Sleep Duration and Breast Cancer: A Prospective Cohort Study

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Abstract

Breast cancer incidence has increased during recent decades for reasons that are only partly understood. Prevalence of sleeping difficulties and sleepiness has increased, whereas sleeping duration per night has decreased. We hypothesized that there is an inverse association between sleep duration and breast cancer risk, possibly due to greater overall melatonin production in longer sleepers. This population-based study includes information from women born in Finland before 1958. Sleep duration, other sleep variables, and breast cancer risk factors were assessed by self-administered questionnaires given in 1975 and in 1981. Breast cancer incidence data for 1976 to 1996 was obtained from the Finnish Cancer Registry. Hazard ratios (HR) and 95% confidence intervals (CI) were obtained from Cox proportional hazards models adjusting for potential confounders. Altogether, 242 cases of breast cancer occurred over the study period among the 12,222 women with sleep duration data in 1975. For these women, the HRs for breast cancer in the short (≤6 hours), average (7-8 hours), and long sleep (≥9 hours) duration groups were 0.85 (CI, 0.54-1.34), 1.0 (referent), and 0.69 (CI, 0.45-1.06), respectively. Analysis restricted to the 7,396 women (146 cases) whose sleep duration in 1975 and 1981 were in the same duration group (stable sleepers) yielded HRs of 1.10 (CI, 0.59-2.05), 1.0, and 0.28 (CI, 0.09-0.88), with a decreasing trend (P = 0.03). This study provides some support for a decreased risk of breast cancer in long sleepers. (Cancer Res 2005; 65(20): 9595-600)

Introduction

Breast cancer risk varies by >5-fold across the world, with the most industrialized societies at the high end and the developing societies at the low end (1). The reasons for much of the variation have not been convincingly explained, although reproductive factors such as age at first birth and duration of breast feeding clearly have important effects on breast cancer risk (2). Symptoms of sleep disorders (including insomnia and insufficient sleep) are common in all age groups (3–8). Daytime sleepiness seems to have increased over time (9), and circumstantial evidence suggests a simultaneous decrease in sleep duration in some (10–12) but not all conditions (13, 14). Additionally, the increasing use of electricity for artificial lighting, television, and other factors have changed our life-styles, sleep habits, and probably also our hormonal rhythms including that of melatonin.

Melatonin is synthesized by the pineal gland and released to the circulation in rhythmic fashion during the dark part of the day-night cycle (15, 16). Its production is controlled by an endogenous circadian timing system and suppressed by light. The hormone also possesses anticarcinogenic properties. Based on the potential for nocturnal illumination to lower blood levels of melatonin, it has previously been suggested that perhaps "light-at-night" explains a part of the worldwide breast cancer burden (17, 18). In addition to artificial lighting at night, we hypothesize that sleep patterns may have an impact on breast cancer risk through changes in melatonin and other hormonal rhythms.

There is evidence from sleep laboratory studies that habitual sleep duration in humans is associated with systematic differences in hormonal secretion. A study of 10 healthy long sleepers (sleep duration >9 hours per night) and 14 healthy short sleepers (<6 hours) reported an ~1 hour longer duration of nocturnal melatonin secretion and 2.5 hours longer duration of nocturnal cortisol secretion under constant dim light in a sleep laboratory (19). Further experimental evidence showed that switching human volunteers from an 8-hour night to a 14-hour night was associated with an increase both in sleep duration (from 7.3 to 8.4 hours) and in nocturnal melatonin secretion (20). Approximate increases of 2 hours have been reported in the duration of nocturnal melatonin secretion under regular wintertime living conditions at high-temperate, subpolar, and polar latitudes (21). However, it seems unclear whether smaller photoperiod changes are associated with changes in melatonin secretion.

We used the Finnish Twin Cohort (22) to ask the question whether longer sleep duration was associated with lower breast cancer risk. In addition, we explored the relations of insufficient sleep and sleep quality with breast cancer.

Materials and Methods

Study population. The older part of the Finnish Twin Cohort was compiled in 1974 for the study of genetic and environmental factors in chronic diseases in the Finnish population (22). The database from the Central Population Registry of Finland was used to form the basis of the Cohort, which includes >32,000 twins born before 1958. The overall response rates were 89% to the baseline questionnaire in 1975, and 84% to the first follow-up questionnaire in 1981. Of the 13,176 female twins who returned the 1975 questionnaire, the present study includes the 12,619 women who answered one or more of the sleep-related questions in 1975 or in 1981; this means that the number of women varies by the analyzed sleep-related factor (sleep duration, n = 12,222; sleep quality, n = 12,084; insufficient sleep, n = 10,844).

Sleep-related variables. The measures for sleep duration and sleep quality were included in the 1975 and 1981 questionnaires; insufficient sleep was assessed in 1981. Sleep duration was obtained by asking "How many

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hours do you usually sleep per 24 hours?" In the 1975 questionnaire, there were seven response alternatives with intervals of 1 hour, ranging from ≤4 hours to ≥10 hours. In the 1981 questionnaire, there were nine alternatives with 30-minute intervals ranging from ≤6 hours to ≥10 hours. Necessary amount of sleep was obtained in 1981 by asking "How many hours of sleep do you usually need during the night to be in good working condition the next day?" There were the same nine response alternatives as for sleep duration. Insufficiency of sleep was calculated (before combining the categories) as the difference of necessary amount of sleep in 1981 and sleep duration in 1981; thus, a positive number for insufficient sleep refers to lack of sleep and a negative number to sufficient, even excessive sleep. The quality of sleep was assessed by asking: "Do you usually sleep well?" The five alternative answers were "well", "fairly well", "fairly poorly", "poorly", and "cannot say."

Confounding variables. The 1975 questionnaire also provided information about subject characteristics (zygosity, weight, and height) and potential breast cancer risk factors (social class, number of children, use of oral contraceptives, alcohol use, smoking and physical activity; ref. 23). Zygosity was determined using a validated questionnaire method (24). Social class was defined by years of education and by physical activity at work (25). Body mass index was calculated as weight (in kg)/height squared (in m^2). The monthly consumed amount of alcohol (in grams) was calculated from the frequency and quantity of beer, wine, and hard liquor consumption. Physical activity in leisure time took into account the frequency, duration, and intensity of exercise. Information on practically all confounding variables was also available in the 1981 questionnaire; the only exception was the number of children.

Cancer data. The malignant neoplasms among the subjects from 1976 to 1996 were identified by record linkage to the Finnish Cancer Registry data using the personal identification number unique to every resident of Finland. The Finnish Cancer Registry is a nationwide database with information on all cancers diagnosed in Finland since 1953 (26). Reporting of cancers has been compulsory since 1961. Notifications on cancer patients are received independently from several sources, such as hospitals, private physicians, pathologic laboratories, and death certificates. In 1995, diagnoses for 95% of cancers were based on microscopic confirmation, and the coverage of breast cancer registration is almost 100% (27). Breast cancers were classified according to the International Classification of Diseases, 7th revision (28), modified by the Finnish Cancer Registry, and include invasive as well as *in situ* breast cancers (although the latter amount to only a small percentage of all breast cancers in Finland). In addition, the study cohort was linked to the Central Population Register to obtain data on death and emigration, as well as birth years of children (to supplement information from the 1975 questionnaire) for the years 1976 to 1981.

Ethical permissions. The existing data sets are approved according to national laws. Data acquisition was preceded by approvals from the National Data Protection Agencies (for registry data), Ethical Research Committees, and other officials (for questionnaire data). The questionnaire studies were based on voluntary, informed participation and participants were provided regular feedback about results from the study.

Statistical analyses. Person-years of follow-up were computed from January 1, 1976 (from January 1, 1982 in the analyses of insufficient sleep) to the date of breast cancer diagnosis, death, emigration, or the end of follow-up (December 31, 1996), whichever came first. Cox proportional hazards models were used to estimate hazard ratios (HR) and their 95% confidence intervals (CI), the latter adjusted for possible intra-pair correlations of the twin data. The analyses were done using Stata version 8.2 (Stata Corporation, College Station, TX).

We used two different categorizations for sleep duration. First, by using those with 8 hours of nightly sleep as a reference, we estimated breast cancer risk in each of the six other categories of sleep duration in 1975. In subsequent analyses, we used three-category classification: ≤6 hours, 7 to 8 hours (reference), and ≥9 hours. Insufficient sleep was analyzed as a two-category variable with the previously used cutoff point of 1 hour (29), and as a continuous variable (from 0 to 4 hours). The latter analysis of insufficient sleep excluded the 1,802 subjects with negative values, i.e., those who slept longer than they felt they needed. For sleep quality, the original response alternatives were used; the subjects who reported "cannot say" were excluded from the analyses of sleep quality. A trend test for a dose-response relation between sleep variable and breast cancer risk was done by using each categorical variable as a continuous variable by assigning scores to consecutive categories starting from one and increasing by one.

First, the analyses were adjusted for age (continuous variable) only. Subsequent multivariable-adjustment included, in addition to age, the following potential breast cancer risk factors: zygosity (monozygotic, dizygotic), social class (blue collar, intermediate, white collar), number of children (0, 1-2, ≥3), use of oral contraceptives (never, ever), body mass index (<25, 25-29, ≥30 kg/m^2), alcohol use (0, 1-399, ≥400 g/mo), smoking status (never, occasionally, formerly, currently), and leisure-time physical activity (sedentary, occasional, conditioning exerciser). The potential confounding effect of age at first full-term birth (<25, ≥25 years) was examined separately by restricting all the analyses to parous women and adjusting, in addition to other factors, for age at first full-term pregnancy. This did not materially change the results (data not shown).

The main analyses were based on sleep-related factors measured at the first available measurement occasion only, that is, the 1975 questionnaire for sleep duration and sleep quality, and the 1981 questionnaire for insufficient sleep. The covariate data for these analyses came, when available, from the same questionnaire providing the initial data on the sleep factor being analyzed.

In addition, we conducted two analyses, which used both the 1975 and 1981 questionnaire data. First, we updated the baseline information on sleep duration and those covariates that are expected to change over time (e.g., alcohol use) with that from the 1981 questionnaire, thus creating time-dependent covariates. In this analysis, sleep duration (and covariates) reported in 1975 was used to predict breast cancer risk from 1976 to 1981 and that reported in 1981 predicted risk from 1982 to 1996. Thus, this approach addressed the possibility that relevant changes in sleep duration and covariates may occur over time.

Secondly, we evaluated the effect of sustained sleep duration on breast cancer risk from 1976 to 1996 by excluding from the analyses women whose reported sleep duration changed between 1975 and 1981 (according to the three-category variable). Assessment of sustained sleep duration, in addition to reducing measurement error, was considered the best surrogate for long-term "exposure" to light/dark at night.

Results

The majority of women in the cohort reported sleeping 7 or 8 hours in 1975 (7.7 hours on average). Table 1 shows the demographic characteristics of women in each of the sleep duration categories. Short sleepers were older, tended to consume more alcohol, be more sedentary exercisers, and to smoke more than others. They were also less likely to be white collar or intermediate workers, fewer of them were nulliparous, and they did not use oral contraceptives as often as average or longer sleepers. Self-reported sleep quality was more often rated as "poor" among the short sleepers and also sleep insufficiency was greatest among them.

Table 2 shows the HRs of breast cancer by sleep duration. When using the seven-category classification, the risk estimates were highest for those sleeping 8 hours per night (reference). Compared with the reference group, the risk estimates were substantially lower for the categories of longer sleepers, and slightly lower for the categories of shorter sleepers. When sleep duration was categorized into three groups (≤6, 7-8, and ≥9 hours per night), the HRs for breast cancer were 0.85 (95% CI, 0.54-1.34), 1.00 (reference), and 0.69 (95% CI, 0.45-1.06) by increasing sleep duration (Table 2). These figures did not materially change when using time-dependent analysis, which updated the baseline data on sleep duration and covariates with the data reported in 1981 (data not shown).

Table 1. Subject characteristics (means or proportions) in a cohort of Finnish women by sleep duration at baseline in 1975

Characteristic	Duration of sleep				
	≤6 h (*n* = 1,181)	7 h (*n* = 3,473)	8 h (*n* = 5,580)	≥9 h (*n* = 1,988)	All (*n* = 12,222)
Age at baseline (y)	43.7	37.1	35.1	35.1	36.5
Age at first full-term pregnancy (y)	24.6	24.4	24.5	24.1	24.4
Number of children (in women with children)	2.6	2.3	2.3	2.2	2.3
Body mass index (kg/m^2)	23.4	22.7	22.5	22.7	22.7
Alcohol use (g/mo)	134	128	108	106	116
Dizygotic twins (%)	67.1	67.4	66.6	69.0	67.3
White collar and intermediate workers (%)	54.5	66.0	66.1	61.5	64.2
Nulliparous women (%)	38.9	44.4	45.0	46.6	44.5
Ever used oral contraceptives (%)	28.3	33.8	33.7	33.9	33.2
Sedentary exercisers (%)	23.3	16.3	15.7	18.2	17.0
Current smokers (%)	29.4	26.1	20.9	20.4	23.1
Insufficient sleep in 1981 ≥1 h (%)	31.4	24.8	19.1	16.5	21.4
Sleep quality rated poor (%)	11.6	1.4	0.8	0.8	2.0

A substantial proportion of women answered the sleep duration question in 1981 differently from the question in 1975. Because the underlying hypothesis was that habitual, and long-term, exposure to a long dark period would be associated with a lower risk of breast cancer, we were particularly interested in those women who reported the same sleep duration in 1975 and 1981. Among these women, the multivariate adjusted HRs were 1.10 (95% CI, 0.59-2.05), 1.00 (reference), and 0.28 (95% CI, 0.09-0.88; Table 2). There was also evidence of a trend of decreasing incidence with increasing sleep duration ($P = 0.03$).

Insufficient sleep and sleep quality were not significantly associated with breast cancer risk (Tables 3 and 4). When the main cohort analyses of sleep factors and breast cancer were repeated with all twin pairs discordant for breast cancer, none of the sleep factors were statistically significantly related to breast cancer risk (data not shown).

Discussion

Overall, there was no statistically significant change in breast cancer risk by sleep duration among all women who answered the question on sleep duration in 1975. However, consistently in all analyses, the risk estimates for breast cancer were lower in long sleepers compared with average sleepers. When the analysis was

Table 2. Sleep duration and breast cancer risk in a cohort of Finnish women, 1976 to 1996

	No. of women (*n* = 12,222)	No. of breast cancers	Age-adjusted HR (95% CI)	Multivariable HR (95% CI)*
Sleep duration in 1975, follow-up 1976 to 1996, seven-category classification				
≤4 h	44	1	0.73 (0.10-5.32)	0.88 (0.11-6.91)
5 h	183	5	0.81 (0.32-2.03)	0.91 (0.36-2.32)
6 h	954	17	0.66 (0.40-1.11)	0.74 (0.44-1.26)
7 h	3,473	68	0.84 (0.63-1.13)	0.81 (0.60-1.10)
8 h (reference)	5,580	120	1.00	1.00
9 h	1,650	25	0.73 (0.48-1.13)	0.64 (0.40-1.02)
≥10 h	338	6	0.82 (0.36-1.88)	0.65 (0.24-1.75)
P for linear trend (categorical)			0.51	0.88
Sleep duration in 1975, follow-up 1976 to 1996, three-category classification				
≤6 h	1,181	23	0.74 (0.48-1.15)	0.85 (0.54-1.34)
7-8 h (reference)	9,053	188	1.00	1.00
≥9 h	1,988	31	0.80 (0.55-1.17)	0.69 (0.45-1.06)
P for linear trend (categorical)			0.94	0.34
Subjects with the same sleep duration in 1975 and 1981, follow-up 1976 to 1996				
≤6 h	476	14	1.03 (0.57-1.84)	1.10 (0.59-2.05)
7-8 h (reference)	6,386	125	1.00	1.00
≥9 h	534	7	0.62 (0.29-1.33)	0.28 (0.09-0.88)
P for linear trend (categorical)			0.31	0.03

*Adjusted for the effects of age, zygosity, social class, number of children, use of oral contraceptives, body mass index, alcohol use, smoking, and physical activity.

Table 3. Insufficient sleep and breast cancer risk in a cohort of Finnish women, 1982 to 1996

Insufficient sleep in 1981	Hours of sleep, mean (median)	No. of women (n = 10,844)	No. of breast cancers	Age-adjusted HR (95% CI)	Multivariable HR (95% CI)*
No lack of sleep (<1 h, reference)	7.8 (8.0)	8,532	138	1.00	1.00
Lack of sleep ≥1 h	7.1 (7.0)	2,312	41	1.17 (0.82-1.67)	1.19 (0.84-1.70)
1 h increase in lack of sleep (0-4 h)	7.6 (7.5)	9,042	144	1.11 (0.86-1.43)	1.12 (0.87-1.45)

*Adjusted for the effects of age, zygosity, social class, number of children, use of oral contraceptives, body mass index, alcohol use, smoking, and physical activity.

restricted to those women who reported the same sleep duration in 1975 and in 1981, we observed a significantly lower risk in women who reported a long duration of sleep (≥9 hours/night) compared with the average duration of 7 or 8 hours. No statistically significant effects were observed for sleep insufficiency and sleep quality.

The major strengths of the present study are that it was prospective in nature, and that we were able to assess sleep duration at two points in time (in 1975 and in 1981). Although some women may have inaccurately reported their sleep duration on either or both of the questionnaires in 1975 and 1981, measurement error seem less likely among the women who reported the same sleep duration in both years. Women who reported in 1981 a sleep duration that was different from that in 1975 may have reported a true change. Reasons for such changes are interesting in their own right (whether due to changes in family structure, occupational environment, or other factors), and for their possible relationship to long-term health. However, the women reporting the same sleep duration on both questionnaires represent the study's exposure of interest more accurately.

The results were adjusted for most known risk factors of breast cancer, although some residual confounding due to factors such as a sedentary life-style, high alcohol consumption, or family history of breast cancer cannot be fully excluded. Likewise, modifying effects by unmeasured characteristics of exposure (lighting in sleeping environment; sleep during the day), woman (menopausal status; or hormonal rhythms), or cancer (estrogen and progesterone status) could not be investigated.

The present study is, to our knowledge, the first to report of an association between sleep length and breast cancer incidence. Other epidemiologic research lines have addressed the question of (inverse) relationship between melatonin and breast cancer using differing approaches. For instance, positive associations between shift work and breast cancer risk have been observed in several studies (30–33). Further indirect support for the melatonin hypothesis comes from studies on blind women who are not sensitive to changes in light (34–37). These studies show an ~20% to 50% reduced risk of breast cancer among. Direct epidemiologic evidence for an association between melatonin and breast cancer risk is available from two studies. The first nested case-control study investigated the association between breast cancer and 6-sulfatoxymelatonin levels in 24-hour urine samples in 127 cases and 253 controls (38). This study reported an odds ratio of 0.95 (95% CI, 0.55-1.65), comparing the middle category with the lowest category of 6-sulfatoxymelatonin, and an odds ratio of 0.99 (0.55-1.65), comparing the highest category with the

Table 4. Sleep quality and breast cancer risk in a cohort of Finnish women, 1976 to 1996

	No. of women (n = 12,084)	No. of breast cancers	Age-adjusted HR (95% CI)	Multivariable HR (95% CI)*
Sleep quality in 1975, follow-up 1976 to 1996				
Good	5,245	103	1.00	1.00
Fairly good	5,803	113	0.84 (0.64-1.10)	0.84 (0.63-1.12)
Fairly poor	787	16	0.66 (0.39-1.13)	0.78 (0.45-1.35)
Poor	249	8	0.99 (0.47-2.07)	1.15 (0.54-2.43)
P for linear trend (categorical)			0.21	0.52
Subjects with the same sleep quality in 1975 and 1981, follow-up 1976 to 1996				
Good	3,047	56	1.00	1.00
Fairly good	3,270	70	0.95 (0.67-1.35)	0.91 (0.62-1.32)
Fairly poor	219	5	0.75 (0.30-1.90)	0.89 (0.35-2.27)
Poor	58	3	1.58 (0.45-5.52)	1.87 (0.52-6.73)
P for linear trend (categorical)			0.92	0.97

*Adjusted for the effects of age, zygosity, social class, number of children, use of oral contraceptives, body mass index, alcohol use, smoking, and physical activity.

lowest category. A recent case-control study, nested within the Nurses' Health Study II cohort, measured the concentration of 6-sulfatoxymelatonin in the first morning urine of 147 women with invasive breast cancer and 291 matched controls (39), finding an odds compared ratio of 0.59 (95% CI, 0.36-0.97) for women in the highest quartile compared with those in the lowest. At least the single morning measurements have been shown to be reasonable markers for long-term melatonin levels (40).

As for biological mechanisms, one contributor to an inverse association between sleep duration and breast cancer risk could be the increased use of artificial light during the night (18). The original hypothesis was based solely on a light-induced suppression of melatonin leading to an as yet unproven increase in estradiol (18). However, many other environmental factors leading to alterations in sleep and/or secretion of melatonin (or other hormones) may also be of relevance.

Since 1987, it has become apparent that a light-at-night lowering of melatonin could have several different biological effects, apart from possibly raising estrogen. These include enhancement of estrogen's interaction with its receptor (41), changes in the metabolism of linoleic acid by tumor cells (42), and effects on immune function (43) and free radical biology (44). Light-at-night may also disrupt the clock gene apparatus yielding downstream changes in cell cycle regulation in the mammary tissue itself (17, 45, 46). For several of these potential mechanisms by which light-at-night may increase breast cancer risk, the prediction is that the longer the duration of dark at night, the lower the risk.

Sleep may also have an impact on breast cancer risk through changes in other circadian rhythms (47). Experimental studies have reported changes, e.g., in the secretion of cortisol (19–21)—another hormone that may have relevance to breast cancer. Rhythmic properties are also encountered in the secretion of dopamine, somatotropin secretion and growth hormone. The epidemiology of breast cancer has thus far largely focused on the role of estrogens, whereas the relations of these other hormones with breast cancer remain widely unknown.

In conclusion, the suggestion of lower breast cancer risk in long sleepers in the Finnish Twin Cohort adds to the body of evidence for a possible anticarcinogenic effect of melatonin. From a public health perspective, insomnia, and other sleep disturbances (rather than excessive sleep) have traditionally been known to impair the mental well-being and quality of life and also to have more life-threatening consequences such as motor vehicle and occupational accidents (3). In contrast, the 2004 review by Youngstedt and Kripke of 26 epidemiologic studies on the association between self-reported sleep duration and subsequent risk of death, draw attention to the adverse effects of long sleep (48). The reviewed epidemiologic studies showed consistently that sleeping >8 hours per night is associated with increased mortality. Thus, the findings of the present study may potentially complicate the public health implications of long sleep further: even if long sleep is associated with increased mortality, it might be protective from breast cancer.

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