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Prolonged Nightly Fasting and Breast Cancer Prognosis

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IMPORTANCE Rodent studies demonstrate that prolonged fasting during the sleep phase positively influences carcinogenesis and metabolic processes that are putatively associated with risk and prognosis of breast cancer. To our knowledge, no studies in humans have examined nightly fasting duration and cancer outcomes.

OBJECTIVE To investigate whether duration of nightly fasting predicted recurrence and mortality among women with early-stage breast cancer and, if so, whether it was associated with risk factors for poor outcomes, including glucoregulation (hemoglobin A_{1c}), chronic inflammation (C-reactive protein), obesity, and sleep.

DESIGN, SETTING, AND PARTICIPANTS Data were collected from 2413 women with breast cancer but without diabetes mellitus who were aged 27 to 70 years at diagnosis and participated in the prospective Women's Healthy Eating and Living study between March 1, 1995, and May 3, 2007. Data analysis was conducted from May 18 to October 5, 2015.

EXPOSURES Nightly fasting duration was estimated from 24-hour dietary recalls collected at baseline, year 1, and year 4.

MAIN OUTCOMES AND MEASURES Clinical outcomes were invasive breast cancer recurrence and new primary breast tumors during a mean of 7.3 years of study follow-up as well as death from breast cancer or any cause during a mean of 11.4 years of surveillance. Baseline sleep duration was self-reported, and archived blood samples were used to assess concentrations of hemoglobin A_{1c} and C-reactive protein.

RESULTS The cohort of 2413 women (mean [SD] age, 52.4 [8.9] years) reported a mean (SD) fasting duration of 12.5 (1.7) hours per night. In repeated-measures Cox proportional hazards regression models, fasting less than 13 hours per night (lower 2 tertiles of nightly fasting distribution) was associated with an increase in the risk of breast cancer recurrence compared with fasting 13 or more hours per night (hazard ratio, 1.36; 95% CI, 1.05-1.76). Nightly fasting less than 13 hours was not associated with a statistically significant higher risk of breast cancer mortality (hazard ratio, 1.21; 95% CI, 0.91-1.60) or a statistically significant higher risk of all-cause mortality (hazard ratio, 1.22; 95% CI, 0.95-1.56). In multivariable linear regression models, each 2-hour increase in the nightly fasting duration was associated with significantly lower hemoglobin A_{1c} levels (β = −0.37; 95% CI, −0.72 to −0.01) and a longer duration of nighttime sleep (β = 0.20; 95% CI, 0.14-0.26).

CONCLUSIONS AND RELEVANCE Prolonging the length of the nightly fasting interval may be a simple, nonpharmacologic strategy for reducing the risk of breast cancer recurrence. Improvements in glucoregulation and sleep may be mechanisms linking nightly fasting with breast cancer prognosis.

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Breast cancer is the most common cause of cancer mortality among women in developing countries and the second most common cause of cancer mortality in developed countries.[1] While it is often presumed that a healthy diet will improve breast cancer outcomes, data on this hypothesis are mixed.[2-5] Much of the research has focused on what to eat to prevent cancer, such as specific foods, food groups, or dietary patterns. Recently, a novel theorem has emerged that when we eat also matters, with research showing that the timing of food intake influences metabolic health and cancer.[6-10] Landmark studies demonstrate that a recurring, prolonged (16-hour) fasting regimen during the sleep phase protects mice who were fed a high-fat diet against abnormal glucose metabolism, inflammation, and weight gain, all of which are associated with poor cancer outcomes.[11,12]

To our knowledge, epidemiologic data on nightly fasting duration and clinical outcomes are nonexistent. However, there are limited data from small trials in humans suggesting that many types of intermittent fasting regimens positively affect risk factors for poor breast cancer outcomes, such as glucoregulation, inflammation, obesity, and sleep.[8] Two analyses have been published of nightly fasting duration and biomarkers of breast cancer risk in women using US National Health and Nutrition Examination Survey data. In the first analysis, among 2122 women without diabetes mellitus, longer nightly fasting was associated with significant improvements in biomarkers of glycemic control.[9] In the second analysis, a longer duration of nightly fasting was associated with significantly lower C-reactive protein (CRP) concentrations in women who eat less than 30% of their total daily energy intake after 5 PM.[10] Taken together, the rodent and human data support the hypothesis that a prolonged nightly fasting interval could reduce cancer risk and improve cancer outcomes.

The Women's Healthy Eating and Living (WHEL) study of patients with breast cancer offers a unique opportunity to examine the influence of nightly fasting because dietary intake was assessed with 24-hour dietary recalls that documented timing of food consumption. We used data from the WHEL study to investigate whether a woman's usual nightly fasting duration was associated with breast cancer recurrence and mortality. We also examined mechanisms by which prolonged nightly fasting might improve breast cancer prognosis, such as glucoregulation, inflammation, obesity, and sleep.

Key Points

Question Does duration of nightly fasting predict breast cancer prognosis?

Findings In this cohort of 2413 patients with early-stage breast cancer, nightly fasting less than 13 hours was associated with a statistically significant 36% increased risk of breast cancer recurrence compared with nightly fasting more than 13 hours but was not associated with a statistically significant increased risk of breast cancer–specific and all-cause mortality.

Meaning Prolonging the length of the nightly fasting interval may be a dietary strategy to reduce risk of breast cancer recurrence in women.

Methods

Study Design and Sample

The WHEL study is a multisite randomized trial conducted between March 1, 1995, and May 3, 2007, enrolling 3088 patients who recently had early-stage invasive breast cancer. This trial aimed to test whether a diet rich in vegetables, fruit, and fiber and low in fat reduced the risk of breast cancer recurrence and mortality. The dietary intervention did not alter breast cancer prognosis during the trial's mean 7.3-year follow-up[3]; therefore, this investigation treats the WHEL study sample as a single cohort.

To be eligible for this analysis, women had time-stamped, 24-hour dietary recall data and complete data on key confounders (eg, breast cancer stage, age, or comorbidity status). This analysis excluded women who reported diabetes at baseline because antidiabetic treatments may confound associations between lifestyle and breast cancer outcomes.[13,14] The institutional review boards at each clinical site (University of California, San Diego; University of California, Davis; Stanford University; Kaiser Permanente, Northern California; M.D. Anderson Cancer Center; Arizona Cancer Center; and Kaiser Permanente Center for Health Research) approved the study protocol and consent forms, and all participants provided written informed consent.

Dietary Assessment

At baseline, year 1, and year 4, dietary intake was assessed by multiple prescheduled, 24-hour dietary recalls collected by telephone on random days during a 3-week period, stratified for weekend vs weekdays.[15] Of 2413 participants in this sample, 2400 (99.5%) completed 3 or more dietary recalls at baseline, 2203 (91.3%) completed 3 or more recalls at year 1, and 1924 (79.7%) completed 3 or more recalls at year 4. Collectively, 25 325 dietary recalls were available for use in this analysis.

Nightly fasting duration was estimated by calculating the elapsed hours between the first and last eating episode for each day and subtracting this time from 24 hours. Potential dietary confounders identified from the literature included daily intake (in kilocalories), eating episodes per day, and eating after 8 PM. Eating episodes per day were defined as the number of times participants consumed 25 kcal or more at a single time point. We also created an indicator variable for individuals who consumed 25 kcal or more after 8 PM (referred to as *eating after 8 PM*).

Other Assessments

Medical records were abstracted for information related to the initial breast cancer diagnosis and treatment, such as stage, grade, hormone receptor status, and use of radiotherapy, chemotherapy, or endocrine therapy (eg, tamoxifen). Demographic characteristics and comorbidities were self-reported. Glycated hemoglobin (HbA_{1c}) and CRP were measured in blood specimens collected at the baseline clinic visit using standard procedures.[16,17]

Height, weight, physical activity levels, and sleep duration were measured at baseline, year 1, and year 4. Physical activity levels were measured using a validated questionnaire adapted from the Women's Health Initiative.[18] Sleep duration was estimated by asking participants, "About how many hours of sleep did you get on a typical night during the past 4 weeks?"

Clinical Outcomes

Breast cancer recurrence was ascertained through active surveillance (semiannual telephone calls) during a mean of 7.3 years of follow-up. Breast cancer recurrence was defined as the combination outcome of invasive breast cancer recurrence (local, regional, or distal) or new primary invasive breast cancer. The breast cancer recurrence-free interval was defined as the date of original breast cancer diagnosis to development of a new breast cancer event or the end of study follow-up.

Participant deaths were ascertained via periodic review of the Social Security Death Index for a mean of 11.4 years. Cause of death was obtained from death certificates of each decedent, which listed the primary cause of death. In some cases, a contributing cause of death was also listed. Using this information, the WHEL data management coordinator used *International Classification of Diseases, Ninth Revision* coding to generate 4 categories for cause of death: breast cancer, other cancer, cardiovascular disease, or other cause. All breast cancer deaths were confirmed by the study oncologist. Survival was assessed as the time from cancer diagnosis to death or the most recent available review of the Social Security Death Index.

Statistical Analysis

Data analysis was conducted from May 18 to October 5, 2015. The repeated measurements of nightly fasting duration at baseline, year 1, and year 4 were analyzed by modeling them as time-varying covariates[19] using Cox proportional hazards regression. These models used delayed entry to account for the interval between breast cancer diagnosis and entry to the WHEL study and controlled for the following variables selected a priori based on their known association with breast cancer prognosis and/or nightly fasting duration: demographics, number of comorbidities, tumor stage and grade, treatment with radiotherapy, tamoxifen use, and menopausal status, as well as other potential dietary confounders (eg, number of eating episodes per day, eating after 8 PM, or kilocalorie intake). We also adjusted for study design variables, including WHEL intervention group, and study site. We investigated adjusting for other breast cancer–related or diet-related variables, such as estrogen and progesterone receptor status, total fat and carbohydrate intake, and dietary index scores. However, because these variables did not change the nightly fasting hazard ratios by more than 10%, they were not included in the multivariable adjusted models. Our primary exposure of nightly fasting duration was categorized using tertile cut points for ease of interpretation. We combined the bottom 2 tertiles because there was no evidence of a dose-response association below the upper tertile. The proportional hazards assumption was examined and satisfied in all Cox proportional hazards regression models by testing the significance of the product terms for our variable of interest and log time.

Linear regression models were used to examine the cross-sectional associations of baseline nightly fasting duration with the baseline metabolic and lifestyle variables hypothesized to link nightly fasting duration with breast cancer outcomes: HbA_{1c}, CRP, body mass index (BMI), and sleep.[16,17,20-22] For consistency, these linear regression models controlled for the same covariates as the Cox proportional hazards regression models described above. To enhance interpretability of the parameter estimates, we used a 2-hour (approximately 1 SD) unit of analysis for the nightly fasting duration variable. C-reactive protein was log transformed to better approximate a gaussian distribution. All statistical tests were 2-sided, and α was set at $P < .05$.

Results

The sample consisted of 2413 patients with breast cancer but without diabetes, with a mean (SD) age of 52.4 (8.9) years and a BMI (calculated as weight in kilograms divided by height in meters squared) of 27.0 (5.9) (**Table 1**). A total of 2064 participants (85.5%) were white and 1335 (55.3%) were college educated. Participants reported a mean (SD) nightly fasting duration of 12.5 (1.7) hours and 4.4 (1.2) eating episodes per day. One-third of the sample (788 [32.7%]) consumed 25 kcal or more after 8 PM. A short nightly fasting duration (<13 hours per night) was significantly associated with college education, a lower BMI, shorter sleep duration, higher self-reported kilocalorie intake, more eating episodes, and eating after 8 PM (Table 1).

In repeated-measures Cox proportional hazards regression models, a short nightly fast was significantly associated with an increased risk for breast cancer recurrence. Specifically, fasting fewer than 13 hours per night was associated with a 36% higher hazard for breast cancer recurrence compared with fasting 13 or more hours per night (hazard ratio, 1.36; 95% CI, 1.05-1.76) (**Table 2**). Short nightly fasting duration was not associated with a higher hazard for breast cancer-specific mortality (hazard ratio, 1.21; 95% CI, 0.91-1.60) or a higher hazard for all-cause mortality (hazard ratio, 1.22; 95% CI, 0.95-1.56). We also examined these associations using competing risk models and the result remained unchanged.

Table 3 provides a cross-sectional analysis of biomarkers and mechanisms postulated to link nightly fasting duration with breast cancer prognosis. Each 2-hour increase in nightly fasting duration was statistically significantly associated with a 0.37-mmol/mol lower HbA_{1c} level (β = −0.37; 95% CI, −0.72 to −0.01) and more hours of sleep per night (β = 0.20; 95% CI, 0.14-0.26). Nightly fasting duration was not associated with BMI or CRP concentrations. With regard to dietary behaviors related to nightly fasting, each additional daily eating episode was associated with significantly lower HbA_{1c} and CRP concentrations and lower BMI. Eating after 8 PM was associated with significantly higher CRP concentrations and BMI.

Table 1. Baseline Characteristics of Patients With Breast Cancer

Characteristic	Full Eligible Sample (N = 2413)	Nightly Fasting Duration <13 h (n = 1595)	Nightly Fasting Duration ≥13 h (n = 818)	*P* Value for Difference[a]
Age, mean (SD), y	52.4 (8.9)	52.3 (8.8)	52.4 (9.3)	.79
White, non-Hispanic, No. (%)	2064 (85.5)	1381 (86.6)	683 (83.5)	.04
College educated, No. (%)	1335 (55.3)	919 (57.6)	416 (50.9)	<.001
Cancer stage at diagnosis, No. (%)				
I	911 (37.8)	613 (38.4)	298 (36.4)	.05
II	1115 (46.2)	747 (46.8)	368 (45.0)	
III	387 (16.0)	235 (14.7)	152 (18.6)	
Grade, No. (%)				
Well differentiated	388 (16.1)	271 (17.0)	117 (14.3)	.24
Moderately differentiated	977 (40.5)	641 (40.2)	336 (41.1)	
Poorly differentiated	888 (36.8)	585 (36.7)	303 (37.0)	
Unspecified	160 (6.6)	98 (6.1)	62 (7.6)	
Radiotherapy, No. (%)				
Yes	1507 (62.5)	1004 (63.0)	503 (61.5)	.56
No	903 (37.4)	591 (37.1)	312 (38.1)	
Chemotherapy, No. (%)				
Yes	1741 (72.2)	1151 (72.2)	590 (72.1)	.99
No	672 (27.9)	444 (27.8)	228 (27.9)	
Tamoxifen use, No. (%)				
Yes	1446 (59.9)	964 (60.4)	482 (58.9)	.30
No	963 (39.9)	627 (39.3)	336 (41.1)	
BMI, mean (SD)	27.0 (5.9)	26.7 (5.6)	27.5 (6.3)	<.01
Physical activity, mean (SD), MET/wk	877.1 (903.8)	899.9 (878.4)	861.7 (952.4)	.33
Sleep, hours per night, No. (%)				
<6	149 (6.2)	109 (6.8)	40 (4.9)	<.001
6-8	2042 (84.6)	1366 (85.6)	676 (82.6)	
>8	140 (5.8)	74 (4.6)	66 (8.4)	
Comorbidities, No. (%)[b]				
0	1394 (57.8)	930 (58.3)	464 (56.7)	.06
1	669 (27.7)	435 (27.3)	234 (28.6)	
2	266 (11.0)	165 (10.3)	101 (12.4)	
≥3	84 (3.5)	65 (4.1)	19 (2.3)	
Menopausal status, No. (%)				
Premenopausal	275 (11.4)	177 (11.1)	98 (12.0)	.79
Postmenopausal	1893 (78.5)	1256 (78.7)	637 (78.2)	
Perimenopausal	241 (10.0)	161 (10.1)	80 (9.6)	
Food intake, mean (SD), kcal/d	1727 (406)	1769 (397)	1644 (411)	<.001
Nightly fasting duration, mean (SD), h	12.5 (1.7)	11.6 (1.1)	14.2 (1.2)	<.001
Eating after 8 PM, any vs none, No. (%)	788 (32.7)	719 (45.1)	69 (8.4)	<.001
Eating episodes per day, mean (SD), No.	4.4 (1.2)	4.8 (1.1)	3.7 (0.9)	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MET, metabolic equivalent task unit.

[a] *P* values reflect statistical comparisons of participant characteristics by tertiles of nightly fasting duration. *t* Tests were used for continuous variables, and χ^2 tests were used for categorical variables.

[b] Comorbidities at baseline include arthritis, osteoporosis, cardiovascular conditions, digestive conditions, and miscellaneous conditions, excluding diabetes.

Discussion

In this large prospective cohort of patients with early-stage breast cancer, a short nightly fasting duration (<13 hours per night) was associated with a 36% higher hazard for breast cancer recurrence. Short nightly fasting was not associated with statistically significant increased risk of early mortality. To our knowledge, this is the first human study to examine the association between nightly fasting and cancer outcomes.

There are limited animal data on the association of time-restricted feeding and tumorigenesis. However, in rodents, calorie restriction is an effective way to reduce cancer and cancer-related risk factors,[23,24] and studies suggest that intermittent calorie restriction prevents mammary tumor development to a similar, or even greater, extent than chronic calorie restriction.[25,26] To our knowledge, only 1 study has tested the effect of meal timing on tumor progression in mice[27]: those with time-restricted feeding regimens had a lower mean tumor weight compared with mice with ad libitum feeding.

Table 2. Associations of Nightly Fasting Duration and Related Mealtime Behaviors With Breast Cancer Recurrence and Mortality[a]

Behavior	Hazard Ratio (95% CI)	*P* Value
Breast Cancer Events (n=390)		
Nightly fasting, h		
<13	1.36 (1.05-1.76)	.02
≥13	1 [Reference]	
Eating episodes per day	0.97 (0.87-1.08)	.60
Eating after 8 PM (yes vs no)	0.97 (0.76-1.24)	.81
Breast Cancer-Specific Mortality (n=329)		
Nightly fasting, h		
<13	1.21 (0.91-1.60)	.19
≥13	1 [Reference]	
Eating episodes per day	1.00 (0.89-1.13)	.96
Eating after 8 PM (yes vs no)	0.98 (0.74-1.28)	.86
All-Cause Mortality (n=420)		
Nightly fasting, h		
<13	1.22 (0.95-1.56)	.12
≥13	1 [Reference]	
Eating episodes per day	0.99 (0.89-1.10)	.86
Eating after 8 PM (yes vs no)	0.97 (0.76-1.24)	.80

[a] Models controlled for age, race/ethnicity, educational level, number of comorbidities, tumor stage, grade, radiotherapy, tamoxifen use, kilocalorie intake, menopausal status, study site, and intervention group assignment. Repeated measurements of nightly fasting duration at baseline, year 1, and year 4 were analyzed.

Table 3. Mechanisms by Which Prolonged Nightly Fasting and Related Food Consumption Behaviors Have Been Postulated to Effect Breast Cancer Risk and Prognosis[a]

Mechanism	β (95% CI)	*P* Value
Model 1: Glucoregulation, HbA_{1c}, mmol/mol		
Nightly fasting duration[b]	−0.37 (−0.72 to −0.01)	.04
Eating episodes per day	−0.27 (−0.53 to −0.01)	.045
Eating after 8 PM (yes vs no)	0.16 (−0.43 to 0.76)	.59
Model 2: Chronic Inflammation, log CRP, mg/L		
Nightly fasting duration[b]	0.04 (−0.03 to 0.12)	.27
Eating episodes per day	−0.07 (−0.13 to −0.01)	.01
Eating after 8 PM (yes vs no)	0.16 (0.04 to 0.29)	.01
Model 3: BMI		
Nightly fasting duration[b]	0.04 (−0.32 to 0.39)	.80
Eating episodes per day	−0.48 (−0.73 to −0.23)	<.001
Eating after 8 PM (yes vs no)	0.64 (0.07 to 1.20)	.03
Model 4: Sleep (Usual Duration), Hours per Night		
Nightly fasting duration[b]	0.20 (0.14 to 0.26)	<.001
Eating episodes per day	0.09 (0.04 to 0.13)	<.001
Eating after 8 PM (yes vs no)	−0.01 (−0.11 to 0.10)	.93

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CRP, C-reactive protein; HbA_{1c}, hemoglobin A_{1c}.

[a] Models controlled for age, race/ethnicity, educational level, number of comorbidities, tumor stage, grade, radiotherapy, tamoxifen use, kilocalorie intake, menopausal status, study site, and intervention group assignment.

[b] A 2-h (approximately 1 SD) unit of analysis was used.

However, mice on these same time-restricted feeding regimens who were fed during the 12-hour period of light exposure had a lower tumor weight than mice fed during darkness (mice are nocturnal). The authors hypothesized that meal timing during light exposure produced an internal desynchronization that slowed tumor progression. More and better-quality animal studies are needed to provide mechanistic data on time-restricted feeding and cancer risk.

Positive metabolic changes associated with intermittent fasting regimens include improved glucoregulation.[8] In this WHEL study cohort, longer nightly fasting duration and more frequent eating were associated with a significantly lower HbA_{1c} level, consistent with a previous analysis of 2212 women in the National Health and Nutrition Examination Survey.[9] As noted in the American Diabetes Association/American Cancer Society consensus report on diabetes and cancer risk,[14] there may be a subset of tumors for which hyperglycemia confers a growth advantage. Several studies have reported associations between diabetes and/or hyperglycemia and breast cancer prognosis.[16,28,29] An analysis of patients with breast cancer in the WHEL cohort found that, compared with women whose HbA_{1c} was less than 6.5%, the risk of all-cause mortality was twice as high in women whose HbA_{1c} was 7.0% or more (hazard ratio, 2.35; 95% CI, 1.56-3.54), and there was a nonsignificant 30% increase in the risk of breast cancer recurrence.[16]

Although rodent studies indicate that time-restricted feeding can reduce markers of inflammation,[11,30] our study found no association between length of nightly fasting and CRP concentration in patients with breast cancer. Nonetheless, a recent analysis of 2019 adult women in the National Health and Nutrition Examination Survey showed that a longer nightly fasting duration was associated with significantly lower CRP concentrations, but only in women who ate less than 30% of their daily calories after 5 PM.[10]

Many trials of intermittent fasting in humans have demonstrated that fasting regimens lead to modest weight loss.[8] However, we found no connection between nightly fasting and BMI, suggesting that the positive effects of prolonged nightly fasting on HbA_{1c} and breast cancer prognosis may be independent of BMI.

Finally, prolonged nightly fasting and more frequent eating were associated with significantly longer sleep duration in our study. Consuming food at abnormal times (eg, late at night) can result in misalignment of circadian rhythms, which can influence sleep patterns and disrupt metabolic factors, such as glucoregulation. Notably, circadian misalignment has been linked to increased risk of many cancers, as evidenced by the well-documented association between shift work and increased risk of breast cancer.[31-34]

A unique strength of this study was the assessment of the nightly fasting interval by use of multiple 24-hour recalls collected at several study time points (baseline, year 1, and year 4). The use of multiple assessments of nightly fasting duration reduced within-person variability in our exposure measure.[35] In addition, this design enabled use of a repeated-measures analysis to analyze the dietary data in Cox proportional hazards regression models,[19] which increased study power relative to sample size. Nonetheless, the use of self-reported dietary data is also a limitation, as recalls are prone

to numerous biases.[36] However, it is unknown whether self-reported timing of energy intake is susceptible to similar biases. We also relied on self-reported data for sleep duration, physical activity, and comorbidities, which may be subject to error. In addition, although *ERBB2* (also known as *Her2/neu* [GenBank X03363.1]) status has become a well-recognized indicator of breast cancer prognosis and response to systemic therapies, the test for *ERBB2* was not a standard of care procedure at the time of study inception. As a result, information on *ERBB2* status was not available for a sizeable number of WHEL participants, and this variable was not included as a covariate in statistical models. Finally, our study included multiple primary end points for breast cancer prognosis (ie, breast cancer recurrence, breast cancer-specific mortality, and all-cause mortality). Because this was an exploratory analysis of a novel association for a modifiable risk factor, we did not adjust for multiple comparisons. Therefore, there could be an increased probability of a type I error.

Conclusions

Our study introduces a novel dietary intervention strategy and indicates that prolonging the length of the nightly fasting interval could be a simple and feasible strategy to reduce breast cancer recurrence. In this cohort of patients with early-stage breast cancer, a longer nightly fasting interval was also associated with significantly lower concentrations of HbA_{1c} and longer sleep duration. Given the associations of nightly fasting with glycemic control and sleep, we hypothesize that interventions to prolong the nightly fasting interval could potentially reduce the risk of type 2 diabetes, cardiovascular disease, and other cancers. Thus, findings from this study have broad and significant implications for public health. Randomized trials are needed to adequately test whether prolonging the nightly fasting interval can reduce the risk of chronic disease.

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Study concept and design: Marinac, Nelson, Hartman, Natarajan, Pierce, Sears, Patterson.
Acquisition, analysis, or interpretation of data: Marinac, Nelson, Breen, Natarajan, Flatt, Sears, Patterson.
Drafting of the manuscript: Marinac, Nelson, Natarajan, Sears, Patterson.
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