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## CHRONOTYPE AND BREAST CANCER RISK IN A COHORT OF U.S. NURSES

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### Abstract

The aim of this study was to examine the relation between chronotype and breast cancer risk. We analyzed the association between chronotype (definite morning type, probable morning type, probable evening type, definite evening type, or neither morning nor evening type) and breast cancer risk among 72 517 women in the Nurses' Health Study II (NHS II). Chronotype was self-reported in 2009, and 1834 breast cancer cases were confirmed among participants between 1989–2007; a 2-year lag period was imposed to account for possible circadian disruptions related to breast cancer diagnosis. Age- and multivariable-adjusted logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). Participants who self-reported as neither morning nor evening chronotype had a 27% increased risk of breast cancer (multivariable-adjusted OR= 1.27; 95% CI, 1.04–1.56), compared to definite morning types. None of the other chronotypes were significantly associated with breast cancer risk (multivariable-adjusted OR= .99, 95% CI, .87–1.12 for probable morning vs. definite morning types, OR=.96, 95% CI, .84–1.09 for probable evening vs. definite morning types, and OR=1.15, 95% CI, .98–1.34 for definite evening vs. definite morning types). Overall, chronotype was not associated with breast cancer risk in our study. A modestly increased risk among neither morning nor evening chronotypes may indicate circadian disruption as a potentially underlying mechanism; however, more studies are needed to confirm our results.

### Keywords

chronotype; night shift work; breast cancer; morningness-eveningness; bimodal

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### DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

## INTRODUCTION

Circadian rhythms are regulated by a master clock located within the suprachiasmatic nuclei (SCN) of the brain (Fu & Lee, 2003). This clock generates rhythms with an approximate 24-hour oscillation pattern, is entrained by the light/dark cycle, and is generated by a set of core clock genes (Savvidis & Koutsilieris, 2012). The circadian system produces rhythms in metabolic, physiological and behavioral functions, including hormone production, sleep-wake behavior, digestive secretion, and immune response (Fu & Lee, 2003; Savvidis & Koutsilieris, 2012). An individual's circadian rhythms and susceptibility to circadian disruption may be influenced by chronotype, which refers to an individual's preference for behavioral timing, particularly the timing of sleep and waking. Chronotype may affect adaptability and tolerance to rotating shift work, and thereby may increase the risk of adverse health outcomes.

Growing evidence suggests that circadian disruption may lead to an increased risk of breast cancer. Multiple studies, including two prospective analyses from within the Nurses' Health Study cohorts, have found rotating night-shift work - a prime disruptor of circadian rhythms - to be associated with elevated breast cancer risk (Hansen & Lassen, 2012; Pukkala et al., 1995; Rafnsson et al., 2001; Schernhammer et al., 2006; Schernhammer et al., 2001; Tynes et al., 1996). While the underlying mechanisms linking night shift work and increased breast cancer risk remain unclear, suppression of the hormone melatonin by light exposure at night, insufficient sleep, lifestyle factors, and/or a general disruption of circadian synchrony have been suggested (Fritschi et al., 2011).

Whether chronotype influences breast cancer risk and whether this association is modified by rotating night shift work status are key questions of interest. To date, one study has examined the association between chronotype and breast cancer risk. Results from this study suggested that individuals with evening chronotype or neither chronotype had a greater risk of breast cancer compared to those with morning chronotype (Hansen & Lassen, 2012). The biological mechanism(s) that may underlie such an association are unclear. Core circadian clock genes have been shown to act as tumor suppressors or oncogenes, suggesting that variations in their expression may be involved in initiation and/or progression of cancer growth (Hoffman et al., 2008; Lee, 2006; Saha & Sassone-Corsi, 2007; Yang et al., 2009; Savvidis & Koutsilieris, 2012). In fact, several clock genes have been linked to breast cancer risk (Hoffman et al., 2010; Zhu et al., 2005; Zhu et al., 2008) and there are also reports that SNPs in clock genes are associated with chronotype (Archer et al., 2003; Carpen et al., 2006; Katzenberg et al., 1998).

Exposure to light at night is a mechanism that has been hypothesized to increase breast cancer risk among shift workers by suppressing melatonin secretion (Fritschi et al., 2011). Melatonin has been reported to have anti-cancer effects in vitro, and decreased levels of melatonin synthesis appear to influence the initiation, promotion, and progression of hormone related cancers such as breast cancer (Blask, 2009). Whether light exposure at night or suppression of melatonin by light at night differ between chronotypes remains

unknown, although the timing of melatonin secretion in non-night shift workers has been demonstrated to be significantly different between chronotypes (Duffy et al., 1999).

Given the finding that night shift work increases breast cancer risk (Pukkala et al., 1995; Rafnsson et al., 2001; Schernhammer et al., 2006; Schernhammer et al., 2001; Tynes et al., 1996), the evidence that morning chronotypes are less tolerant of night shift work (Saksvik et al., 2011; Gamble et al., 2011; Smith et al., 2005; Saksvik-Lehouillier et al., 2012), and the recent report of an association between chronotype and breast cancer risk (Hansen & Lassen, 2012), whether chronotype influences breast cancer risk after accounting for a history of night-shift work remains unclear. To address these issues, we examined the association between chronotype and breast cancer risk among 72 517 women in the Nurses' Health Study II.

## MATERIALS AND METHODS

The Nurses' Health Study II is an ongoing prospective cohort comprised of 116 434 female registered nurses, aged 25 to 42 years and living in 14 U.S. states at baseline. Cohort members completed a baseline questionnaire in 1989 and subsequent questionnaires have been mailed every two years to obtain updated information on lifestyle factors, medical history, and newly diagnosed disease. Initial participation and follow-up rates have been approximately 90% (Schernhammer et al., 2011).

### Assessment of chronotype

In 2009, participants were asked about their chronotype with the question, "One hears about morning and evening types of people. Which ONE of these types do you consider yourself to be?". Response categories were given as "definitely a morning type", "more of a morning than an evening type", "more of an evening than a morning type", "definitely an evening type", and "neither" (in that order). Chronotype has typically been assessed with questionnaires comprised of a series of questions, such as the Horne-Ostberg morningness-eveningness questionnaire (MEQ) (Horne & Ostberg, 1976). This is a validated questionnaire consisting of 19 questions about preferred times to do different types of activities during the day, and its scoring follows a Likert-type response format. The answers to the 19 questions are summed to determine chronotype in one of 5 categories although the response to item 19 (upon which our question was based) has been shown to be correlated with overall chronotype determined from all 19 questions (Roenneberg et al., 2007).

### Assessment of rotating night shift work

Detailed information on total years during which the nurse had worked on rotating night shifts was available from the 1989 questionnaire, with an update in 1991, 1993, 1997, 2001, 2005, and 2009. The 1991 and 1993 questionnaire collected information about total number of months during which the nurse had worked rotating night shifts with at least 3 nights per month in addition to days or evenings in that month (since June 1989 and 1991, respectively). Pre-specified categories on total numbers of months working on rotating night shifts were "none, 1–4 months, 5–9, 10–14, 15–19, and 20 months or more." In addition, in 2001, gaps were filled by asking for number of months worked on rotating night shifts

between 1995 and 1997, as well as 1997 and 1999. Specifically, nurses were asked “During the following time periods, how many months have you worked *rotating* night shifts (at least 3 nights per month in addition to other days and evenings in that month)?”.

### Documentation of breast cancer cases and death

Study participants were asked if they had been previously diagnosed with breast cancer in the initial questionnaire in 1989, and they were asked in each follow-up questionnaire, from 1991 to 2009, if they had been diagnosed with breast cancer within the past two years. If newly diagnosed breast cancer was reported, permission to access medical records was obtained and diagnosis was confirmed by the participant’s doctor, medical records, or pathology reports. Breast cancer was additionally reported during death follow-up when family members, postal service, or the National Death Index informed the study that a participant was deceased. After each follow-up cycle, the National Death Index was also reviewed for study participants who were unresponsive, and if death was confirmed the death certificate was used to identify the cause of death.

### Population for analysis

In total, 90 480 women completed the NHS II questionnaire in 2009. Of these, we excluded 665 cases of breast cancer in situ, and 4783 cases of other cancer (except for non-melanoma skin cancer), occurring between baseline in 1989 and 2007. In addition, 12 515 women were excluded because they did not answer the chronotype question (i.e., an 85% response rate among women who answered the 2009 questionnaire). Thus, the base population for this analysis was comprised of 72 517 women from NHS II. Participants who provided chronotype information generally were similar to those who did not provide chronotype information (mean age=52.9 vs. 52.7 years, mean body mass index for both groups=27.5 kg/m<sup>2</sup>).

### Statistical analysis

We used multivariable-adjusted logistic regression models to estimate odds ratios (OR) and 95% confidence intervals (CI) of breast cancer across five categories of chronotype (definite morning type, probable morning type, probable evening type, definite evening type, and neither morning nor evening type). Definite morning type was used as the referent group because it represented the largest group of women in our study and we assumed that this group would experience the least circadian disruption. We imposed a 2-year lag period to ensure that breast cancer cases occurred at least 2 years prior to chronotype reporting, because we were concerned that factors related to diagnosis (e.g., treatment effects) might alter a woman’s perception of her usual chronotype. We calculated age-adjusted estimates, and additionally adjusted for the following potential confounding factors: family history of breast cancer (yes, no), age at menarche (<12, 12, 13, 14), history of rotating night-shift work in years (never, 1–9, 10 years), smoking status (never smoker/past smoker, current smoker <25 cigarettes per day, current smoker ≥25 cigarettes per day), body mass index (BMI) in kg/m<sup>2</sup> (<18.5, 18.5–19.9, 20.0–22.4, 22.5–24.9, 25.0–29.9, ≥30 kg/m<sup>2</sup>), alcohol intake in g/day (non-drinkers, <5, 5–9.9, 10–19.9, and ≥20 g/day), physical activity in MET-hours/week (quintiles), history of benign breast disease (yes, no), oral contraceptive use

(never, ever), menopausal status (premenopausal, postmenopausal), age at menopause in years (<48, 48, 49, 50), parity and age at first birth (nulliparous; age at first birth <25, 1–2 children; age at first birth 25–29, 1–2 children; age at first birth 30, 1–2 children; age at first birth <25, 3 children; age at first birth 25, 3 children), and postmenopausal hormone use (never, ever). All covariates were determined in 2007.

We conducted several secondary analyses. First, we stratified by history of rotating night-shift work status (never, 1–9, 10 years) to evaluate whether the association between chronotype and breast cancer risk was similar among women with different histories of rotating night-shift work. Second, we examined whether the association between chronotype and the risk of breast cancer was stronger among women with body mass index  $\geq 25$  kg/m<sup>2</sup> compared to women with body mass index <25 kg/m<sup>2</sup>, as previous studies have indicated that individuals with evening chronotype have an increased risk of obesity. Likelihood ratio tests were used to test for interaction in both of these analyses.

All p-values were based on two-sided tests and were considered statistically significant if  $p < .05$ . We used SAS software, version 9 (SAS Institute Inc., Cary, North Carolina, U.S.) for all statistical analyses.

## RESULTS

We documented a total of 1834 prevalent cases of invasive breast cancer between 1989 and 2007. The chronotype distribution in this sample was as follows: 34% definite morning types, 26% probable morning types, 23% probable evening types, 12% definite evening types, and 5% neither morning nor evening types. Overall, the individuals in the chronotype groups were fairly similar in terms of their age and age-standardized characteristics (shown in Table 1). Definite evening types were more likely to be obese and smoke, consumed less alcohol, and had lower physical activity levels compared to morning types. Probable evening types were also less physically active than morning types. Moreover, definite evening and neither types appeared to be more likely to engage in long term rotating night shift work, compared to morning types.

Table 2 shows age-adjusted and multivariable-adjusted associations between chronotype and breast cancer risk; we present multivariable-adjusted results only because results were very similar to the unadjusted results. In multivariable models, adjusting for a variety of possible confounding factors, probable morning and probable evening chronotypes were not associated with breast cancer risk (OR=.99, 95% CI .87–1.12 for probable morning vs. definite morning types, and OR=.96, 95% CI .84–1.09 for probable evening vs. definite morning types). Women who reported being neither morning nor evening chronotype had a 27% increased risk of breast cancer, compared to women with definite morning chronotype (multivariable-adjusted OR=1.27, 95% CI 1.04–1.56). In addition, definite evening chronotype was related to a 15% increased risk of breast cancer (multivariable-adjusted OR=1.15, 95% CI .98–1.34), but was not statistically significant. Results did not differ according to estrogen receptor status of the breast tumors (data not shown).

We found no evidence that the association between chronotype and breast cancer risk differed according to history of night-shift work (LRT statistic= $1.07 < \chi^2_{1 \text{ df}}=3.84$ , therefore  $p>.05$ ). Among women without a history of rotating night shift work, those who were neither morning nor evening chronotype had a 46% increased risk of breast cancer compared to definite morning types (number of cases=534; multivariate-adjusted OR=1.46, 95% CI 1.01–2.12); among women with neither chronotype who had 1–9 years of shift work history, the relative risk of breast cancer was increased by 26% above definite morning types (number of cases=1119; multivariable-adjusted OR=1.26, 95% CI=.97–1.64), and among women with neither chronotype and 10 years of shift work history, breast cancer risk decreased by 8% when compared to women with definite morning type (number of cases=170; multivariable-adjusted OR=.92, 95% CI=.45, 1.86). When we stratified analyses by BMI category, the association between women with neither chronotype and breast cancer risk was somewhat stronger among women with a body mass index  $\geq 25 \text{ kg/m}^2$  (number of cases=999; multivariable-adjusted OR=1.40, 95% CI 1.07–1.83 comparing neither vs. definite morning types) than among women with a body mass index  $<25 \text{ kg/m}^2$  (number of cases=738; multivariable-adjusted OR=1.13, 95% CI .81–1.58 comparing neither vs. definite morning types). However, the interaction term was not significant in multivariable-adjusted models (LRT statistic=.19  $< \chi^2_{1 \text{ df}}=3.84$ , therefore  $p>.05$ ).

## DISCUSSION

In this study, we observed an elevated risk of breast cancer among women with neither morning nor evening chronotypes, compared to definite morning chronotypes, after adjustment for possible confounders. Although there was a marginally increased risk of breast cancer in definite evening types compared to definite morning types, this association was not significant. Results were similar when analyses were restricted to participants without a history of shift work.

A recent nested case-control study of cumulative shift work on breast cancer risk included an analysis by self-reported chronotype (morning, evening, and neither/mixed preference) among a cohort of 18 551 women in the Danish military (Hansen & Lassen, 2012). The authors reported an increased breast cancer risk among women who worked night shifts and had an evening preference compared to those with morning preference (OR =1.8; 95% CI 1.2 – 2.9) as well as those with mixed/neither preference compared to those with morning preference (OR =1.6; 95% CI 1.0–2.7). Even though the Danish cohort differed from ours in terms of how chronotype was assessed, we too, observed an increased risk of breast cancer among the neither chronotype group in our analysis and a marginally increased risk (although not statistically significant) of breast cancer among definite evening types.

Despite the lack of a significant association between evening chronotype and breast cancer risk in our analysis, the increased risk among neither chronotype is intriguing. One possible explanation is that our findings are due to chance given the small number of neither chronotypes in our sample. Further, the neither types could represent individuals who misclassified themselves due to misunderstanding the chronotype question (Randler & Vollmer, 2012). Alternatively, our results may indicate that the neither types (just like the mixed/neither types in the Danish study) may have less regulated circadian rhythms, leading

to a higher risk for circadian disruption. Recently, the possibility of an additional chronotype that represents a bimodal circadian pattern has been suggested (Randler & Vollmer, 2012; Martynhak et al., 2010). Bimodal chronotypes are described as having traits that are consistent with both morning and evening types, hypothesized to be due to a dual morning and evening oscillator (Martynhak et al., 2010). When taking Likert-type surveys to assess morningness-eveningness, bimodal chronotypes will answer some questions with a morning type response and other questions with an evening type response. This results in their overall responses being summed up as a neither type score even though their individual responses to the questions do not fall in the middle between morning and evening type responses, as do those of more typical neither types (Randler & Vollmer, 2012). It is possible that neither chronotypes in our analysis may be bimodal types, and we hypothesize that such individuals may be at higher risk for breast cancer due to their bimodal circadian rhythms, which may increase susceptibility to circadian disruption. However, this hypothesized link between bimodal circadian rhythms and circadian disruption has not been demonstrated. Nonetheless, our findings, together with those from the study of Hansen & Lassen (2012), warrant further investigation of the association between neither chronotype and breast cancer risk, and better understanding of bimodal chronotypes.

There are several limitations to our analysis. First, the assessment of chronotype was self-reported after the occurrence of breast cancer, and hence was collected retrospectively. Chronotype has been documented to change towards morningness as age increases (Taillard et al., 2004), thus it is possible that women who were evening/neither types at the time of breast cancer incidence might have rated themselves as morning types on the subsequent chronotype assessment in 2009. As a result, associations may be harder to detect with evening/neither types and may have biased our result toward the null. In addition, chronotype was measured with one question instead of a series of questions, such as the Horne and Ostberg morningness-eveningness questionnaire (MEQ) (Horne & Ostberg, 1976). Although it is somewhat difficult to determine how this might have influenced our findings, results from a one-question assessment such as we used have been shown to correlate well with chronotype classifications derived from a more detailed questionnaire (Roenneberg et al., 2007). Second, this is an observational study and therefore we cannot rule out the possibility of residual confounding. However, we accounted for well-established breast cancer risk factors and adjustment for these risk factors did not substantially change our estimates. Third, the Nurses' Health Study II is a cohort of health professionals with a high percentage of rotating and night shift workers, which could limit the generalizability of our findings. However, when we excluded night shift workers from our analysis, this did not change the association between chronotype and breast cancer risk. Lastly, despite the long survival after breast cancer diagnosis, there were 158 women with a breast cancer diagnosis who died prior to chronotype assessment in 2009. To ensure that the inclusion of prevalent cases still alive in 2009 did not bias our estimates (i.e., women had to be alive in 2009 to answer the chronotype question and be included in our study), we compared the tumor histopathology of cases in our analyses vs. cases that were excluded because they did not have information on chronotype. The breast tumors of cases in our study were largely comparable to tumors of women who had died prior to 2009, although they tended to be slightly better differentiated and a larger proportion of them were ER positive. However, the

association between chronotype and breast cancer was not different among women with ER positive vs. negative or more vs. less differentiated tumors in our sample. Nonetheless, although it appears unlikely that chronotype is associated with breast cancer survival, we cannot entirely rule out the possibility that the association between chronotype and breast cancer risk was different among women who died prior to chronotype assessment. Finally, recall bias appears unlikely in our prevalent cases because, to our knowledge, the public does not perceive chronotype as carcinogenic.

In conclusion, we observed an increased risk of breast cancer among women with self-reported chronotypes that were neither morning nor evening types. There is a lack of research on neither chronotypes, and further research is warranted to understand this population and the underlying mechanisms that may be driving the increased risk of breast cancer.

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Age and age-standardized characteristics in 2007 across categories of chronotype among 72 517 women in the Nurses' Health Study II \*

Table 1

	Definitely morning type N= 25 038 (34%)	More of a morning than an evening type N=18 892 (26%)	More of an evening than a morning type N=16 343 (23%)	Definitely evening type N=8542 (12%)	Neither morning nor evening type N=3702 (5%)
Age, in years, mean	53.2	52.8	52.7	52.9	53.1
Family history of breast cancer, %	16	17	17	17	16
Age at menarche, % 14 years	18	18	18	18	18
History of rotating night-shift work, in years, % 10 years	8	8	10	13	12
Smoking status, % never or past	94	94	93	90	95
Body-mass index, % 30 kg/m <sup>2</sup>	23	27	32	38	27
Alcohol intake, % non-drinkers	41	40	44	48	48
Physical activity, in MET-hours/week, mean	23.9	20.9	18.3	17.8	20.7
History of benign breast disease, %	54	55	56	54	52
Oral contraceptives, % ever used	88	89	89	88	87
Menopausal status, % premenopausal	37	38	37	36	38
Parity, % nulliparous	19	18	19	23	21
Postmenopausal hormone use, % ever used	30	31	32	31	29

\* Percentages are of non-missing values.

**Table 2**  
The association of chronotype and breast cancer risk among 72 517 women in the Nurses' Health Study II

Chronotype	Number of cases	Age-adjusted OR (95% CI)	Multivariable-adjusted OR (95% CI) *
Definite morning type <sup>†</sup>	647	1.00	1.00
More morning than evening type	456	.97 (.86–1.09)	.99 (.87–1.12)
More evening than morning type	376	.92 (.81–1.05)	.96 (.84–1.09)
Definite evening type	238	1.11 (.95–1.29)	1.15 (.98–1.34)
Neither morning nor evening type	117	1.24 (1.02–1.52)	1.27 (1.04–1.56)
Total	1834	--	--

\* Odds ratios adjusted for age (continuous), family history of breast cancer (yes, no), age at menarche (<12, 12, 13, 14), history of rotating night-shift work in years (never, 1–9, 10), smoking status (never smoker/past smoker, current smoker <25 cigarettes per day, current smoker 25–49 cigarettes per day, current smoker ≥50 cigarettes per day), body mass index in kg/m<sup>2</sup> (<18.5, 18.5–24.9, 25.0–29.9, ≥30 kg/m<sup>2</sup>), alcohol intake in g/day (non-drinkers, <5, 5–9.9, 10–19.9, and ≥20 g/day), physical activity in MET-hours/week (quintiles), history of benign breast disease (yes, no), oral contraceptive use (never, ever), menopausal status (premenopausal, postmenopausal), age at menopause in years (<48, 48–49, 50), parity and age at first birth (nulliparous; age at first birth <25, 1–2 children; age at first birth 25–29, 1–2 children; age at first birth ≥30, 1–2 children; age at first birth ≥30, 3 children), and postmenopausal hormone use (never, ever).

<sup>†</sup> Reference category in all analyses.