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Chronotype and Risk of Post-Menopausal Endometrial Cancer in the California Teachers Study

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Abstract

Working at night causes circadian disruption and it has been classified as a probable carcinogen. An evening chronotype, or preference for late day activity, has been shown to increase risk for several adverse health effects, such as metabolic disorders and recently, breast cancer. To further explore this emerging area of interest, we examined the association between endometrial cancer (EC) risk, another common cancer in women, and chronotype. The women in this study were members of the California Teachers Study cohort, which was established in 1995. Chronotype was reported on a subsequent questionnaire (Q5), administered in 2012–2013. The women included in this analysis were under age 90 years, were post-menopausal at Q5, and had no hysterectomy. The cancer cases, identified through linkages to the California Cancer Registry, were diagnosed between 1996 and 2014. We used unconditional logistic regression models to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) of the associations between chronotype and EC diagnosis. There were 437 EC cases and 26,753 cancer-free controls included in this analysis. Controls were more likely to classify themselves as current morning chronotypes than were cases (39% and 34% respectively). Compared to morning types, women who were definite evening types had a statistically significantly elevated OR of 1.44 (95% CI 1.09–1.91). This association was more pronounced among obese women as compared to non-obese women. For evening type compared to morning type, the OR among obese women was 2.01 (95% CI 1.23, 3.29) while

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the OR for non-obese women was 1.12 (95% CI 0.77, 1.63). To our knowledge, the association between EC risk and evening chronotype has not been previously reported, but is consistent with the small body of literature which suggests increased breast cancer risks among evening chronotypes. Because this study was based on a retrospective analysis in a cohort of mostly white female teachers in California, further analysis of chronotype as a potential EC risk factor should be considered in other cohorts and in prospective analyses in order to further explore this relationship.

Keywords

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

Introduction

An area of emerging interest in cancer etiology is the role of circadian disruption. Shift work that involves circadian disruption was initially classified as a probable carcinogen by the International Agency for Research on Cancer (IARC) in 2010 (International Agency for Research on Cancer (IARC) 2010). In addition to strong laboratory evidence, this classification was largely based on the observation of increased breast cancer risk among nurses and flight attendants who work the night shift. IARC recently re-evaluated shift work as a potential human carcinogen and updated the review with many additional publications, including studies continuing to link shift work to breast cancer as well as other cancer sites, including prostate cancer and colorectal cancer (International Agency for Research on Cancer (IARC) 2020). While fewer studies on shift work have been conducted for other types of cancers, increased risk of endometrial cancer (EC) was associated with night shift work in a cohort of nurses (Viswanathan et al. 2007).

Chronotype is defined as an individual's diurnal preference for activity, often colloquially characterized as 'morning larks' and 'night owls.' While it is typically characterized by the behavioral manifestation of one's underlying circadian rhythm, chronotype is primarily determined by the expression of at least a dozen core circadian genes (Fu & Lee 2003; Chen et al. 2005; Dai et al. 2011). Circadian disruption occurs when the timing of daily activities is misaligned with one's intrinsic chronotype, leading to the breakdown of the coordinated molecular and cellular processes that are normally governed by circadian rhythms necessary for the maintenance of good health. A number of adverse physical and mental health conditions, such as depression and metabolic disorders, have been associated with evening chronotype (Kitamura et al. 2010; Kanerva et al. 2012; Kantermann et al. 2012; Wong et al. 2015; Yu et al. 2015; Fabbian et al. 2016; Taylor & Hasler 2018; Gariepy et al. 2019). It is unclear whether such associations are reflective of behavioral factors more common among evening chronotypes, such as poor eating habits or lack of physical activity (Fritschi et al. 2011), or whether these conditions are driven by greater susceptibility of people with evening chronotypes to circadian disruption (Erren 2013). The potential mismatch between timing of work hours and chronotype, sometimes referred to as social jetlag, may play a key role in these increased risks observed in evening types (Fischer et al. 2016).

Increased breast cancer risk was modestly associated with evening chronotype in a recent analysis of post-menopausal women in the California Teachers Study (CTS) (Hurley et al. 2019). These results and the findings of elevated EC risks associated with night shift work in the Nurses' Health Study (Viswanathan et al., 2007) led us to extend the analysis of chronotype in a cohort of teachers to examine its potential relationship to endometrial cancer.

Materials and methods

Study Population

The California Teachers Study (CTS) is an ongoing prospective cohort study of female professional employees who responded to a questionnaire that was mailed to them in 1995–1996. The initial questionnaires were sent to 329,000 active and retired females enrolled in California's State Teachers Retirement System. A total of 133,477 women completed the baseline questionnaire that included information on pregnancy history, personal and family medical history, health behaviors, body size, smoking, diet, and other lifestyle factors, as previously described (Bernstein et al. 2002). Six additional 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 2012–2013. There were 65,298 respondents to Q5, which was approximately 60% of the initial cohort still alive and potentially eligible to participate. The use of human subjects in the CTS has been approved by the Institutional Review Boards at all participating institutions and by the California Health and Human Services Agency Committee for the Protection of Human Subjects. This research conforms to the international ethical standards for biological rhythm studies (Portaluppi et al. 2010).

Identification of Endometrial Cancer Cases and Controls—For this analysis, we restricted the cohort to members who answered the Q5 question on chronotype, were under age 90 years at the time they completed Q5, and were post-menopausal at Q5. Cancer cases were identified through annual linkages of the CTS cohort to the California Cancer Registry files. We included endometrial cancer cases that were diagnosed between 1996 and 2014, after the participant entered the initial cohort and before the participant filled out the fifth questionnaire. We included cases of invasive endometrial cancer with International Classification of Diseases for Onocology-3 (ICD-O-3) site codes C54.1 and C54.9. We excluded 4,737 women diagnosed with other types of cancer during this same time period and we excluded 6,098 women who moved out of California between filling out the baseline questionnaire and filling out the fifth questionnaire. We also excluded 12,507 women who had a hysterectomy prior to Q5 based on either self-report or hospitalization records. The final study population included in this analysis was 27,190 women, with 437 endometrial cases and 26,753 cancer-free controls.

Definition of Chronotypes

The chronotype question on the fifth questionnaire was developed as an abbreviated version of the widely-used and validated Horne-Ostberg Morningness-Eveningness Questionnaire (Horne & Ostberg 1976). This question asked the following: "One hears about 'morning'

and ‘evening’ types of people. Which do you consider yourself to be?” The response choices were “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”, or “definitely an evening type”. Participants were asked to answer this question for three different time periods in their life: “now’, “in your 30–40’s”, and “in your teens/in college”. These periods of time were asked to assess possible changes in chronotype as women aged.

Statistical analysis

We used unconditional logistic regression models to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) of the associations between chronotype and EC diagnosis. Statistical analyses were conducted in SAS version 9.4 (SAS Institute, Cary, North Carolina). Multivariable logistic regression models included variables chosen by backward selection to identify covariates of interest. Initial models included age at entry into cohort (baseline), race/ethnicity, chronotype, smoking history, body mass index (BMI) at baseline, height, physical activity history reported on Q5, alcohol consumption, family history of endometrial cancer, family history of breast cancer, age at menarche, diabetes reported at baseline, non-steroidal anti-inflammatory drug (NSAID) use reported on Q5, oral contraceptive (OC) use (ever or never), hormone replacement therapy use (ever or never), age at menopause, history of live births combined with months of breast feeding, and hours of average nightly sleep duration reported on Q5. The variables were categorized as shown in Table 1. BMI values less than 16 or ≥54.9 were considered unreliable and coded as unknown. The backward selection forced inclusion of age, race/ethnicity, and chronotype and kept variables with Wald Chi-square <0.10. The remaining covariates were BMI at baseline, height, family history of endometrial cancer, family history of breast cancer, NSAID use, OC use, , and history of livebirths combined with breast feeding. We evaluated possible interactions between chronotype and these covariates by likelihood ratio tests.

Results

The characteristics of the study participants by chronotypes are shown in Table 1 and the characteristics of the 437 EC cases and 26,753 controls are shown in Table 2. The most commonly reported current chronotype in this cohort was definite morning type (39%), followed by “more a morning than an evening type” (21%). Definite evening type was the least frequently reported (12%). An additional 15% of respondents said that they were “more an evening than a morning type” and 13% that they were “neither a morning or an evening type”. Most participants (61%) reported that their current chronotype was the same as in their teenage/college years. Controls were more likely to classify themselves as current morning chronotypes than were cases (39% and 34% respectively).

Table 2 also shows the distributions of potential EC risk factors by case-control status. These potential risk factors included age, race/ethnicity, pregnancy and breast feeding history, body mass index (BMI) at baseline, height, family history of breast cancer, family history of endometrial cancer, OC use, and NSAID use at Q5. The observed case control differences were generally consistent with the literature on established risk factors for EC (S. G. O. Clinical Practice Endometrial Cancer Working Group et al. 2014) and with previous

publications on EC risk in the California Teachers Study (Canchola et al. 2010; Razavi et al. 2010; Dieli-Conwright et al. 2013; Canchola et al. 2015; Horn-Ross et al. 2016).

Table 3 shows the Odds Ratios (OR) and 95% confidence intervals for chronotype and EC risk from both the age and race/ethnicity only adjusted model and the fully-adjusted multivariable model. Compared to morning types, women who were definite evening types at the time of questionnaire 5 (post-menopause) had a statistically significantly elevated OR of 1.65 (95%CI 1.25, 2.18) when adjusted for age and race/ethnicity only. This OR for evening types was reduced, although still statistically significantly elevated, to 1.44 (95%CI 1.09, 1.91) in the fully adjusted multivariable model. The ORs for the other chronotypes were close to one when compared to morning types as the reference group. Participants were also asked about chronotype in their 30s-40s and teen/college years. The adjusted OR for evening type as a teen was1.25 (95% CI 0.94, 1.67). For the time period of life when they were in their 30s and 40s, the evening chronotype OR was approximately the same as for current chronotype with an adjusted OR of 1.45 (95% CI 1.07, 1.96).

Based on tests for interactions between chronotype and the covariates, none were statistically significant at p-value <0.10. However, because of the differences in EC risk for night shift work reported between the obese and non-obese women in the Nurses' Health Study (Viswanathan, Hankinson et al. 2007), we stratified the analyses for chronotype by BMI. When we did this, the elevated OR for evening chronotype was observed among obese (BMI at baseline ≥30) women only (Table 4). For definite evening type compared to morning type, the OR among obese women was 2.01 (95% CI 1.23, 3.29) while the OR for non-obese women (BMI at basline <30) was only 1.12 (95% CI 0.77, 1.63). We also examined risks stratified for BMI at the time of questionnaire 5. Generally, the results remained the same, with similarly elevated OR of 2.26 (95% CI 1.42, 3.61) for evening types who were obese at Q5. One difference worth noting was that among the obese women at Q5, the OR for more morning than evening types was elevated, though not statistically significant (OR 1.51, 95% CI 0.91, 2.51) whereas among the women obese at baseline the OR was below one (OR 0.97 95%CI 0.54, 1.76).

Because the chronotype question was asked on the questionnaire (Q5) after the time of the endometrial cancer diagnosis, we conducted an analysis on a subset of women who were diagnosed two or more years prior to completing Q5, to reduce the chance that the more recent cancer diagnosis and treatment may have influenced the response about perceived chronotype. The OR for evening chronotype in this subset of women was somewhat reduced to 1.35 (95% CI 1.00, 1.82), although still elevated, compared to the definite morning types. The OR for the "more morning than evening" type in this group was 1.06 (95% CI 0.80, 1.41), the OR for neither type was 0.87 (95% CI 0.62, 1.23), and the OR for "more evening than morning" was 1.08 (95% CI: 0.79, 1.47) compared to definite morning types.

We also conducted analyses stratified by chronotype stability by comparing reported chronotype in teens/college to current chronotype (Table 5). Among women with the same chronotype over time, the OR for evening type compared to morning type was statistically significantly elevated at 1.50 (95% CI 1.09, 2.07). Among the women who reported changes

in chronotype over time, the OR for evening type was somewhat lower (1.37, 95% 0.77, 2.46).

Discussion

This study found increased risk of EC associated with evening chronotype in post-menopausal women, which was strongly modified by BMI. The greatest increased risk for evening type compared to morning type was among obese women. To our knowledge this is the first study to directly examine the association between chronotype and EC risk. Our finding of increased risk among obese women is consistent with results from a study on night shift work and EC in the Nurses' Health Study (Viswanathan, Hankinson et al. 2007). In the cohort of U.S. nurses, obese women who worked 20 or more years on the rotating night shifts had increased EC risk compared to women who never worked nights (OR 2.09, 9% CI 1.24, 3.53). In contrast, the non-obese women who worked 20 or more years on the rotating night shifts did not have increased EC risk (OR 1.07, 9% CI 0.60, 1.92).

It is unclear why the elevated risks for evening chronotype in our study and for night shift work in the Nurses' Health Study were observed among obese women. Increased BMI is a very strong, well-established risk factor for endometrial cancer (Renehan et al. 2008; Onstad et al. 2016). Obesity may increase risk of EC through several mechanisms including increased aromatase activity which increases conversion of androgens to estrogens and there may also be inflammation associated with obesity that can increase insulin-like growth factor and increase endometrial proliferation (Onstad, Schmandt et al. 2016). Recent literature has suggested that evening chronotype is associated with higher intake of calories late in the day (Maukonen et al. 2017) and late timing of meals is associated with increased BMI (McHill et al. 2017). Evening types who have diabetes may be at risk for poorer control of glucose levels (Reutrakul et al. 2013; Reutrakul et al. 2014). A study among adolescents found that evening chronotypes had higher BMI and poorer diets compared to morning chronotypes (Arora & Taheri 2015). In our study population, we observed that 16% of morning types were obese at Q5 compared to 25% of evening types (Table 1). Similarly, the proportion of diabetics at Q5 among morning types was lower (6%) than among evening types (11%) (Table 1). Residual confounding could play a role in the observed differences by obesity status. Since some known risk factors such as obesity and diabetes appear to be higher among evening types, it is possible that the association we observed between increased EC risk and evening types in the CTS is related to differences in these types of risk factors that we cannot completely control for or capture in this retrospective, self-reported data.

While no other studies that we know of have specifically examined chronotype and EC risk, a few studies have evaluated other factors that may be indicators of circadian disruption, including sleep duration and night shift work. In an analysis of data from the Women's Health Initiative (WHI) Observational Study, Sturgeon et al. reported a slightly reduced risk of EC with long sleep duration (9 or more hours per night), although this finding was not statistically significant (OR 0.87, 95% 0.51, 1.46) (Sturgeon et al. 2012). In contrast, a previous analysis of sleep duration in the CTS found slightly increased EC risk among long-duration sleepers (10 or more hours per night) compared to women who slept 7–9 hours

per night although this finding was also not statistically significant (OR 1.22, 95% CI 0.67, 22.23) (Hurley et al. 2015). It is not clear why these two studies found different associations with sleep duration and EC risk. There were 452 endometrial cancer cases included in the WHI analyses and 957 endometrial cancer cases included in the CTS analyses, although neither study found statistically significant associations with sleep duration. Gu et al. examined sleep duration and risk of many types of cancer, including endometrial, in a cohort of retired Americans (Gu et al. 2016). They did not find any statistically significant difference in EC risk by sleep duration categories.

Although associations between chronotype and EC risk have not been previously reported, several studies have evaluated the risk of chronotype with breast cancer risk (Hansen & Lassen 2012; Ramin et al. 2013; Wirth et al. 2014; Papantoniou et al. 2016; Hurley, Goldberg et al. 2019; Richmond et al. 2019). Our findings on EC are consistent with this small body of breast cancer literature which suggests increased breast cancer risks among evening chronotypes. In our previous analysis of chronotype in the California Teachers Study we observed a modest increase in breast cancer risk among self-reported evening types compared to morning types (OR = 1.20, 95 % CI 1.06–1.35) which is similar, although a little lower, than the OR observed for EC risk for evening type (OR = 1.41, 95%CI 1.06–1.86) in the present analysis (Hurley, Goldberg et al. 2019). Two previous studies of occupational cohorts with many night shift workers, nurses and military personnel, reported that both evening types and people with no morning or evening preference had increased risk of breast cancer compared to morning types (Hansen & Lassen 2012; Ramin, Devore et al. 2013). In a Spanish case-control study, Papantoniou et al. found a slightly higher risk for breast cancer associated with night shift work among women who were evening types compared to other chronotypes (Papantoniou, Castano-Vinyals et al. 2016). A recent study from the United Kingdom (UK), which incorporated genetic information from the UK Biobank, also found morning types had lower risk of breast cancer compared to others (Richmond, Anderson et al. 2019).

It is beyond the scope of this study to elucidate the mechanisms potentially driving the observed association between chronotype and EC risk. Melatonin, however, is considered a primary mediator of and marker for circadian disruption (Greene 2012). The oncostatic properties of melatonin have been well-documented in laboratory studies (Blask et al. 2005; Blask 2009) and alterations in melatonin secretion have been documented in night shift workers (Razavi et al. 2019; Wei et al. 2020). A Danish breast cancer study reported elevated risks for long-term night shift workers that were stronger in morning chronotypes compared to evening chronotypes (Hansen & Lassen 2012), leading to the hypotheses that susceptibility to the carcinogenic effects of circadian disruption induced by night shift work might be modified by chronotype (Erren 2013). In the current study, elevated EC risks for evening chronotypes was observed among a population of current and former school employees that were not engaged in night shift work and generally started work early in the morning, which may have been more difficult and disruptive for natural evening-types.

Beyond its direct oncostatic properties, melatonin also appears to play a pivotal role in fat metabolism and energy balance (Barrenetxe et al. 2004; Cipolla-Neto et al. 2014). Melatonin levels have been shown to be lower in obese individuals (Davis et al. 2001; Travis et al.

2004; Cocco et al. 2005; Schernhammer et al. 2006). Unfortunately, we did not measure melatonin levels in our study. It is however plausible that the relationship between evening chronotype and EC risk that was observed only among obese individuals in our study was due to a threshold effect. It may be that the 'night owl' lifestyles of the evening chronotypes induced reductions in melatonin levels but these reductions were sufficient to increase EC risk only amongst the backdrop of already suppressed melatonin levels in the obese. Melatonin is also a hormone that can act to modulate estrogen metabolism (Menendez-Menendez & Martinez-Campa 2018) and it may be possible that both melatonin and obesity can interact with estrogen pathways. Additionally, melatonin can interact directly with estrogen receptors in hormone-sensitive tumors leading to interference with estrogen signaling pathways (Cos et al. 2006).

The main strength of this study is that it was conducted in a large cohort of women with detailed information on participants from multiple questionnaires over a 20 year time period. In addition, the cancer cases were ascertained from linkage to the population-based cancer registry data in California and the cohort is routinely updated through linkages with death data, hospital discharges, and address records for ascertaining movers.

This study has several limitations that are worth noting. The cancer cases were diagnosed before the women completed the questions on chronotype. It is possible that EC cancer diagnosis and treatment could have influenced changes in actual chronotype patterns or in participants' perceptions of chronotype. When we examined the EC risk by chronotype restricted to women diagnosed two or more years prior to answering the chronotype questions, we observed a somewhat reduced risk of evening types compared to morning types, although the OR was still elevated. Selection bias is also a possible limitation in this type of case-control study. Approximately 60% of the original eligible cohort members completed Q5 and 96% provided valid responses for the chronotype questions. The Q5 participants and non-responders were generally similar in terms of their sociodemographic profiles, although Q5 responders were slightly older at baseline and slightly more non-Hispanic white (data not shown)(Hurley, Goldberg et al. 2019). Additionally, participants who died prior to the completion of Q5 were not included. . Another limitation of the current analysis is that we had a relatively small number of EC cases for inclusion (437 cases), as compared to our breast cancer analysis in this cohort which had 2,716 cases (Hurley, Goldberg et al. 2019). There is a possibility for residual confounding, especially regarding the different findings by BMI. Finally, it is worth noting again that chronotype was self-reported and we did not have measures of activity patterns which would be useful to validate participants' perceptions of morning and evening preferences.

In summary, this study found that post-menopausal women with evening chronotypes may be at increased risk of EC, especially among women in the highest BMI category of 30 or more, traditionally considered "obese". Little is known about chronotypes and EC risk and it is not clear if this finding is generalizable to other populations. The current study findings are based on a retrospective case-control analysis nested with a cohort of mostly white female teachers in California. Further analysis of chronotype as a potential EC risk factor should be considered in other cohorts and in prospective analyses in order to further

explore this relationship and tease out other factors such as BMI that could be modifiable risk factors for EC prevention.

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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.

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Table 1.

Characteristics of study participants by chronotype, California Teachers Study

Covariate	Current Chronotype (post-menopause)										Total	
	Morning		More morning than evening		Neither morning/ evening		More evening than morning		Evening			
	N	%	N	%	N	%	N	%	N	%	N	%
Total	10577	100	5632	100	3618	100	4044	100	3319	100	27190	100
Age at baseline												
<40 years	1311	12	785	14	398	11	485	12	382	12	3361	12
40–49 years	4413	42	2336	41	1414	39	1655	41	1320	40	11138	41
50–59 years	3296	31	1706	30	1154	32	1267	31	1053	32	8476	31
60–69 years	1397	13	714	13	560	15	552	14	494	15	3717	14
≥70+	160	2	91	2	92	3	85	2	70	2	498	2
Race/Ethnicity												
White, not Hispanic	9311	88	4883	87	3175	88	3481	86	2859	86	23709	87
Black	205	2	105	2	51	1	91	2	66	2	518	2
Hispanic	418	4	259	5	160	4	184	5	140	4	1161	4
Asian or Pacific Islander	403	4	260	5	147	4	199	5	176	5	1185	4
Other	240	2	125	2	85	2	89	2	78	2	617	2
Chronotype in 30s-40s												
Morning	7520	71	896	16	357	10	261	6	82	2	9116	34
More morning than evening	1752	17	2652	47	679	19	570	14	172	5	5825	21
Neither	588	6	899	16	1704	47	561	14	226	7	3978	15
More evening than morning	360	3	642	11	614	17	2045	51	632	19	4293	16
Evening	86	1	165	3	164	5	435	11	2102	63	2952	11
Unknown	271	3	378	7	100	3	172	4	105	3	1026	4
Chronotype in teens/ college												
Morning	6112	58	874	16	505	14	422	10	194	6	8107	30
More morning than evening	1315	12	1801	32	302	8	341	8	126	4	3885	14
Neither	1107	10	712	13	1447	40	582	14	376	11	4224	16
More evening than morning	1174	11	1300	23	773	21	1824	45	561	17	5632	21
Evening	567	5	594	11	495	14	700	17	1990	60	4346	16
Unknown	302	3	351	6	96	3	175	4	72	2	996	4
Chronotype stability between teens/college and current												
Stable Chronotype	7427	70	2675	47	1447	40	2524	62	2551	77	16624	61

Covariate	Current Chronotype (post-menopause)										Total	
	Morning		More morning than evening		Neither morning/ evening		More evening than morning		Evening			
	N	%	N	%	N	%	N	%	N	%	N	%
Non-Stable Chronotype	2848	27	2606	46	2075	57	1345	33	696	21	9570	35
Unknown	302	3	351	6	96	3	175	4	72	2	996	4
Pregnancy and Breast Feeding												
No live birth	2327	22	1319	23	881	24	977	24	918	28	6422	24
One or more live births, no breast feeding	1372	13	635	11	443	12	512	13	416	13	3378	12
One or more live births, breast feeding 1–11 months	3161	30	1684	30	1078	30	1194	30	963	29	8080	30
One or more live births, breast feeding for 12 or more months	3487	33	1874	33	1150	32	1281	32	954	29	8746	32
Unknown	230	2	120	2	66	2	80	2	68	2	564	2
History of Oral Contraceptive use												
No	3187	30	1741	31	1105	31	1234	31	1037	31	8304	31
Yes	7309	69	3850	68	2493	69	2769	68	2250	68	18671	69
Unknown	81	1	41	1	20	1	41	1	32	1	215	1
BMI at Q1 (kg/m2)												
<25	6831	65	3645	65	2302	64	2468	61	1844	56	17090	63
25–29 (overweight)	2361	22	1238	22	772	21	933	23	817	25	6121	23
≥30 (obese)	1133	11	605	11	447	12	548	14	575	17	3308	12
Outlier or unknown	252	2	144	3	97	3	95	2	83	3	671	2
BMI at Q5 (kg/m2)												
<25	5560	53	2883	51	1831	51	1855	46	1360	41	13489	50
25–29 (overweight)	2876	27	1586	28	963	27	1214	30	981	30	7620	28
≥30 (obese)	1691	16	889	16	666	18	792	20	836	25	4874	18
Outlier or unknown	450	4	274	5	158	4	183	5	142	4	1207	4
Diabetes at Q1												
no	10437	99	5554	99	3548	98	3945	98	3214	97	26698	98
yes	140	1	78	1	70	2	99	2	105	3	492	2
Diabetes at Q5												
no	9824	93	5218	93	3286	91	3645	90	2916	88	24889	92
yes	686	6	371	7	306	8	362	9	370	11	2095	8
unknown	67	1	43	1	26	1	37	1	33	1	206	1
Height												
Average (63–66 inches)	5814	55	3083	55	2022	56	2284	56	1788	54	14991	55
Short (<63 inches)	2037	19	1112	20	699	19	798	20	713	21	5359	20

Covariate	Current Chronotype (post-menopause)										Total	
	Morning		More morning than evening		Neither morning/ evening		More evening than morning		Evening			
	N	%	N	%	N	%	N	%	N	%	N	%
Tall (≥67 inches)	2712	26	1423	25	889	25	954	24	812	24	6790	25
Unknown	14	0	14	0	8	0	8	0	6	0	50	0
Family history of breast cancer												
No	8551	81	4579	81	2903	80	3322	82	2657	80	22012	81
Yes	1723	16	893	16	617	17	628	16	571	17	4432	16
Unknown	303	3	160	3	98	3	94	2	91	3	746	3
Family history of endometrial cancer												
No	9916	94	5272	94	3378	93	3792	94	3114	94	25472	94
Yes	340	3	194	3	142	4	149	4	109	3	934	3
Unknown	321	3	166	3	98	3	103	3	96	3	784	3
Non-steroidal anti-inflammatory drug use												
No	4418	42	2355	42	1504	42	1582	39	1324	40	11183	41
Yes	5593	53	2966	53	1949	54	2246	56	1835	55	14589	54
Unknown	566	5	311	6	165	5	216	5	160	5	1418	5

Table 2.

Distribution of chronotype and endometrial cancer risk factors by case control status, California Teachers Study.

Characteristics	Case control status				Total	
	non-case		case			
	N	%	N	%	N	%
Total	26753	100	437	100	27190	100
Current Chronotype (post-menopause)						
Morning type	10427	39	150	34	10577	39
More morning than evening type	5549	21	83	19	5632	21
Neither morning/evening type	3562	13	56	13	3618	13
More evening than morning type	3975	15	69	16	4044	15
Evening type	3240	12	79	18	3319	12
Chronotype in 30s-40s						
Morning type	8982	34	134	31	9116	34
More morning than evening type	5732	21	93	21	5825	21
Neither morning/evening type	3921	15	57	13	3978	15
More evening than morning type	4227	16	66	15	4293	16
Evening type	2886	11	66	15	2952	11
Unknown	1005	4	21	5	1026	4
Chronotype as teen/college						
Morning type	7980	30	127	29	8107	30
More morning than evening type	3822	14	63	14	3885	14
Neither morning/evening type	4149	16	75	17	4224	16
More evening than morning type	5553	21	79	18	5632	21
Evening type	4267	16	79	18	4346	16
Unknown	982	4	14	3	996	4
Chronotype stability between teens/college and current						
Stable Chornotype	16350	61	274	63	16624	61
Non-Stable Chronotype	9421	35	149	34	9570	35
Unknown	982	4	14	3	996	4
Age at entry into cohort (baseline)						
<40 years	3348	13	13	3	3361	12
40–49 years	11012	41	126	29	11138	41
50–59 years	8296	31	180	41	8476	31
60–69 years	3609	13	108	25	3717	14
≥70 years	488	2	10	2	498	2
Race/Ethnicity						
White, not Hispanic	23314	87	395	90	23709	87
Black	513	2	5	1	518	2

Characteristics	Case control status				Total	
	non-case		case			
	N	%	N	%	N	%
Hispanic	1151	4	10	2	1161	4
Asian or Pacific Islander	1167	4	18	4	1185	4
Other	608	2	9	2	617	2
Pregnancy and Breast Feeding						
No live birth	6274	23	148	34	6422	24
One or more live births, no breast feeding	3309	12	69	16	3378	12
One or more live births, breast feeding 1–11 months	7958	30	122	28	8080	30
One or more live births, breast feeding for 12 or more months	8657	32	89	20	8746	32
Unknown	555	2	9	2	564	2
History of Oral Contraceptive use						
No	8114	30	190	43	8304	31
Yes	18432	69	239	55	18671	69
Unknown	207	1	8	2	215	1
Body Mass Index at baseline (kg/m2)						
<25	16890	63	200	46	17090	63
25–29 (overweight)	6023	23	98	22	6121	23
≥30 (obese)	3184	12	124	28	3308	12
unknown or outlier	656	2	15	3	671	2
Height						
Average (63–66 inches)	14761	55	230	53	14991	55
Short (<63 inches)	5286	20	73	17	5359	20
Tall (≥67 inches)	6659	25	131	30	6790	25
Unknown	47	0	3	1	50	0
Family history of breast cancer						
No	21686	81	326	75	22012	81
Yes	4330	16	102	23	4432	16
Unknown	737	3	9	2	746	3
Family history of endometrial cancer						
No	25072	94	400	92	25472	94
Yes	907	3	27	6	934	3
Unknown	774	3	10	2	784	3
Non-steroidal anti-inflammatory drug use						
No	10998	41	185	42	11183	41
Yes	14356	54	233	53	14589	54
Unknown	1399	5	19	4	1418	5

Table 3.

Odds Ratios for chronotype and endometrial cancer risk among post-menopausal women in the California Teachers Study.

Chronotype by Life Stage	Number of Cases	Number of Controls	Age and race/ethnicity adjusted OR (95% CI)	Multivariable adjusted* OR (95% CI)
Chronotype at Questionnaire 5 (post-menopause)				
Morning type (referent)	150	10,427	1.00	1.00
More morning than evening	83	5,549	1.06 (0.81, 1.39)	1.06 (0.81, 1.39)
Neither	56	3,562	1.05 (0.77, 1.43)	1.00 (0.74, 1.37)
More evening than morning	69	3,975	1.20 (0.90, 1.60)	1.14 (0.85, 1.52)
Evening type	79	3,240	1.65 (1.25, 2.18)	1.44 (1.09, 1.91)
Chronotype in 30s-40s				
Morning type (referent)	134	8,982	1.00	1.00
More morning than evening	93	5,732	1.10 (0.84, 1.44)	1.10 (0.84, 1.43)
Neither	57	3,921	0.91 (0.66, 1.24)	0.90 (0.66, 1.24)
More evening than morning	66	4,227	1.07 (0.79, 1.44)	1.00 (0.74, 1.36)
Evening type	66	2,886	1.58 (1.18, 2.14)	1.45 (1.07, 1.96)
Chronotype in Teens/College				
Morning type (referent)	127	7,980	1.00	1.00
More morning than evening	63	3,822	1.06 (0.78, 1.44)	1.07 (0.79, 1.45)
Neither	75	4,149	1.08 (0.81, 1.45)	1.10 (0.82, 1.47)
More evening than morning	79	5,553	0.98 (0.73, 1.30)	0.97 (0.73, 1.30)
Evening type	79	4,267	1.32 (0.99 1.76)	1.25 (0.94, 1.67)

*Multivariable models included age at baseline, race/ethnicity, BMI at baseline, height, family history of endometrial cancer, family history of breast cancer, history of oral contraceptive (OC) use, history of live births combined with breast feeding, , history of NSAID use (from questionnaire 5).

Table 4.

Adjusted** Odds Ratios for chronotype and endometrial cancer risk among post-menopausal women in the California Teachers Study, stratified by body mass index (BMI) at baseline (questionnaire 1) and BMI at questionnaire 5.

	Not Obese at Baseline (BMI <30)			Obese at Baseline (BMI ≥ 30)		
Chronotype at Questionnaire 5 (post-menopause)	**Number of cases**	**Number of Controls**	**OR (95% CI)**	**Number of cases**	**Number of Controls**	**OR (95% CI)**
Morning type (referent)	111	9,081	1.00	33	1,100	1.00
More morning than evening	63	4,820	1.10 (0.80, 1.50)	18	587	0.97 (0.54, 1.76)
Neither	37	3,037	0.94 (0.65, 1.38)	17	430	1.20 (0.66, 2.21)
More evening than morning	49	3,352	1.22 (0.87, 1.71)	20	528	1.19 (0.67, 2.11)
Evening type	38	2,623	1.12 (0.77, 1.63)	36	539	2.01 (1.23, 3.29)
	Not Obese at Questionnaire 5 (BMI <30)			**Obese at Questionnaire 5 (BMI ≥ 30)**		
Morning type (referent)	108	8,328	1.00	35	1,656	1.00
More morning than evening	53	4,416	0.95 (0.68, 1.33)	28	861	1.51 (0.91, 2.51)
Neither	33	2,761	0.87 (0.58, 1.29)	19	647	1.30 (0.73, 2.30)
More evening than morning	51	3,018	1.31 (0.94, 1.84)	14	778	0.84 (0.45, 1.59)
Evening type	36	2,305	1.11 (0.76, 1.63)	41	795	2.26 (1.42, 3.61)

** Multivariable models included age atat baseline, race/ethnicity, height, family history of endometrial cancer, family history of breast cancer, history of oral contraceptive (OC) use, history of live births combined with breast feeding, and history of NSAID use (from questionnaire 5. Excluded unknown and outlier BMIs.

Table 5.

Adjusted* Odds Ratios for chronotype and endometrial cancer risk among post-menopausal women in the California Teachers Study, stratified by chronotype stability.

	Stable chronotype**			Not stable chronotype**		
Chronotype at Questionnaire 5 (post-menopause)	**Number of Cases**	**Number of Controls**	**OR (05% CI)**	**Number of Cases**	**Number of Controls**	**OR (05% CI)**
Morning type (referent)	107	7,320	1.00	38	2,810	1.00
More morning than evening	43	2,632	1.10 (0.77, 1.58)	36	2,570	1.08 (0.68, 1.72)
Neither	27	1,420	1.18 (0.77, 1.81)	27	2,048	0.88 (0.53, 1.45)
More evening than morning	36	2,488	1.05 (0.71, 1.54)	30	1,315	1.31 (0.80, 2.16)
Evening type	61	2,490	1.50 (1.09, 2.07)	18	678	1.37 (0.77, 2.46)

*Multivariable models included age at baseline, race/ethnicity, BMI at baseline, height, family history of endometrial cancer, family history of breast cancer, history of oral contraceptive (OC) use, history of live births combined with breast feeding, and NSAID use.

**Stable chronotype was defined as having the same chronotype reported on questionnaire 5 (post-menopause) as in teens and college years.