Dietary correlates of urinary 6-sulfatoxymelatonin concentrations in the Nurses' Health Study cohorts[1–3]

Eva S Schernhammer, Diane Feskanich, Caroline Niu, Regina Dopfel, Michelle D Holmes, and Susan E Hankinson

ABSTRACT

Background: Age and certain lifestyle factors, including a higher body mass index and exposure to light at night, are related to lower circulating concentrations of melatonin—a hormone with probable cancer-protective properties. Although melatonin is a direct derivative of the essential amino acid tryptophan, little is known about the relation of diet with melatonin concentrations.

Objective: The objective was to examine cross-sectional associations of various nutrients and dietary factors as well as food groups with creatinine-adjusted first morning urinary melatonin (6-sulfatoxymelatonin; aMT6s) concentrations.

Design: Participants were 998 healthy women from 2 independent cohorts: the Nurses' Health Study (NHS; $n = 585$) and NHS II ($n = 413$). We computed least-squares mean hormone concentrations across categories of dietary variables, with adjustment for total energy intake, age, and other nondietary factors known to be associated with aMT6s concentrations.

Results: In multivariate analyses, we found no significant associations between the intake of various nutrients, including tryptophan and urinary melatonin concentrations. A higher intake of meat, particularly red meat, was associated with lower concentrations of aMT6s (adjusted mean concentrations of aMT6s across increasing quartiles of red meat intake were 17.9, 17.0, 18.1, and 15.3 ng/mg creatinine; P for trend = 0.02). In contrast, neither poultry intake (including turkey) nor fish intake was associated with aMT6s concentrations.

Conclusion: Although no specific nutrients were associated with altered concentrations of melatonin, our findings raise the possibility that several specific foods, including red meat, could affect cancer risk through the lowering of melatonin concentrations. *Am J Clin Nutr* 2009;90:975–85.

INTRODUCTION

Melatonin (5-methoxytryptamine) has oncostatic properties (1–3) and is secreted by the pineal gland predominantly during the dark phase of the light-dark cycle, after a rhythm of ≈24 h (4). Serum melatonin is rapidly metabolized, mainly in the liver (5), and is excreted by the kidneys as melatonin's major urinary metabolite, 6-sulfatoxymelatonin (aMT6s). In contrast with single plasma or saliva melatonin measures, aMT6s measured in first morning samples accurately reflects peak plasma melatonin concentrations of the previous night (6, 7), which makes it a very practical marker, especially in large-scale epidemiologic studies.

Apart from circadian variation, there is also considerable interindividual variation in circulating melatonin. For example, night work, which (through exposure to light at night) appears to increase cancer risk (8–12), has been associated with lower melatonin concentrations (13–17). Other potentially modifiable factors that have been linked to lower melatonin concentrations include older age, a higher body mass index (BMI), nulliparity, and smoking (18–20).

Tryptophan, the precursor of melatonin, cannot be produced by humans and therefore must be part of their diet. Thus, foods high in tryptophan such as milk, poultry (including turkey), fish, sesame seeds, beans, lentils, rice, and certain nuts may be associated with variations in melatonin concentrations. Few studies have explored the influence of these and other nutritional factors on melatonin concentrations. The aim of our study was to examine dietary factors that were previously shown or seem likely to affect melatonin concentrations. We examined the cross-sectional associations of food and nutrient intakes and dietary patterns with melatonin concentrations in 998 healthy women using 2 large prospective databases—the Nurses' Health Study (NHS) cohorts.

SUBJECTS AND METHODS

Study cohorts

Nurses' Health Study

In 1976, 121,700 female registered nurses from 11 large US states, ages 30–55 y and of primarily white descent, were enrolled in the NHS. Since baseline, they have completed biennial mailed questionnaires that comprise items about their health status, medical history, and known or suspected risk factors for cancer (21) and heart disease (22). Diet was assessed every 4 y with a food-frequency questionnaire (FFQ). Between 2000 and 2002, first spot morning urine samples without specifically requesting first voids were collected from 18,643 women. The samples were

[1] From the Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA (ESS, DF, CN, MDH, and SEH); the [2]Department of Epidemiology, Harvard School of Public Health, Boston, MA (ESS and SEH); and LBI-ACR VIEnna & ACR-ITR VIEnna, Vienna, Austria (ESS); and Harvard University, A.L.M Program, Biological Sciences, Cambridge, MA (RD).

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[3] Address correspondence to ES Schernhammer, Channing Laboratory, 181 Longwood Avenue, Boston, MA 02115. E-mail: eva.schernhammer@channing.harvard.edu.

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returned by overnight mail, with a frozen water bottle to keep them cool. On arrival in the laboratory, the samples were separated into aliquots into labeled 4.5-mL cryotubes. The tubes were then stored in the vapor phase of liquid nitrogen freezers without preservative. Further details of the NHS were published previously (23, 24).

Nurses' Health Study II

NHS II is a prospective cohort study that started in 1989, when 116,430 registered female US nurses aged 25–42 y were enrolled. Similar to NHS, all participants have been followed biennially with the use of a mailed questionnaire and every 4 y with an FFQ. Further details of the cohort are described elsewhere (25). From 1996 to 1999, 29,616 of these women participated in the urine collection substudy for the NHS II cohort. For the women who participated in this study, a spot morning urine sample was collected a mean (±) SD of 7.4 ± 3.1 d before the next menstrual cycle. Urine collection methods were identical to those used in the NHS.

Diet and covariate assessment

Dietary data were derived from the FFQ, which has been described in detail and its validity and reproducibility have been documented elsewhere (26). For food and nutrient intakes, we used the average of the 1998 and 2002 data in NHS and the 1995 and 1999 data in NHS II because in a previous study of dietary correlates of steroid hormone concentrations in NHS, we found that associations were stronger for the average of the 2 dietary assessments than for the 1 closest to urine collection (27), likely because averaging 2 measurements of dietary intake reduces random error. Only one FFQ contributed to the food and nutrient intakes in 6% of the study population because of a missing response. Nutrient intakes were total energy adjusted by using the residual method (28) and categorized into quintiles. We report results for the total nutrient (which includes supplement intake), because associations for nutrient intake from food sources only were very similar to those for total nutrient intake. Because the FFQ allows 9 choices of frequency of consumption for foods, the distribution of intake for a specific food is more discontinuous than that of nutrients because nutrients can come from many foods. Therefore, foods were divided into approximate quartiles or tertiles of intake. Generally, cohort-specific cutoffs for quantiles were created. Further details on specific categories and questions of the NHS questionnaires are available at http://www.channing.harvard.edu/nhs/questionnaires/index.shtml.

On the basis of the correlation of food, we determined dietary pattern factors by means of principal component analysis, as described in detail in earlier studies from the NHS cohorts (29–31). In brief, we collapsed 116 food items collected by FFQ in the NHS cohort to 38 foods or food groups on the basis of the similarity of nutrient composition and biological origin. Details of food groupings are described in detail elsewhere (32). We then used SAS PROC FACTOR to conduct a principal component analysis. For better interpretability, we used an orthogonal rotation procedure that results in factors (ie, dietary patterns) that are not correlated with each other. Based on the amount of variation explained by each pattern, we determined the number of factors to retain and identified 2 major dietary patterns: the "prudent" pattern and the "Western" pattern, as described previously (29–31). Using the average of data from 2 FFQs, each individual received a score for both patterns with a higher score suggesting better adherence to a certain dietary pattern.

All other covariates were assessed closest to the time of urine collection. Information on parity, age at first birth, age at menopause, smoking status, current weight, family history of breast cancer, personal history of benign breast disease, and physical activity were taken from the 2002 (NHS) and 1999 (NHSII) questionnaires. Physical activity was measured with a validated questionnaire (33) in MET-h/wk. BMI was calculated as weight (in kg) divided by height (in m) squared.

Urine collection

The vast majority (92% in NHS II and 95% in NHS) of all urine samples were first morning urine samples. After collection, the samples were returned by overnight mail, with a frozen water bottle to keep them cool. Women also noted the date of collection and the number of nights worked in the prior 2 wk. On arrival in the laboratory, the samples were portioned into aliquots and stored at ≤ -130°C without preservative. We previously showed that concentrations of urinary aMT6s remain stable when processing is delayed for 24 and even 48 h (20).

Study population

Study participants were selected from among 1042 women for whom urinary melatonin was previously assessed: 376 NHS II control subjects who participated in a nested case-control study of urinary melatonin concentrations and breast cancer risk (1), 80 NHS II premenopausal women who took part in the previously described validation study (20), and 586 NHS women who participated in a nested case-control study of urinary melatonin concentrations and postmenopausal breast cancer risk (34). Of these, 40 women were excluded because they reported having worked a rotating night shift during the 2 wk preceding urine collection, and 4 women were excluded because of missing dietary information, which left 998 women with valid data for our analyses. Participants had no previously diagnosed cancer (except nonmelanoma skin cancer). A woman was defined as premenopausal if she had had at least one natural menstrual cycle during the previous 12 mo or was younger than 48 y (if she was a nonsmoker) or younger than 46 y (if a current smoker) after hysterectomy without bilateral oophorectomy. At these ages, $<10\%$ of the NHS cohort had had a natural menopause. A woman was defined as postmenopausal if she reported a natural menopause or bilateral oophorectomy. The study was approved by the Committee on the Use of Human Subjects in Research at the Brigham and Women's Hospital.

Laboratory methods

Urinary aMT6s was assayed by the Endocrine Core Laboratory of M Wilson (Yerkes National Primate Research Center, Emory University, Atlanta, GA) by using Bühlmann 6-SMT enzyme-linked immunosorbent assay kits (ALPCO, Windham, NH). This commercially available aMT6s enzyme-linked immunosorbent assay kits is a competitive immunoassay using an antibody-capture technique with a lower detection limit of 0.8 ng/mL for aMT6s. Because urine samples were not collected over a 24-h period and total urinary output was unknown, creatinine

concentrations were also measured for each sample by the same laboratory, using Sigma Diagnostics creatinine reagents. All aMT6s concentrations were creatinine-standardized (aMT6s concentration divided by concentration of creatinine) to account for differences arising from variations in urine concentrations. To assess the reproducibility of the laboratory methods, masked split specimens included within each batch (10% of the total samples) were used to calculate the CV within batches. Within-batch CVs among the case control samples ranged between 9.5% and 15% for urinary aMT6s and between 3.1% and 9% for creatinine (1, 20).

Urine samples were collected from 113 randomly selected participants in the NHS II cohort who were *1*) premenopausal, *2*) had not used oral contraceptives or other hormonal preparations (eg, for infertility) in the previous 6 mo, *3*) had not been pregnant or lactating in the previous 6 mo, and *4*) had no history of cancer (except nonmelanoma skin cancer). Samples consisted of 3 complete sets of luteal urine collected over a 3-y period: the initial sample collection in 1996 and 2 additional samples in 1998 and 1999. For a randomly selected 80 of these 113 women, aMT6s concentrations were assessed for all 3 samples and were found to be reasonably well correlated over time (intraclass correlation: 0.72; 95% CI: 0.65, 0.82) (20).

Statistical analysis

If aMT6s measurements were below the detection limit of the assay (0.8 pg/mL), which was the case for 10 women from NHS II and 27 from NHS, these measurements were set equal to the detection limit as a conservative estimate, before the value was normalized to creatinine concentrations. We used the natural logarithms of urinary aMT6s in the analyses because the transformed values were more normally distributed.

We categorized nutrient intakes, food consumption (reported in servings/d), and diet pattern factors into quartiles and quintiles. Because cohort-specific quantiles were almost identical to overall quantiles, we present quantiles based on all women combined. In multivariate analyses, we adjusted for cohort, total energy intake (kcal/d in quintiles), age in 8 categories ($<$45, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, and $\geq$75 y), parity (nulliparous, 1–2, 3–4, and $\geq$5), BMI (in kg/m^2; $<$21, 21–22.9, 23–24.9, 25–29.9, and $\geq$30), smoking status (never or past smoker and current smoker), and time of urine collection (first morning urine or not). We first evaluated the age- and total energy intake–adjusted associations of aMT6s with macronutrients, vitamins, several food groups, and the prudent and Western dietary patterns by cohort. Next, in models based on the combined data set, we included an indicator variable for type of cohort, time of urine collection, and other factors previously shown to be associated with urinary melatonin concentrations (age, parity, BMI, and smoking). Because the results of multivariate analyses were not vastly different, we chose to present only those here. Moreover, in secondary analyses, excluding the $\leq$8% of women whose urine samples were not first morning samples, the results were virtually unchanged; therefore, we kept them in our primary analyses. Because the findings were essentially the same between the 2 cohorts, we present results of both cohorts combined only.

Statistical analyses were performed with SAS software (version 9.1; SAS Institute, Cary, NC). To test for differences in aMT6s concentrations by categories of covariates, we used mixed-effects regression models for clustered data (PROC MIXED) with nurses' ID as the clustering variable, to adjust for possible confounding due to other lifestyle and reproductive factors (35). We report *P* values for the linear trend across food or nutrient intake calculated with median intake in each quintile as a continuous variable. All *P* values were based on 2-sided tests and were considered statistically significant if $\leq$0.05.

RESULTS

There were 998 women included in the study. Participants ranged in age from 34 to 80 y at urine collection. Women in the NHS II were, on average, younger and more likely to be premenopausal (28.1% compared with 1.4%) than were women from within the NHS cohort. Other differences between the 2 cohorts were only modest. Across both cohorts, 19.3% of all women were obese (BMI $\geq$ 30), with a median BMI of 24.9 (10th to 90th percentile: 20.5–33.0), and 4.9% were currently smoking. The median value for aMT6s was 19.1 ng/mg creatinine (10th to 90th percentile: 4.5–48.3). Median total energy intake was 1750 kcal/d (10th to 90th percentile: 1183–2444 kcal/d). The distributions of other covariates are described in **Table 1** and elsewhere (19).

Overall, there were no significant associations between the examined nutrient intakes and circulating melatonin (**Table 2** and **Table 3**). None of the individual fats examined, including total fat, were associated with aMT6s. Furthermore, none of the other vitamins and nutrients we examined or the total caloric intake or intake of caffeine appeared to be related to aMT6s. Also, dietary tryptophan intake was not associated with circulating aMT6s concentration (Table 2).

Next, we examined 10 different food groups (Table 3). Overall, neither fruit nor vegetable intake was related to aMT6s. When examining individual sources of fruit and vegetable consumption (data not shown), $\geq$1 small glass of orange juice/d appeared to be associated with higher aMT6s concentrations compared with no orange juice consumption, though the trend test was not significant (bottom compared with top quartile of orange juice, with the top quartile representing $\geq$1 small glass of orange juice/d: aMT6s = 14.9 compared with 18.4 ng/mg creatinine; *P* for difference = 0.01 and *P* for trend = 0.25). In contrast, increasing servings of tomato intake lowered aMT6s concentration (bottom compared with top quartile of tomato intake, with the top quartile representing $\geq$1 tomato/d: aMT6s = 17.8 compared with 16.6 ng/mg creatinine; *P* for trend = 0.02). No other individual fruit or vegetable was associated with aMT6s.

Total meat intake (bottom compared with top quartile: aMT6s = 17.8 compared with 15.5 ng/mg creatinine; *P* for trend = 0.04), and specifically intake of red meat (bottom compared with top quartile: aMT6s = 17.9 compared with 15.3 ng/mg creatinine; *P* for trend = 0.02), were associated with significantly lower aMT6s concentrations, whereas intake of poultry (including chicken and turkey) showed no association with aMT6s (bottom compared with top quartile: aMT6s = 18.0 compared with 17.8 ng/mg creatinine; *P* for trend = 0.88).

Neither dairy products overall (data not shown) nor milk or cheese individually were associated with aMT6s (Table 3). However, women who reported a higher intake of dairy cream had significantly lower melatonin concentrations than did those

TABLE 1
Characteristics at the time of urine collection for 998 healthy women from 2 large prospective cohorts[1]

Characteristic	Nurses' Health Study (n = 585)	Nurses' Health Study II (n = 413)	P for difference[2]
Age (y)	66.9 ± 6.9[3]	43.7 ± 3.2	<0.001
Age at menarche <12 y (%)	14.0	9.5	0.35
Premenopausal (%)	1.4	28.1	<0.001
No. of births[4]	3.1 ± 1.3	2.3 ± 1.0	<0.001
BMI (kg/m^2)	26.5 ± 5.2	25.3 ± 5.6	0.001
Alcohol consumed (g/d)	5.4 ± 9.1	4.3 ± 6.2	0.02
Current smoker (%)	4.1	6.1	0.16
Energy intake (kcal/d)	1758 ± 476	1820 ± 481	0.04
First morning urine (%)	95.3	92.0	0.01
aMT6s concentration (ng/mg creatinine)	28.6 ± 37	20.8 ± 15	<0.001
Urinary creatinine (mg/L)	638 ± 392	1020 ± 545	<0.001

[1] aMT6s, 6-sulfatoxymelatonin.
[2] Derived with a chi-square test (proportions) or t test (continuous variables).
[3] Mean ± SD (all such values).
[4] Among parous women only.

with lower intakes (bottom compared with top tertile of cream intake: aMT6s = 18.2 compared with 15.9 ng/mg creatinine; P for trend = 0.01). Last, in analyses evaluating whether a prudent or Western dietary pattern score was associated with aMT6s, neither of the 2 dietary patterns showed significant associations with aMT6s (data not shown).

DISCUSSION

In our evaluation of various nutrients and food groups and their association with circulating melatonin, we observed few significant associations. Besides marginal associations between orange juice, tomato, and dairy cream consumption and aMT6s, only meat consumption was significantly and inversely associated with aMT6s concentrations in these 2 cohorts of women.

Several studies have determined that tryptophan or melatonin is found in foods and edible plants. Melatonin was identified in the edible organs of wild tomato and domestic tomato, rice, orange, apple, banana, cucumber, cabbage, and beetroot, ranging between 2 and 5300 pg/g (36, 37). Concentrations were highest in seeds of *Poaceae* [eg, rice and oat (37)] and in fresh cherries (38), whereas they tended to be low in banana and pineapple (39, 40). Melatonin was also identified in 5 species of green algae (41)—foods that are commonly eaten in Asia. Seeds from 15 edible plants have further been found to have melatonin (39). Ranging between 2 and 190 ng/g dry weight of seed, the highest concentrations were found in black (*Brassica nigra*) and white (*Brassica hirta*) mustard, with 189 and 129 ng/g dry weight of seed, respectively. All other seeds contained melatonin at varying lower concentrations, including almond (39 ng/g dry seed), sunflower (29 ng/g dry seed), fennel (28 ng/g dry seed), and green cardamom (15 ng/g dry seed). Furthermore, 64 commonly used Chinese medicinal herbs assayed for presence of melatonin had melatonin concentrations >10 ng/g dry weight (42). Tryptophan, on the other hand, is contained by the medicinal plants feverfew (*Tanacetum parthenium*), St John's Wort (*Hypericum perforatum*), and *Aloe vera* (43–45). Feeding chicks with melatonin-rich plants was shown to increase their circulating melatonin concentrations (37).

The role of fasting in changing melatonin concentrations is not well understood. Whereas some animal models seem to suggest that caloric restriction can delay the age-associated decline of melatonin concentrations (46, 47), others describe an association of lower melatonin concentrations with caloric restriction (48). Moreover, a sharp decline in plasma melatonin concentrations under high-caloric diet conditions has been found among rats (49). More recently, fasting conditions were shown to up-regulate the expression of melatonin receptor MT1 mRNA in the rat intestine (50). Human studies that have tested these hypotheses have been small and inconclusive, but nonetheless support the hypothesis that fasting decreases melatonin concentrations (51) and seems to suggest that fasting can advance the circadian clock (52). None of our participants may have been truly calorie restricted, but our study does not support an association between caloric intake and circulating melatonin in these well-nourished women.

In prior animal studies, zinc (53) and folate (54) deficiency appeared to reduce melatonin concentrations, whereas supplementation of zinc (53), tryptophan, and vitamin B-6 (49) increased circulating melatonin concentrations. In humans, the role of minerals and vitamins in changing melatonin concentrations is less well studied. In Japanese perimenopausal women, folate intake as assessed via FFQ was not associated with urinary aMT6s concentrations (P = 0.10) (37). Similarly, we did not observe an association between folate intake, nor was zinc or vitamin B-6 intake significantly associated with urinary melatonin in our study.

The only other study, to date, to evaluate associations between plant intake and circulating melatonin in humans—a study of 289 community-dwelling Japanese women (mean age: 48 y)—found a higher intake of vegetables to be associated with higher urinary aMT6s concentrations (55). Specifically, mean aMT6s concentrations, as measured in first morning urine sample, were 32.7 ng/mg creatinine among the women with the lowest quartile of green and yellow vegetable intake and 38.3 ng/mg creatinine among women in the highest quartile, after adjustment for age, BMI, smoking status, and many other important covariates. Similar to our findings, the Japanese study did not observe an association

TABLE 2
Multivariate-adjusted mean concentrations of 6-sulfatoxymelatonin (aMT6s), by quintile (Q) of total energy and nutrient intakes, and *P* values for the linear trend across quintiles among 998 women from the Nurses' Health Study (NHS; $n = 582$) and NHS II ($n = 413$)[1]

Dietary variable within quintiles	aMT6s			
	Geometric mean	Lower level of 95% CI	Upper level of 95% CI	P^2
	ng/mg creatinine			
Total energy				0.24
Q1: <1353 kcal/d	17.6	15.5	20.0	
Q2: 1353–1632 kcal/d	18.3	16.2	20.7	
Q3: 1633–1882 kcal/d	16.8	14.8	19.1	
Q4: 1883–2159 kcal/d	16.3	14.4	18.5	
Q5: >2159 kcal/d	16.4	14.5	18.6	
Total fat				0.87
Q1: <44.9 g/d	16.9	14.9	19.2	
Q2: 44.9–51.3 g/d	17.6	15.6	19.9	
Q3: 51.4–57.4 g/d	16.9	14.8	19.3	
Q4: 57.5–64.5 g/d	17.0	14.8	19.4	
Q5: >64.5 g/d	16.9	14.9	19.2	
Animal fat				0.22
Q1: <19.2 g/d	18.3	15.9	21.0	
Q2: 19.2–23.9 g/d	16.2	14.2	18.6	
Q3: 24.0–28.2 g/d	17.8	15.6	21.3	
Q4: 28.3–34.3 g/d	17.8	15.9	20.0	
Q5: >34.3 g/d	15.4	13.3	17.7	
Vegetable fat				0.94
Q1: <21.7 g/d	17.7	16.1	20.2	
Q2: 21.7–25.4 g/d	17.6	15.5	19.9	
Q3: 25.5–29.1 g/d	15.4	13.4	17.7	
Q4: 29.2–33.7 g/d	16.7	14.7	19.1	
Q5: >33.7 g/d	17.9	15.7	20.4	
Saturated fat				0.43
Q1: <13.9 g/d	17.6	15.5	20.3	
Q2: 13.9–16.4 g/d	16.7	14.6	19.0	
Q3: 16.5–18.6 g/d	16.8	14.8	19.1	
Q4: 18.7–21.9 g/d	18.8	16.8	21.1	
Q5: >21.9 g/d	15.5	13.4	17.9	
Monounsaturated fat				0.79
Q1: <16.8 g/d	17.0	14.9	19.3	
Q2: 16.8–19.9 g/d	16.2	14.2	18.5	
Q3: 20.0–22.4 g/d	18.7	16.5	21.2	
Q4: 22.5–26.2 g/d	17.6	15.6	19.8	
Q5: >26.2 g/d	16.1	14.1	18.4	
Polyunsaturated fat				0.79
Q1: <9.55 g/d	16.9	15.1	19.0	
Q2: 9.55–11.05 g/d	17.6	15.6	19.7	
Q3: 11.06–12.58 g/d	16.7	14.7	18.9	
Q4: 12.59–14.65 g/d	16.4	14.3	18.8	
Q5: >14.65 g/d	17.8	15.5	20.4	
trans-Unsaturated fat				0.22
Q1: <1.3 g/d	18.7	16.2	21.6	
Q2: 1.4–1.7 g/d	17.1	14.8	19.7	
Q3: 1.8–2.1 g/d	17.5	15.6	19.7	
Q4: 2.2–3.1 g/d	16.1	14.1	18.3	
Q5: >3.1 g/d	16.1	14.0	18.5	
Total omega-3 fats				0.82
Q1: <0.91 g/d	17.3	15.1	19.9	
Q2: 0.91–1.08 g/d	16.5	14.7	18.5	
Q3: 1.09–1.25 g/d	17.9	15.9	20.1	
Q4: 1.26–1.54 g/d	17.0	15.0	19.2	
Q5: >1.54 g/d	16.8	14.6	19.2	

(Continued)

TABLE 2 (*Continued*)

Dietary variable within quintiles	aMT6s			P^2
	Geometric mean	Lower level of 95% CI	Upper level of 95% CI	
		ng/mg creatinine		
Total protein				0.76
Q1: <62.5 g/d	17.8	15.3	20.6	
Q2: 62.5–69.9 g/d	16.7	14.6	19.0	
Q3: 70.0–77.0 g/d	16.6	14.7	18.7	
Q4: 77.1–85.2 g/d	17.6	15.6	19.9	
Q5: >85.2 g/d	16.7	14.6	19.2	
Animal protein				0.87
Q1: <39.1 g/d	17.4	15.1	20.0	
Q2: 39.1–45.6 g/d	16.4	14.4	18.8	
Q3: 45.7–52.4 g/d	17.2	15.1	19.5	
Q4: 52.5–61.4 g/d	17.9	15.9	20.2	
Q5: >61.4 g/d	16.5	14.4	18.9	
Vegetable protein				0.75
Q1: <19.9 g/d	16.8	14.8	19.1	
Q2: 19.9–22.2 g/d	16.8	14.7	19.1	
Q3: 22.3–24.6 g/d	17.5	15.5	19.7	
Q4: 24.7–27.9 g/d	17.0	14.9	19.4	
Q5: >27.9 g/d	17.3	15.3	19.6	
Carbohydrates				0.65
Q1: <199.1 g/d	16.5	14.3	19.0	
Q2: 199.1–216.5 g/d	17.9	15.7	20.4	
Q3: 216.6–232.5 g/d	16.4	14.4	18.6	
Q4: 232.6–251.0 g/d	16.9	15.0	19.1	
Q5: >251.0 g/d	17.7	15.7	20.0	
Fiber				0.69
Q1: <4.2 g/d	16.9	14.8	19.2	
Q2: 4.2–4.9 g/d	17.1	15.1	19.4	
Q3: 5.0–5.6 g/d	16.7	14.8	18.8	
Q4: 5.7–6.6 g/d	17.3	15.2	19.7	
Q5: >6.6 g/d	17.4	15.3	19.9	
Total vitamin D				0.74
Q1: <213.7 IU/d	15.8	14.0	17.8	
Q2: 213.7–363.3 IU/d	17.4	15.4	19.7	
Q3: 363.4–514.8 IU/d	17.5	15.4	19.8	
Q4: 514.9–656.4 IU/d	19.0	16.7	21.7	
Q5: >656.4 IU/d	15.9	13.9	18.2	
Total calcium				0.31
Q1: <839 mg/d	16.6	14.6	18.9	
Q2: 839–1125 mg/d	16.8	14.9	18.9	
Q3: 1126–1386 mg/d	17.7	15.7	20.0	
Q4: 1387–1763 mg/d	15.7	13.8	17.9	
Q5: >1763 mg/d	18.8	16.4	21.5	
α-Carotene				0.61
Q1: <415.5 μg/d	17.1	15.3	19.3	
Q2: 415.5–615.9 μg/d	15.7	13.9	17.7	
Q3: 616.0–819.9 μg/d	19.2	16.9	21.8	
Q4: 820.0–1170 μg/d	15.7	13.8	17.8	
Q5: >1170 μg/d	17.9	15.6	20.4	
β-Carotene				0.79
Q1: <2549 μg/d	16.8	14.9	18.8	
Q2: 2549–3546 μg/d	15.8	14.0	18.0	
Q3: 3547–4472 μg/d	18.8	16.6	21.3	
Q4: 4473–5959 μg/d	17.2	15.2	20.0	
Q5: >5959 μg/d	16.9	14.8	19.3	

(Continued)

TABLE 2 (*Continued*)

Dietary variable within quintiles	aMT6s			P^2
	Geometric mean	Lower level of 95% CI	Upper level of 95% CI	
		ng/mg creatinine		
β-Cryptoxanthin				0.20
Q1: <80.5 μg/d	16.3	14.4	18.5	
Q2: 80.6–119.8 μg/d	16.0	14.0	18.2	
Q3: 119.9–178.1 μg/d	17.6	15.6	20.0	
Q4: 178.2–245.7 μg/d	17.8	15.7	20.1	
Q5: >245.7 μg/d	17.9	17.5	20.3	
Lutein/zeaxanthin				0.46
Q1: <1587 μg/d	16.6	14.7	18.7	
Q2: 1587–2198 μg/d	18.1	16.0	20.5	
Q3: 2199–2917 μg/d	15.1	13.3	17.2	
Q4: 2918–3959 μg/d	18.0	15.7	20.4	
Q5: >3959 μg/d	17.9	15.6	20.2	
Lycopene				0.96
Q1: <3476 μg/d	18.3	16.0	20.9	
Q2: 3476–4939 μg/d	16.1	14.1	18.4	
Q3: 4940–6517 μg/d	17.7	15.7	20.0	
Q4: 6518–9153 μg/d	15.7	13.8	17.8	
Q5: >9153 μg/d	17.8	15.6	20.3	
Total retinol				0.49
Q1: <1553 IU/d	16.5	14.6	18.7	
Q2: 1553–2716 IU/d	17.2	15.3	19.5	
Q3: 2717–3913 IU/d	16.3	14.4	18.6	
Q4: 3914–5412 IU/d	17.7	15.5	20.1	
Q5: >5412 IU/d	17.6	15.5	20.0	
Total vitamin A[3]				0.20
Q1: <1258 μg RAE/d	16.1	14.3	18.0	
Q2: 1258–1772 μg RAE/d	17.2	15.1	19.6	
Q3: 1773–2346 μg RAE/d	16.0	14.1	18.1	
Q4: 2347–3068 μg RAE/d	17.6	15.5	20.0	
Q5: >3068 μg RAE/d	19.2	16.8	21.9	
Total vitamin C				0.34
Q1: <137.0 mg/d	16.2	14.4	18.2	
Q2: 137.0–198.9 mg/d	17.1	15.0	19.4	
Q3: 199.0–293.2 mg/d	17.3	15.2	19.7	
Q4: 293.3–614.4 mg/d	16.7	14.8	18.8	
Q5: >614.4 mg/d	18.1	15.7	20.9	
Total vitamin E as tocopherol				0.85
Q1: <8.1 mg/d	16.6	14.6	18.8	
Q2: 8.1–18.6 mg/d	16.2	14.3	18.5	
Q3: 18.7–108.1 mg/d	18.4	16.2	20.8	
Q4: 108.2–189.9 mg/d	18.1	16.1	20.4	
Q5: >189.9 mg/d	16.7	14.5	19.2	
Total zinc				0.73
Q1: <10.4 mg/d	16.3	14.4	18.5	
Q2: 10.4–13.6 mg/d	17.5	15.6	19.7	
Q3: 13.7–19.0 mg/d	16.8	14.8	19.1	
Q4: 19.1–24.9 mg/d	17.7	15.7	20.0	
Q5: >24.9 mg/d	17.0	14.7	19.7	
Total selenium				0.54
Q1: <0.01 μg/d	16.5	14.4	19.1	
Q2: 0.01–0.50 μg/d	18.1	15.9	20.6	
Q3: 0.51–9.80 μg/d	17.1	14.8	19.9	
Q4: 9.81–20.5 μg/d	15.4	13.6	17.5	
Q5: >20.5 μg/d	18.2	15.8	21.0	

(Continued)

TABLE 2 (*Continued*)

Dietary variable within quintiles	aMT6s			P^2
	Geometric mean	Lower level of 95% CI	Upper level of 95% CI	
	ng/mg creatinine			
Total folate				0.23
Q1: <422 μg/d	17.5	15.6	19.7	
Q2: 422–587 μg/d	15.6	13.8	17.7	
Q3: 588–743 μg/d	16.7	14.6	19.2	
Q4: 744–874 μg/d	16.6	14.5	19.0	
Q5: >874 μg/d	19.2	16.9	21.8	
Total vitamin B-6				0.61
Q1: <2.12 mg/d	17.8	15.8	20.0	
Q2: 2.12–3.15 mg/d	14.9	13.2	16.8	
Q3: 3.16–4.28 mg/d	19.2	16.9	21.9	
Q4: 4.29–14.9 mg/d	17.2	15.3	19.4	
Q5: >14.9 mg/d	16.5	14.4	19.0	
Caffeine				0.86
Q1: <28.5 mg/d	17.2	15.1	19.6	
Q2: 28.5–113.0 mg/d	17.2	15.1	19.6	
Q3: 113.1–193.0 mg/d	16.7	14.7	19.1	
Q4: 193.1–331.5 mg/d	17.5	15.6	19.7	
Q5: >331.5 mg/d	16.7	14.8	18.9	
Tryptophan				0.93
Q1: <0.71 g/d	17.4	15.0	20.2	
Q2: 0.71–0.79 g/d	17.1	14.9	19.6	
Q3: 0.80–0.88 g/d	16.2	14.2	18.5	
Q4: 0.89–0.99 g/d	17.6	15.6	19.8	
Q5: >0.99 g/d	17.0	14.8	19.6	

[1] All nutrients were adjusted for total energy intake (quintiles), cohort (NHS or NHS II), age (<45, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, and ≥75 y), parity (nulliparous, 1–2, 3–4, and ≥5), BMI (in kg/m^2; <21, 21–22.9, 23–24.9, 25–29.9, and ≥30), smoking status (never or past smoker and current smoker), and time of urine collection. RAE, retinol activity equivalent.

[2] *P* values representing the linear trend in aMT6s across nutrient intake were calculated with median intake in each quintile as a continuous variable.

[3] 1 μg RAE corresponds to 1 μg retinol, 2 μg β-carotene from supplements, 12 μg β-carotene from food, or 24 μg other dietary provitamin-A carotenoids.

between fruit intake and aMT6s concentrations (55), although no breakdown by specific fruit is provided. When we examined individual fruit and vegetables, we observed a positive association between orange juice consumption and an inverse association between tomato intake and melatonin. As opposed to other fruit intake, orange juice is commonly fortified with vitamin D in the United States, but vitamin D was not independently associated with aMT6 in our study. The tomato finding is contrary to what one would have expected and requires confirmation.

Animal models have suggested that the ingestion of walnuts increases circulating concentrations of melatonin (56); however, in the only other study in humans to date, no association between nut intake and first morning aMT6s concentrations was observed (37), which agrees with our finding of no association between nut intake and melatonin.

Ours was the first study to examine associations between dairy intake and circulating melatonin concentrations. We observed significantly lower melatonin concentrations in women with higher dairy cream consumption, but more studies are needed to confirm our finding.

Whether meat consumption affects circulating melatonin in humans has also not been studied to date. Earlier evidence supports a stronger association between red meat intake and premenopausal breast cancer risk than that in older women (57). That red meat consumption during early adult life increases breast cancer risk was previously described in the NHS II cohort (58), but there is now supportive new evidence from within the same cohort that red meat consumption, particularly if consumed during early adolescence, may increase the breast cancer risk later in life (59). Our findings of lower melatonin concentrations being associated with a higher intake of red meat could provide indirect mechanistic support for these associations, given prior evidence of an inverse association between circulating melatonin and breast cancer risk (1, 34, 60). Furthermore, although we observed no significant trend, the lower melatonin concentrations associated with a higher intake of animal and saturated fat in our data lend further support to this notion. Given ours is the first report on this association, again, confirmation is required.

The strengths of our study include its fairly large size and the extensive information on dietary and lifestyle factors collected over >30 y. A potential limitation of our study was its cross-sectional nature; there is no way to know whether factors associated with aMT6s concentrations determine those concentrations or are in fact determined by them. Moreover, because of

TABLE 3
Multivariate-adjusted mean concentrations of 6-sulfatoxymelatonin (aMT6s), by quartile (Q) or tertile (T) of food intake, and *P* values for linear trend across categories among 998 women from the Nurses' Health Study (NHS; *n* = 582) and NHS II (*n* = 413)[1]

Dietary variable[2] and range of intake within categories	aMT6s			*P*[3]
	Geometric mean	Lower level of 95% CI	Upper level of 95% CI	
		ng/mg creatinine		
Fruit				0.97
Q1: <1.30 servings/d	17.5	15.6	19.7	
Q2: 1.30–2.05 servings/d	15.8	14.1	17.8	
Q3: 2.06–2.88 servings/d	17.6	15.7	19.7	
Q4: >2.88 servings/d	17.4	15.6	19.5	
Vegetables				0.66
Q1: <2.45 servings/d	17.8	16.0	19.8	
Q2: 2.45–3.46 servings/d	16.8	15.1	18.7	
Q3: 3.47–4.73 servings/d	16.9	15.1	18.9	
Q4: >4.73 servings/d	16.9	14.9	19.1	
Total meat				0.04
Q1: <0.53 serving/d	17.8	15.8	20.1	
Q2: 0.53–0.81 serving/d	18.1	16.2	20.2	
Q3: 0.82–1.21 servings/d	17.1	15.3	19.1	
Q4: >1.21 servings/d	15.5	13.8	17.3	
Red meat				0.01
Q1: <0.21 serving/d	17.9	15.9	20.2	
Q2: 0.21–0.36 serving/d	17.0	15.2	19.1	
Q3: 0.37–0.60 serving/d	18.1	16.2	20.2	
Q4: >0.60 serving/d	15.3	13.7	17.2	
Poultry				0.88
Q1: <0.25 serving/d	18.0	16.1	20.1	
Q2: 0.25–0.39 serving/d	16.2	14.4	18.1	
Q3: 0.40–0.57 serving/d	16.3	14.7	18.2	
Q4: >0.57 serving/d	17.8	15.8	19.9	
Fish				0.53
Q1: <0.14 serving/d	17.1	15.3	19.1	
Q2: 0.14–0.18 serving/d	17.9	15.9	20.1	
Q3: 0.19–0.32 serving/d	16.0	14.5	17.7	
Q4: >0.32 serving/d	17.8	15.7	20.2	
Nuts				0.79
Q1: <0.10 serving/d	16.9	15.2	18.9	
Q2: 0.10–0.21 serving/d	17.5	15.6	19.5	
Q3: 0.22–0.47 serving/d	17.2	15.3	19.4	
Q4: >0.47 serving/d	16.6	14.8	18.7	
Cheese				0.96
Q1: <0.28 serving/d	16.8	15.1	18.7	
Q2: 0.28–0.46 serving/d	16.9	15.3	18.8	
Q3: 0.47–0.68 serving/d	17.1	15.1	19.3	
Q4: >0.68 serving/d	17.5	15.5	19.7	
Milk				0.51
Q1: <0.40 serving/d	17.2	15.4	19.1	
Q2: 0.40–0.90 serving/d	17.3	15.3	19.6	
Q3: 0.91–1.72 servings/d	16.9	15.0	18.9	
Q4: >1.72 servings/d	16.9	15.2	18.8	
Cream				0.01
T1: <0.03 serving/d	18.2	16.7	19.9	
T2: 0.03–0.07 serving/d	16.7	15.1	18.4	
T3: >0.07 serving/d	15.9	14.2	17.7	
Rice				0.45
Q1: <0.07 serving/d	17.1	14.8	19.8	
Q2: 0.07–0.11 serving/d	17.3	15.8	19.0	
Q3: 0.12–0.22 serving/d	17.4	15.4	19.5	
Q4: >0.22 serving/d	16.4	14.6	18.4	

(Continued)

TABLE 3 (*Continued*)

Dietary variable[2] and range of intake within categories	aMT6s			P^3
	Geometric mean	Lower level of 95% CI	Upper level of 95% CI	
	ng/mg creatinine			
Breads				0.88
Q1: <0.72 serving/d	16.8	15.0	18.8	
Q2: 0.72–1.11 servings/d	17.4	15.7	19.3	
Q3: 1.12–1.90 servings/d	16.9	15.1	19.0	
Q4: >1.90 servings/d	17.1	15.2	19.4	

[1] All dietary factors were adjusted for cohort (NHS or NHSII), age (<45, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, and ≥75 y), parity (nulliparous, 1–2, 3–4, and ≥5), BMI (in kg/m^2; <21, 21–22.9, 23–24.9, 25–29.9, and ≥30), smoking status (never or past smoker and current smoker), and time of urine collection.

[2] Serving sizes: fruit and vegetables, 1 serving ≈ 1 piece, 1/2 cup (118.5 mL), or a small glass (of juice); meat, 1 serving ≈ 4–6 oz; poultry, 1 serving ≈ 3 oz; fish, 1 serving ≈ 3–5 oz; nuts, 1 serving ≈ small packet or 1 oz; cheese, 1 serving ≈ 1 slice or 1 oz serving; milk, 1 serving ≈ 8 oz glass; dairy cream, 1 serving ≈ 1 Tbs (15 mL); rice, 1 serving ≈ 1 cup; and bread, 1 serving ≈ 1 slice. One ounce corresponds to 28.4 g.

[3] *P* values representing the linear trend in aMT6s across food intake were calculated with median intake in each category as a continuous variable.

the modest nature of our few significant *P* values and multiple comparisons, chance cannot be ruled out. In few instances, the collection of urine specimens may have preceded assessments of food and nutrient intakes. However, because we generally used the average of 2 assessments to reduce random error (1), it appears unlikely that both assessments would have preceded urine collection and we therefore do not expect this to have had a major affect on our results. Other limitations include the lack of information on the use of β-blockers and other drugs that may affect melatonin concentrations. Roughly 10% of the women in our study reported regular use of any antidepressants. We did not observe an association between antidepressants and aMT6s concentrations. However, assessment may have been incomplete; moreover, the type of antidepressant medication was unknown in our study. Another potential limitation is that we had only one measure of melatonin: although urinary aMT6s concentrations correlated well over time (20, 61, 62), the one-time measurement of melatonin limited our ability to take into account circadian phase, amplitude, and duration. Finally, it is conceivable that dietary tryptophan intake affects gastrointestinal production, but is not well reflected in circulating concentrations: administering tryptophan has induced melatonin synthesis and release in the gastrointestinal tract of chicks and rats (63), with the concentration of daytime melatonin in the gastrointestinal tissue surpassing blood concentrations by 10–100 times (64).

In summary, our data show a few associations between nutrients and food intake, requiring confirmation by other studies. Overall, they suggest that intake of meat may have the potential to alter circulating melatonin concentrations. Future studies should examine diet and melatonin associations in other populations, including Asians, because their diets may be richer in melatonin content than diets in the United States.

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