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Chronotype and postmenopausal breast cancer risk among women in the California Teachers Study

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Abstract

Chronotype is the behavioral manifestation of an individual's underlying circadian rhythm, generally characterized by one's propensity to sleep at a particular time during the 24-hour cycle. Evening chronotypes ("night owls") generally suffer from worse physical and mental health compared to morning chronotypes ("morning larks") – for reasons that have yet to be explained. One hypothesis is that evening chronotypes may be more susceptible to circadian disruption, a condition where the coordinated timing of biologic processes breaks down. The role of chronotype as an independent or modifying risk factor for cancer has not been widely explored. The objective of the current study was to evaluate the risk of breast cancer associated with chronotype in a case-control study nested within the California Teachers Study (CTS) cohort. The study population consisted of 39686 post-menopausal CTS participants who provided information on chronotype by completing a questionnaire in 2012-2013. 2719 cases of primary invasive breast cancer diagnosed from 1995/1996 through completion of the chronotype questionnaire were identified by linkage of the CTS to the California Cancer Registry. 36967 CTS participants who had remained cancer-free during this same time period served as controls. Chronotype was ascertained by responses to an abbreviated version of the Horne-Ostberg Morningness-Eveningness Questionnaire (MEQ) and was characterized into five categories: definite morning, more morning than evening, neither morning or evening, more evening than morning, definite evening. Multivariable unconditional logistic regression analyses were performed to estimate the odds ratios (ORs) and 95% confidence intervals (95% CIs) for each of the chronotypes, adjusted for established breast cancer risk factors. Compared to definite morning types, definite evening types had an increased risk of breast cancer with elevated ORs that were statistically significant in both the crude (OR = 1.24, 95% CI: 1.10 – 1.40) and fully-adjusted models (OR = 1.20, 95% CI: 1.06-1.35). The risk estimates in the fully-adjusted model for all other chronotypes did not significantly differ from one. These results suggest that evening chronotype may be an independent risk factor for breast cancer among a population of women who are not known to have engaged in any substantial night shift work. Further research in other populations of non-shift workers is warranted.

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DATA AVAILABILITY STATEMENT

All of the data associated with this publication and in the California Teachers Study are available for research use. The California Teachers Study welcomes all such inquiries and encourages individuals to visit https://www.calteachersstudy.org/for-researchers.

Keywords

chronotype; breast cancer risk; circadian disruption; case-control; circadian rhythm

INTRODUCTION

Nearly all human physiologic processes are governed to some degree by endogenous daily cellular oscillations, referred to as circadian rhythms. These rhythms not only regulate sleep/wake cycles, they modulate metabolism, hormonal secretions, immune function, and cell cycle control that are critical to maintaining normal behavior and physiology (1). Circadian rhythms are orchestrated by the circadian clock, a collection of specialized neurons in the suprachiasmatic nuclei (SCN) located in the hypothalamus – the proper functioning of which is contingent on external environmental cues (2). The daily oscillation of daytime light and nighttime darkness serves as the primary environmental cue that entrains this system to maintain a regular periodicity of approximately 24 hours. When environmental cues of entrainment are absent or experienced at times out-of-sync with the 24-hour light-dark cycle, the coordinated timing of biologic processes breaks down, resulting in circadian disruption (2).

Chronotype is the behavioral manifestation of an individual's underlying circadian rhythms, primarily characterized by one's propensity to sleep at a particular time during the 24-hour cycle. Evening chronotypes or "night owls" are those individuals who tend to be more active in the evening and go to sleep later than their "morning lark" counterparts. For reasons that have yet to be explained, evening chronotypes generally suffer from worse physical and mental health compared to morning chronotype (3–7). One hypothesis that has been set forth is that evening chronotypes may be more susceptible to circadian disruption (8).

The recognition that a number of biologic processes critical to carcinogenesis, including cellular proliferation, apoptosis, and DNA repair mechanisms operate under strong circadian rhythms, has led to the hypothesis that circadian disruption may be an important risk factor for the development and progression of cancer (3, 9–17). This hypothesis gained prominence with the classification in 2011 of "shiftwork that involves circadian disruption" as a probable human carcinogen by the International Agency for Research on Cancer (IARC) (18). In addition to strong laboratory evidence for carcinogenic effects of light-at-night exposures in rodents, the IARC classification was largely based on epidemiologic evidence for increased breast cancer risks among female night shift workers – primarily nurses and flight attendants. The degree to which these epidemiologic findings have been confounded by evening chronotypes self-selecting into these professions is a matter of debate and the role that chronotype plays as either an independent risk factor or modifying factor in the development of breast cancer remains unclear.

To date there have been only a handful of epidemiologic studies conducted to examine the association between chronotype and breast cancer risk, yielding conflicting results. A hospital-based case-control study conducted in India (in which less than 3% of the study population had reported ever working night shifts), found that both morning and evening types had increased risks of breast cancer compared to 'neither morning nor evening' types

(19). Findings from two other studies conducted among occupations with large proportions of night shift workers (but controlling for night-shift work), suggested that compared to morning types, both evening and 'neither morning nor evening' types may have elevated risks of breast cancer compared to morning types (20, 21).

The objective of the current analysis was to examine the association between chronotype and breast cancer risk among approximately 39,000 post-menopausal participants in the California Teachers Study –a population of women who are not known to have engaged in any substantial night shift work.

MATERIALS AND METHODS

The California Teachers Study (CTS) is an ongoing prospective cohort study comprised of over 133,000 female California professional employees who responded to a 1995-1996 mailing that was sent to 329,000 active and retired female enrollees in California's State Teachers Retirement System. Upon entry into the cohort, CTS members completed a baseline questionnaire that included questions on reproductive history, personal and family medical history, health behaviors and other lifestyle factors. Six subsequent mailed questionnaires have been administered to update the baseline data and collect new information on exposures, risk factors, and health outcomes of emerging interest. Chronotype was assessed on the fifth CTS Questionnaire (Q5), administered in 2012-2015.

The CTS cohort has been actively followed since its inception in 1995/1996. Probabilistic data record linkages of the CTS are conducted annually to ascertain cancer diagnosis, death and change of address. State and national mortality files, as well as reports from relatives, are used to ascertain date and cause of death. Address changes for continued follow-up are obtained by several methods including annual mailings, notifications of moves received from participants, and linkages to nationwide consumer reporting companies and the U.S. Postal Service National Change of Address database. Cancer outcomes are identified from annual linkages with the California Cancer Registry (CCR), a legally mandated statewide population-based cancer reporting system. Case ascertainment for the CCR is estimated to be 99% complete (22). Details of the creation and characteristics of the CTS cohort appear elsewhere (23). Upon entry into the study, all participants provided their informed consent to use their data for research purposes such as this study. Subsequent to enrollment, two CTS participants requested to be withdrawn from the study and are not included in the present analysis. The use of human subjects in the CTS has been approved by the Institutional Review Boards at all participating institutions and by the California Committee for the Protection of Human Subjects, California Health and Human Services Agency.

Eligible Population for Analysis

The study population eligible for the current analysis was drawn from the population of 45724 post-menopausal CTS participants who provided chronotype information on the CTS Q5 prior to January 1, 2014, were under the age of 90 years, and had resided in California continuously since entry into the CTS cohort. Ninety-six percent of Q5 respondents provided information on chronotype. From these, we excluded 2401 women who had a diagnosis of any cancer prior to baseline entry into the cohort (identified through both self-

report and via the CCR-CTS data linkages) to identify a pool of 43323 eligible women from which our cases and controls were drawn.

Identification of Breast Cancer Cases and Controls

For the purpose of the current analysis, a breast cancer case was defined as having a diagnosis of primary invasive carcinoma of the breast (SEER site = 26000) identified by the annual linkages of the CTS to the CCR during the time interval between joining the cohort in 1995/1996 and December 31, 2013. Participants diagnosed with *in situ* cancer of the breast were excluded. The remainder of our eligible population (as described above) served as our controls, excluding those who had any cancer diagnosis at any site prior to the time of Q5 completion, identified by the routine CTS-CCR linkages. This process resulted in the identification of 2719 cases of primary invasive breast cancer and 36967 cancer-free controls included in our analysis.

Assessment of Chronotype

Chronotype was ascertained by information collected on the CTS Q5 survey. Overall, approximately 60% of CTS members who were alive and eligible to participate responded to the CTS Q5 survey, 96% of whom provided valid data on chronotype. Information on chronotype was collected using an abbreviated version of the Horne-Ostberg Morningness-Eveningness Questionnaire (MEQ). The MEQ is a widely-used, standardized and validated survey instrument (24) that has been shown to correlate with physiologic measures of chronotype (25, 26). Although the original MEQ consists of 19 questions, it has been demonstrated that one question (question 19) predicts chronotype nearly as well as the full 19-item MEQ (14, 27). This question asks: “One hears about ‘morning’ and ‘evening’ types of people. Which one of these types do you consider yourself to be?.” The response categories include “definitely a morning type,” “more a morning than an evening type,” “neither a morning or an evening type,” “more an evening than a morning type,” and “definitely an evening type.” In order to capture potential changes in chronotype throughout life, we adapted this question to ask about which chronotypes respondents considered themselves to be “at different times in your life” including three time frames: “now,” “in your 30-40’s”, and “in your teens/in college.”

Statistical Analysis

Unconditional logistic regression models were run using PROC LOGISTIC in the SAS/STAT software version 9.4 of the SAS system (28) to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for each of the four chronotypes (“more morning than evening,” “neither morning or evening,” “more evening than morning,” “definite evening”) with “definite morning” serving as the referent category. Both crude and multivariable-adjusted ORs were estimated adjusting for age and the following breast cancer risk factors: race/ethnicity; family history of breast cancer, age at menarche, age at first full-term pregnancy, breast feeding history, age at menopause, menopausal hormone therapy (HT) use, body mass index (BMI), strenuous and moderate physical activity, alcohol consumption, and smoking pack-years (see Table 3a footnotes for details of covariate specification).

Initially, models were run for chronotype assessed at each of the three different time periods (e.g., “now”, in “30-40’s”, “in teens/in college”). However, most participants (61%) reported stable chronotype throughout their lives and the risk estimates for earlier periods in life were generally similar to those reported for “now” (i.e. concurrent to Q5 completion) *(data not shown)*. Therefore, we present our results only for the “now” chronotype.

We also conducted a number of subset analyses. To address the possibility that a case’s perception of her chronotype might be influenced by her disease or treatment, we repeated our analyses, excluding the 352 breast cancer cases that were diagnosed within two years prior to completing Q5. We also repeated our analyses restricted to the subset of participants who reported stable chronotype throughout their lives. To identify stable chronotypes, we first collapsed the “definite mornings” and “more mornings” into one “morning” category and the “definite evening” and the “more evening” into one “evening category.” We then classified respondents as “Stable Chronotypes” if they reported the same chronotype for “now” as they did for their “teens/in college” (i.e. they were either “morning”, “evening”, or “neither” at both points in time). This resulted in the identification of 24111 individuals with stable chronotypes. We also stratified the data by BMI (< 25 kg/m^2, ≥ 25kg/m^2) and tumor hormone receptor status (ER− and PR−, ER+ or PR+); likelihood-ratio tests were used to formally test for interactions effects for these two factors. All p-values are based on two-sided tests with a p-value of < 0.05 considered to be statistically significant.

RESULTS

Morning chronotypes were the most common chronotype in this population of 39686 post-menopausal women. At the time of the CTS Q5 survey, 38% reported their current chronotype as ‘definite morning’, 21% reported ‘more morning than evening’, 15% reported ‘more evening than morning’, 13% reported ‘definite evening’, and 13% reported ‘neither morning nor evening’ (Table 1). The prevalence of definite morning and definite evening types was similar to what was reported in the NHS II while the prevalence of neither type was considerably higher in our population (Supplemental Table 1). In comparison to women enrolled in the Indian hospital-based study, the distribution of chronotype was similar. However, the Indian women, while having a roughly similar distribution of morning types, skewed much more heavily towards ‘definite’ rather than ‘more’ morning types than did the women in our study (Supplemental Table 1).

The proportion of women in our study who described themselves as morning chronotypes was slightly lower for earlier periods of life (Table 1). Overall 60% were identified as having a stable chronotype by virtue of reporting the same chronotype in their teen/college years as at the time of Q5 completion. Twenty-percent of participants reported shifting towards a morning chronotype later in life; 8% reported shifting towards an evening chronotype and 8% towards a neither chronotype (*data not shown*).

The distributions of breast cancer risk factors and chronotype by case status are presented in Table 2. The distributions of breast cancer risk factors were consistent with the established literature on breast cancer risk factors and consistent with those reported in previous analyses of the full CTS cohort (23). Overall the distribution of chronotype did not appear to

substantially differ between cases and controls, but cases were significantly less likely to report definite morning chronotype (38% vs. 35%, p=0.002).

The estimated risks of breast cancer associated with chronotype are shown in Table 3a. Point estimates of risk were similar from the crude and fully-adjusted multivariable models. Compared to definite morning types, definite evening types had an increased risk of breast cancer with elevated ORs that were statistically significant in both the crude (OR = 1.24, 95% CI: 1.10 – 1.40) and fully-adjusted models (OR = 1.20, 95% CI: 1.06-1.35). None of the other chronotypes was significantly related to breast cancer risk in fully adjusted models. To address the concern that the perception of chronotype might be influenced by a woman's diagnosis or treatment for breast cancer, we excluded all breast cancer cases who responded less than 2 years after completing the questionnaire -- as was done in the NHS II analysis (21). While modestly attenuated, results from these analyses (Table 3b) were similar to those observed among the full set of breast cancer cases.

When the data were stratified by stable versus non-stable chronotypes, estimated breast cancer risks were somewhat more robust among women who reported stable chronotypes (adjusted ORs for definite evening types=1.20, 95% CI=1.04-1.40 among stable chronotypes and 1.14, 95% CI = 0.88 – 1.47 among non-stable chronotypes) but the log-likelihood ratio test for interaction was not significant ($p > 0.05$). Stratification by BMI (< 25 kg/m^2 vs ≥ 25 kg/m^2) resulted in similar, albeit slightly higher, estimated adjusted ORs among women with high BMI than those with lower BMI ($OR_{adj} = 1.23$, 95% CI: 1.04-1.46 vs $OR_{adj} = 1.18$, 95% CI: 0.97-1.43) but the log-likelihood test for interaction was not significant ($p > 0.05$). Among the small subset of cases (n=331) whose tumors were estrogen and progesterone receptor negative (ER−/PR−), the point estimate of risk associated with evening chronotype appeared marginally higher than that for the 2162 cases with hormonally responsive tumors (ER+ or PR+) but confidence intervals were wide and overlapping ($OR_{adj} = 1.36$, 95% CI=0.98-1.88 for ER−/PR− cases versus $OR_{adj}=1.18$, 95% CI=1.02 – 1.35 for ER+/PR+ cases).

DISCUSSION

This study found a modest, but statistically significant, elevated risk of post-menopausal breast cancer for women with a definite evening chronotype compared to those with a definite morning chronotype, after adjustment for established breast cancer risk factors. These findings add to the small body of epidemiologic literature on chronotype and breast cancer risk. Our results are consistent with those from two other studies that suggested higher breast cancer risks associated with evening chronotypes. In a nested case-control study of Danish military night shift workers, an adjusted OR of 1.8 (95% CI: 1.2 – 2.9) for breast cancer was reported for evening compared to morning chronotypes (20). Likewise, although of only borderline statistical significance, a nested-control study among the Nurses Health Study (NHS) II cohort, also reported a similar magnitude of elevated risks for definite evening compared to definite morning chronotypes ($OR_{adjusted}=1.15$, 95% CI: 0.98-1.34)(21). Both of these analyses that were conducted among shift workers were adjusted for night-shift work, suggesting that evening chronotypes are intrinsically more prone to breast cancer, independent of circadian disruption. A population-based study in

India (the only study other than our own to be conducted primarily among non-shift workers) reported elevated risks for both evening and morning chronotypes compared to those with a preference for neither morning nor evening (19). Unfortunately, the choice of a different referent category in the India study makes it difficult to directly compare their results to our own. Both the Danish military study and the NHS II study also reported elevated breast cancer risks for women who reported a preference for neither morning nor evening compared to morning chronotypes, with ORs of 1.6 (95% CI: 1.0 – 2.7) and 1.27 (95% CI: 1.04 – 1.56), respectively. In our study, the point estimate for the neither chronotype category was marginally elevated but was not statistically significant.

Our results, in the context of these other epidemiologic findings, suggest that evening chronotype may be a risk factor for breast cancer. These findings are further supported by a substantial body of evidence from laboratory studies that suggest potentially relevant etiologic mechanisms. Although the concept of chronotype dates back centuries (3, 14), it is only recently that we have begun to understand its genetic and molecular underpinnings (2, 3, 15). Today, chronotype is thought to be primarily a reflection of one's genes (3, 14, 29). Circadian rhythms are regulated by a complex feedback system modulated by the transcriptional expression of at least a dozen core circadian genes, many of which act as tumor suppressors, including the circadian locomotor output cycles kaput (*CLOCK*), period (*Per1, Per2, Per3),* and cytochrome *(Cry1, Cry2)* genes (2, 30, 31). As described in a number of recent review articles certain polymorphisms in these core circadian genes have been shown to be both correlated with cellular and physiologic processes considered to be hallmarks of cancer (2, 3, 11, 13, 15, 32, 33) and associated with chronotype (34, 35). The etiologic relevance of chronotype to breast cancer, in particular, is further underscored by *in vivo* evidence that the circadian clock interacts with estrogen and androgen signaling pathways and the observation that *Per1* and *Per2* gene expression is suppressed more commonly in breast cancer tumors than in normal breast tissue (2, 3, 7, 15, 32).

Beyond its independent role in carcinogenesis, it has been hypothesized that chronotype may be an important susceptibility factor to consider when evaluating circadian disruption in studies of shift work (8, 36, 37). Few epidemiologic studies of shift workers have had information on chronotype and findings have been somewhat inconsistent (20, 38–40). Results from the aforementioned Danish study of military shift workers, however, lends credence to this hypothesis. Specifically, the Danish study reported breast cancer risks associated with long-term night shift work that was considerably stronger among morning than among evening chronotypes (20). Presumably, this is a reflection of a greater propensity for circadian disruption among morning chronotypes working at night – a time that is out-of-sync with their intrinsic circadian rhythms. While in our study we did not have information about shift work, as a study of active and retired teachers, the participants in our study are unlikely to have engaged in night shift work. However, among our study population who typically need to report to their school jobs early in the morning, it may be the evening chronotypes who are especially vulnerable to circadian disruption.

This study has a number of strengths worth noting. Other than the small hospital-based case-control study conducted in India, our study is the only study to date conducted among women not employed in night shift work. The large size of our study population provided

sufficient numbers of subjects to evaluate five gradations of chronotype to capture the extremes and reduce the potential for misclassification. While reliance on a single question to characterize chronotype may have introduced some misclassification, this single question has been shown to robustly correlate (r=0.89) with chronotype based on the full MEQ (27). Furthermore, the nesting of our study within a well-defined cohort with excellent follow-up provides reassurance that cases and controls were drawn from a common base population with equal opportunity to be identified as a case.

As a retrospective case-control study, however, our study has a few limitations worth noting. Chronotype was ascertained by self-report after case diagnosis. If the onset of breast cancer altered chronotype, or the perception of chronotype, our results could be biased by differential recall between cases and controls. However, chronotype is not widely recognized as a risk factor for breast cancer so it seems unlikely that cases would differentially recall their chronotype based on perceived risks associated with their disease. The similarity of our results based on reported chronotype during earlier periods of life, and risks that persisted in both those who reported stable and non-stable chronotypes during the life course, offer support to the validity of our findings. Additionally, when we excluded from our analyses cases that were diagnosed within two years of completing the Q5 survey, results remained essentially unchanged.

Another concern inherent to the case-control study design is selection bias. The overall Q5 survey participation rate was reasonable (approximately 60%) and nearly all responders (96%) provided valid chronotype data. Although Q5 responders were slightly less likely to be in the very youngest age group at baseline and slightly more likely to be non-Hispanic white than non-responders, the sociodemographic profiles of Q5 responders and non-responders were generally similar (*data not shown*). Thus, our results are likely to be generalizable to the full CTS cohort.

Survival bias, however, must also be considered when interpreting results from retrospective case-control cancer studies such as this one. It is difficult to ascertain the degree to which survival bias may have impacted our results. A modestly higher proportion of cases (43%) than controls (31%) were excluded from our analyses because they were deceased at the time of the Q5 survey. Among the breast cancer cases diagnosed since baseline, an evaluation of the distribution of summary stage at diagnosis indicated that compared to those not included in our study, the cases that were included in our study were less likely to be diagnosed at a remote late stage (0.8% versus 3.4%). These observations suggest that the cases in our study may disproportionately represent cases diagnosed at an earlier stage and with better survival and thus may not be fully representative of all breast cancers that occurred in the CTS since baseline. If chronotype is related to survival among cases, this could lead to biased estimates of risk. The degree to which chronotype might influence survival of breast cancer patients is not known. To our knowledge, the only breast cancer study that has addressed this issue reported slower breast cancer progression among morning chronotypes and no difference in progression for evening chronotypes when compared to neither chronotypes (12). Without knowing if chronotype similarly affects survival among controls, it is not possible to ascertain the degree and direction of any possible survival bias. There is however, emerging evidence that among the general population morning

chronotypes may also have lower rates of overall mortality compared to evening chronotypes (41).

Overall, our results suggest that chronotype may be an independent risk factor for post-menopausal breast cancer. Our findings are notable in that they were observed among women who are unlikely to have engaged in night shift work. The degree to which our findings can be extended to other women, including premenopausal women, is not known. Studies in other populations of non-shift workers are warranted. While beyond the scope of the current analysis, a greater understanding of the mechanisms by which chronotype affects breast cancer risk could ultimately yield important etiologic clues leading to new strategies for prevention and treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Distribution of self-reported chronotype at three different times of life among 39686 California Teacher Study (CTS) participants.

Chronotype	Now (at Q5) (Age 40-80s)		Age 30-40's		Teen/College Years	
	n	%	n	%	n	%
Definite morning	15175	38	13312	34	12076	30
More morning than evening	8241	21	8593	22	5693	14
Neither morning or evening	5308	13	5798	15	6156	16
More evening than morning	5935	15	6172	16	8142	20
Definite evening	5027	13	4247	11	6121	15
Unknown	-	-	1564	2	1498	5

Table 2.

Distribution of chronotype and breast cancer risk factor characteristics, by case-control status among 39686 California Teacher Study (CTS) participants.

Characteristic[a]	Case control status				All		
	Non-case		Case				
	N	%	N	%	N	%	p value
All	36967	100	2719	100	39686	100	
Chronotype							0.002
Definite morning type	14220	38	955	35	15175	38	
More morning than evening type	7678	21	563	21	8241	21	
Neither morning/evening type	4923	13	385	14	5308	13	
More evening than morning type	5511	15	424	16	5935	15	
Definite Evening type	4635	13	392	14	5027	13	
Age							<0.001
40-49 years	686	2	33	1	719	2	
50-59 years	6423	17	283	10	6706	17	
60-69 years	15562	42	969	36	16531	42	
70-79 years	9605	26	963	35	10568	27	
80-89 years	4691	13	471	17	5162	13	
Race/Ethnicity[b]							0.049
White	32316	87	2422	89	34738	88	
Black	810	2	55	2	865	2	
Hispanic	1525	4	82	3	1607	4	
Asian/Pacific Islander	1486	4	105	4	1591	4	
Other	830	2	55	2	885	2	
Smoking pack-years[b]							<0.001
Never smokers	24731	67	1667	61	26398	67	
≤10	6517	18	500	18	7017	18	
11-20	2156	6	189	7	2345	6	
21-30	1172	3	103	4	1275	3	
≥31	1229	3	152	6	1381	3	
Unknown	1162	3	108	4	1270	3	
BMI (kg/m^2)							0.011
15-24	17780	48	1236	45	19016	48	
25-29	10585	29	841	31	11426	29	
30-54.8	6826	18	492	18	7318	18	
Unknown	1776	5	150	6	1926	5	

Characteristic[a]	Case control status				All		
	Non-case		Case				
	N	%	N	%	N	%	p value
Alcohol consumption (g/day) [b]							<0.001
None	10992	30	755	28	11747	30	
<20	21744	59	1580	58	23324	59	
≥20	2938	8	282	10	3220	8	
Unknown	1293	3	102	4	1395	4	
Physical activity (hours per week) [d]							<0.001
0 to < 2.25	11226	30	951	35	12177	31	
2.25 to < 5.50	12430	34	915	34	13345	34	
5.50 to 24.00	13216	36	846	31	14062	35	
Unknown	95	0	7	0	102	0	
Family history of breast cancer[c]							<0.001
No	29867	81	2009	74	31876	80	
Yes	6113	17	626	23	6739	17	
Unknown	987	3	84	3	1071	3	
Age at menarche (years)[b]							0.307
≤11	8546	23	669	25	9215	23	
12-13	20978	57	1499	55	22477	57	
≥14	7017	19	519	19	7536	19	
Unknown/Never	426	1	32	1	458	1	
Age at 1st full-term pregnancy (years) [b]							0.650
No full-term pregnancy	8420	23	625	23	9045	23	
≤24	9967	27	710	26	10677	27	
25-29	11301	31	864	32	12165	31	
≥30	6758	18	485	18	7243	18	
Unknown	521	1	35	1	556	1	
Breast feeding history (months) [b]							0.031
Never pregnant	6328	17	468	17	6796	17	
Pregnancy, but no live birth	2055	6	155	6	2210	6	
0	5311	14	452	17	5763	15	
>0 and <6	6148	17	461	17	6609	17	
6-11	5445	15	373	14	5818	15	
≥12	11028	30	769	27	11797	30	
Unknown	652	2	41	2	693	2	

Characteristic[a]	Case control status				All		
	Non-case		Case				
	N	%	N	%	N	%	p value
Age at menopause (years)							0.063
< 40	2919	8	188	7	3107	8	
40-49	9810	27	776	29	10586	27	
50-54	11903	32	831	31	12734	32	
55-59	4818	13	346	13	5164	13	
60-70	623	2	45	2	668	2	
Unknown	6894	19	533	20	7427	19	
Hormone therapy (HT) use[e]							<0.001
Never	13010	35	825	30	13835	35	
Ever	23920	65	1891	70	25811	65	
Unknown	37	0	3	0	40	0	

[a] Unless otherwise noted, covariate assessment was based on the CTS Q5 survey

[b] Assessment based on the CTS baseline survey

[c] Assessment based on reporting family history (in a first degree relative) on any of the CTS surveys from baseline through the Q4 survey

[e] Assessment based on ever reporting use of HT on any of the CTS surveys from baseline through the Q5 survey

[d] Average strenuous and moderate physical activity during past three years as reported on Q5 survey

Table 3a.

Risk of breast cancer associated with chronotype: results from logistic regression analysis among 39686 California Teacher Study participants

Chronotype	# cases	Crude Odds Ratio [a]	95% CI	Multivariate Adjusted Odds Ratio [b]	95% CI
Definite morning	955	1.00	–	1.00	–
More morning than evening	563	1.10	0.99 – 1.23	1.09	0.98 – 1.22
Neither morning/evening	385	1.13	1.00 – 1.28	1.11	0.98 – 1.25
More evening than morning	424	1.14	1.01 – 1.29	1.11	0.99 – 1.26
Definite evening type	392	1.24	1.10 – 1.40	1.20	1.06 – 1.35

[a] Adjusted for age

[b] Adjusted for age, race, family history of breast cancer, age at menarche, smoking pack-years, BMI, alcohol consumption, physical activity, age at first full-term pregnancy, breast feeding history, age at menopause, ever use of hormone therapy.

Table 3b.

Risk of breast cancer associated with chronotype: results from logistic regression analysis among 39334 California Teacher Study participants, excluding cases who were diagnosed within two years of completing the Q5 questionnaire (n=352).

Chronotype	# cases	Crude Odds Ratio [a]	95% CI	Multivariate Adjusted Odds Ratio [b]	95% CI
Definite morning	844	1.00	–	1.00	–
More morning than evening	492	1.09	0.97 – 1.22	1.08	0.96 – 1.21
Neither morning/evening	336	1.11	0.98 – 1.27	1.09	0.96 – 1.25
More evening than morning	359	1.09	0.96 – 1.24	1.07	0.94 – 1.22
Definite evening type	336	1.20	1.05 – 1.37	1.16	1.02 – 1.33

[a] Adjusted for age

[b] Adjusted for age, race, family history of breast cancer, age at menarche, smoking pack-years, BMI, alcohol consumption, physical activity, age at first full-term pregnancy, breast feeding history, age at menopause, ever use of hormone therapy.