)	Case (n=123)	Control (n=122)
≤ 18.49	28 (11%)	22 (9%)*	16 (12%)	12 (10%)	12 (10%)	10 (8%)
18.50 – 24.99[a]	142 (57%)	110 (45%)	86 (67%)	58 (47%)	56 (47%)	52 (43%)
25.00 – 29.99	59 (24%)	78 (32%)*	24 (19%)	38 (31%)*	35 (30%)	40 (33%)
≥ 30	18 (7%)	36 (15%)*	3 (2%)	16 (13%)*	15 (13%)	20 (16%)
Waist-to-Hip Ratio						
≤ 0.82[a]	38 (16%)	78 (32%)	22 (17%)	44 (35%)	16 (14%)	34 (28%)
0.83 – 0.86	57 (23%)	57 (23%)*	24 (19%)	27 (22%)	33 (28%)	30 (25%)*
0.87 – 0.90	75 (31%)	54 (22%)*	41 (32%)	30 (24%)*	34 (29%)	27 (22%)*
> 0.90	75 (31%)	54 (22%)*	40 (32%)	23 (19%)*	35 (30%)	31 (25%)*
Total Walking Activity (hrs/week)						
≤ 2	85 (34%)	72 (29%)	53 (41%)	42 (34%)	32 (26%)	30 (25%)
3 – 4	73 (29%)	105 (43%)*	36 (27%)	48 (38%)	37 (30%)	57 (47%)*
> 4[a]	95 (38%)	70 (28%)	42 (32%)	35 (28%)	53 (43%)	35 (29%)
Tobacco Use						
Yes	38 (15%)	17(7%)*	14 (11%)	8 (6%)	24 (20%)	9 (7%)*
No	217 (85%)	232 (93%)	118 (89%)	119 (94%)	99 (80%)	113 (93%)
Tobacco Use by Family Members						
Yes	60 (24%)	38 (15%)*	29 (22%)	18 (14%)	31 (25%)	20 (16%)
No	194 (76%)	211 (85%)	103 (78%)	109 (86%)	91 (75%)	102 (84%)
Mosquito Repellant Use (Weeks)						
No Use[a]	87 (34%)	95 (38%)	44 (34%)	50 (39%)	43 (35%)	45 (37%)
≤ 100	67 (26%)	36 (14%)*	33 (25%)	23 (18%)	34 (28%)	13 (11%)*
101 – 500	56 (22%)	51 (20%)	29 (22%)	24 (19%)	27 (22%)	27 (22%)
> 500	43 (17%)	67 (27%)	25 (19%)	30 (24%)	18 (15%)	37 (30%)
Household Chemical Use (Weeks)						
No Use[a]	67 (26%)	50 (20%)	35 (27%)	26 (21%)	32 (26%)	24 (20%)
≤ 150	60 (24%)	48 (19%)	36 (27%)	35 (28%)	24 (20%)	13 (11%)

Characteristic	All Women		Premenopausal		Postmenopausal	
	Case (n=255)	Control (n=249)	Case (n=132)	Control (n=127)	Case (n=123)	Control (n=122)
151 – 750	73 (29%)	67 (27%)	37 (28%)	33 (26%)	36 (30%)	34 (28%)
> 750	53 (21%)	83 (33%)*	23 (18%)	32 (25%)	30 (25%)	51 (42%)*
Diastolic Blood Pressure (mm Hg)						
≤ 80	186 (75%)	130 (53%)	103 (79%)	68 (55%)*	83 (72%)	62 (52%)*
81 – 89[a]	49 (20%)	84 (34%)	23 (18%)	40 (32%)	26 (22%)	44 (37%)
> 89	12 (5%)	30 (12%)	5 (4%)	16 (13%)	7 (6%)	14 (12%)
Months of Breastfeeding						
≤ 25	89 (35%)	100 (40%)	53 (40%)	50 (39%)	36 (30%)	50 (41%)
26 – 60	95 (38%)	87 (35%)	51 (39%)	48 (38%)	44 (36%)	39 (32%)
> 60[a]	69 (27%)	62 (25%)	27 (21%)	29 (23%)	42 (34%)	33 (27%)
Number of Pregnancies						
≤ 2	82 (32%)	81 (33%)	57 (44%)	56 (44%)	25 (20%)	25 (20%)
3 – 4	122 (48%)	110 (44%)	58 (44%)	50 (39%)	64 (52%)	60 (49%)
> 4[a]	49 (19%)	58 (23%)	16 (12%)	21 (17%)	33 (27%)	37 (30%)
Age at First Menses (years)						
≤ 13	102 (40%)	84 (34%)	61 (47%)	47 (37%)	41 (34%)	37 (30%)
14 – 15	110 (43%)	111 (45%)	52 (40%)	54 (43%)	58 (48%)	57 (47%)
> 15[a]	41 (16%)	53 (21%)	18 (14%)	25 (20%)	23 (19%)	28 (23%)
Oral Contraceptive Use						
Yes	29 (11%)	20 (8%)	13 (10%)	11 (9%)	16 (13%)	9 (7%)
No	224 (89%)	229 (92%)	118 (90%)	116 (91%)	106 (87%)	113 (93%)

*Statistically significant difference ($p<0.05$) between cases and controls based on univariate logistic regression.

[a]Represents reference level for univariate logistic regression. Stratum specific frequencies may not equal total number of cases or controls due to missing data. Percentages may not equal 100 due to rounding.

Table 2

Relationship Between Breast Cancer Status and Chronotype or *PER3* VNTR Genotype, BRCA GEL Study, Mumbai, India, 2010–2012

Characteristic	Cases n (%)	Controls n (%)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
All Women (n=504)				
***PER3* VNTR**				
4/4	85 (37%)	81 (38%)	1.0 (Referent)	1.0 (Referent)
4/5 + 5/5	144 (63%)	131 (62%)	1.05 (0.71–1.54)	1.33 (0.83–2.14)
Chronotype				
Morning	158 (62%)	151 (61%)	1.20 (0.69–2.11)	2.43 (1.23–4.81)
No Preference	27 (11%)	31 (12%)	1.0 (Referent)	1.0 (Referent)
Evening	68 (27%)	67 (27%)	1.17 (0.63–2.16)	2.55 (1.19–5.47)
Premenopausal Women (n=259)				
***PER3* VNTR**				
4/4	43 (36%)	45 (41%)	1.0 (Referent)	1.0 (Referent)
4/5 + 5/5	75 (64%)	64 (59%)	1.23 (0.72–2.09)	1.43 (0.73–2.81)
Chronotype				
Morning	75 (57%)	77 (61%)	0.75 (0.31–1.81)	1.54 (0.55–4.29)
No Preference	13 (10%)	10 (8%)	1.0 (Referent)	1.0 (Referent)
Evening	43 (33%)	40 (32%)	0.83 (0.33–2.10)	1.95 (0.65–5.88)
Postmenopausal Women (n=245)				
***PER3* VNTR**				
4/4	42 (38%)	36 (35%)	1.0 (Referent)	1.0 (Referent)
4/5 + 5/5	69 (62%)	67 (65%)	0.88 (0.51–1.54)	1.31 (0.63–2.73)
Chronotype				
Morning	83 (68%)	74 (61%)	1.68 (0.80–3.55)	4.51 (1.62–12.58)
No Preference	14 (11%)	21 (17%)	1.0 (Referent)	1.0 (Referent)
Evening	25 (20%)	27 (22%)	1.39 (0.58–3.31)	3.02 (0.92–9.96)

[a] Analyses adjusted for: age, marital status, tobacco use, family tobacco use, waist-to-hip ratio, walking activity, income, body mass index, and mineral intake. Additional adjustments for Morning/Evening type included: diastolic blood pressure, mosquito repellant use; and for PER3 VNTR: contraceptive use, diastolic blood pressure, consanguinity, vitamin C intake. The 4/5 and 5/5 *PER3* VNTR genotypes were combined due to sparse data. Percentages may not equal 100 due to rounding; stratum specific frequencies may not equal total number of cases or controls due to missing data. VNTR: variable number tandem repeat. OR: odds ratio. CI: confidence interval.

Table 3

Relationship Between Breast Cancer Status and Chronotype, Stratified by *PER3* VNTR Genotype, BRCA GEL Study, Mumbai, India, 2010–2012

Characteristic	Cases n (%)	Controls n (%)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
4/4 *PER3* VNTR Women (n=166)				
Chronotype				
Morning	51 (61%)	42 (52%)	0.88 (0.33–2.40)	1.31 (0.34–5.04)
No Preference	11 (13%)	8 (10%)	1.0 (Referent)	1.0 (Referent)
Evening	22 (26%)	31 (38%)	0.52 (0.18–1.49)	0.67 (0.16–2.80)
4/5+5/5 *PER3* VNTR Women (n=275)				
Chronotype				
Morning	90 (63%)	84 (64%)	1.43 (0.69–2.97)	3.83 (1.50–9.81)
No Preference	15 (10%)	20 (15%)	1.0 (Referent)	1.0 (Referent)
Evening	39 (27%)	27 (21%)	1.93 (0.84–4.42)	6.35 (2.14–18.84)

[a] Includes both pre- and post-menopausal women. Analyses adjusted for: age, marital status, tobacco use, family tobacco use, waist-to-hip ratio, walking activity, income, body mass index, diastolic blood pressure, mosquito repellant use and mineral intake. Percentages may not equal 100 due to rounding; stratum specific frequencies may not equal total number of cases or controls due to missing data. VNTR: variable number tandem repeat. OR: odds ratio. CI: confidence interval.