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# Total and Cause-Specific Mortality of U.S. Nurses Working Rotating Night Shifts

**Fangyi Gu, MD, ScD**, **Jiali Han, PhD**, **Francine Laden, ScD**, **An Pan, PhD**, **Neil E. Caporaso, MD**, **Meir J. Stampfer, MD, DrPH**, **Ichiro Kawachi, MD, PhD**, **Kathryn M. Rexrode, MD, MPH**, **Walter C. Willett, MD, DrPH**, **Susan E. Hankinson, ScD**, **Frank Speizer, MD**, and **Eva S. Schernhammer, MD, DrPH**

From the Division of Cancer Epidemiology & Genetics (Gu, Caporaso), Genetic Epidemiology Branch, National Cancer Institute, Bethesda, Maryland; Channing Division of Network Medicine (Han, Stampfer, Hankinson, Speizer, Schernhammer); Clinical Research Program (Han), Department of Dermatology; Division of Preventive Medicine (Rexrode); Division of Sleep Medicine (Schernhammer), Department of Medicine, Brigham and Women's Hospital and Harvard Medical School; Department of Environmental Health (Laden), Department of Epidemiology (Laden, Stampfer), Department of Social and Behavioral Sciences (Kawachi), and Department of Nutrition (Willett), Harvard School of Public Health, Boston; Division of Biostatistics and Epidemiology (Hankinson), University of Massachusetts, Amherst, Massachusetts; Department of Epidemiology (Han), Richard M. Fairbanks School of Public Health, Simon Cancer Center, Indiana University, Indianapolis, Indiana; Saw Swee Hock School of Public Health and Yong Loo Lin School of Medicine (Pan), National University of Singapore and National University Health System, Singapore; and Applied Cancer Research—Institution for Translational Research Vienna (ACR-ITR VIEnna) (Schernhammer), Vienna, Austria

## Abstract

**Background—**Rotating night shift work imposes circadian strain and is linked to the risk of several chronic diseases.

**Purpose—**To examine associations between rotating night shift work and all-cause, cardiovascular disease (CVD), and cancer mortality in a prospective cohort study of 74,862 registered U.S. nurses from the Nurses' Health Study.

**Methods—**Lifetime rotating night shift work (defined as ≥3 nights/month) information was collected in 1988. During 22 years (1988–2010) of follow-up, 14,181 deaths were documented,



Address correspondence to: Eva S. Schernhammer, MD, DrPH, Channing Division of Network Medicine, 181 Longwood Avenue, Boston MA 02115. eva.schernhammer@channing.harvard.edu.



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including 3,062 CVD and 5,413 cancer deaths. Cox proportional hazards models (2013) estimated multivariable-adjusted hazard ratios (HRs) and 95% CIs.

**Results—**All-cause and CVD mortality were significantly increased among women with ≥5 years of rotating night shift work, compared to women who never worked night shifts. Specifically, for women with 6–14 and ≥15 years of rotating night shift work, the HRs were 1.11 (95% CI=1.06, 1.17) and 1.11 (95% CI=1.05, 1.18) for all-cause mortality and 1.19 (95% CI=1.07, 1.33) and 1.23 (95% CI=1.09, 1.38) for CVD mortality. There was no association between rotating night shift work and all-cancer mortality ($HR_{\geq 15 years}$=1.08, 95% CI=0.89, 1.19) or any other cancer, with the exception of lung cancer ($HR_{\geq 15 years}$=1.25, 95% CI=1.04, 1.51).

**Conclusions—**Women working rotating night shifts for ≥5 five years have a modest increase in all-cause and CVD mortality; those working ≥15 years of rotating night shift work have a modest increase in lung cancer mortality. These results add to prior evidence of a potentially detrimental effect of rotating night shift work on health and longevity.

## Introduction

Shift work including a nighttime rotation is common, with up to 20% of the western workforce encountering alternate work schedules some time during their career.[1] Observational studies consistently suggest positive associations of night shift work and cardiovascular disease (CVD)[2] and cancer risk.[3-18] Thus, the WHO in 2007 classified night work as a probable carcinogen.[19] In addition to the link with cancer and CVD risk, other health outcomes including diabetes, hypertension, chronic fatigue, various sleep problems,[20-23] and higher body weight[22] are associated with shift work.[24-26] However, evidence is more limited and inconsistent[27] on associations between night shift work and all-cause and cause-specific mortality in observational studies.[18,28-32]

The circadian system and its prime marker, melatonin, are considered to have antitumor effects through multiple pathways, including antioxidant activity, anti-inflammatory effects, and immune enhancement.[33-37] They also exhibit beneficial actions on cardiovascular health by enhancing endothelial function, maintaining metabolic homeostasis,[38] and reducing inflammation.[39,40] Direct nocturnal light exposure suppresses melatonin production[41] and resets the timing of the circadian clock.[33,42,43] In addition, sleep disruption may also accentuate the negative effects of night work on health.[44,45] Taken together, substantial biological evidence supports the role of night shift work in the development of poor health conditions including cancer, CVD, and ultimately, mortality.

The current analysis is based on 22 years of follow-up of 74,862 women participating in the Nurses' Health Study (NHS). This large U.S. cohort of nurses provides a unique opportunity to study associations between duration of rotating night shift work, all-cause, and cause-specific mortality. The baseline age range (30–55 years), high death rate, and nearly complete follow-up allows for a powerful analysis of night shift work and mortality, with repeat measures available on a number of important confounding factors. The 1988 assessment of lifetime night work likely captures most of the night shift work history of women retained in this cohort, as, based on data from the NHS2 cohort,[46] <5% of nurses

continue to work night shifts in middle age and <2% commence working night shifts at this age.

## Methods

### Study Population

The NHS cohort was established in 1976 when 121,701 U.S. female registered nurses aged 30–55 years were enrolled. All women completed an initial questionnaire at baseline about their lifestyle factors, health behaviors, and medical history, and have since been followed using biennial questionnaires to update exposure status and disease diagnoses.[47] Night shift work information was collected in 1988. Of the 103,613 nurses who responded to the 1988 questionnaire, 85,197 (82.2%) answered the question about shift work. These women did not differ substantially from non-respondents in terms of their risk profile.[48] After excluding women with pre-existing CVD (*n*=2,444) or any cancer other than non-melanoma skin cancer in or before 1988 (*n*=7,891), 74,862 women were included in the analytic sample. The study protocol was approved by the IRBs of Brigham and Women's Hospital and Harvard School of Public Health (Boston, MA).

### Measures

Information on lifetime rotating night shift work was collected once in 1988. On the 1988 questionnaire, participants were asked What is the total number of years during which you worked rotating night shifts at least 3 nights/month in addition to days or evenings in that month?, with eight prespecified response categories: *never*, *1–2*, *3–5*, *6–9*, *10–14*, *15–19*, *20–29*, and ≥*30* years. This definition of rotating night shifts (i.e., ≥3 nights/month) did not specifically distinguish between rotating or permanent night shifts.

Deaths in the cohort were identified by reports from next of kin and via postal authorities. In addition, names of non-responders were searched in the National Death Index, which is highly sensitive and specific in this cohort.[49] The underlying cause of death was determined by physician review primarily based on medical records and death certificates. ICD-8 was used to distinguish deaths due to cancer (ICD codes 140-207) and CVD (ICD codes 390–459 and 795). Cause-specific death from CVD and cancer sites with >100 deaths included in analysis were: ischemic heart disease (IHD; 410–414), cerebrovascular disease (430–438), and any other CVD (390–459 and 795 excluding 410–414 and 430–438); cancers of the lung (162), breast (174), ovaries (183), pancreas (157), colon or rectum (153), brain (191), kidney (189), uterus (182); and non-Hodgkin's lymphoma (200, 202, 204), myeloma (203), leukemia (205–207), and other cancers (199). Follow-up rates for this cohort remain at approximately 90%, and the overall death follow-up is >98% complete.[49]

### Statistical Analysis

Age and age-adjusted demographic and lifestyle factors were summarized at the midpoint of follow-up (1998) according to night shift work categories (never, 1–5, 6–14, ≥15 years). Cox proportional hazards regression models were used (2013) to estimate hazard ratios (HRs) and 95% CIs were calculated for all-cause mortality, CVD and cancer mortality, and mortality from specific CVD and cancer sites with >100 deaths. Person-years of follow-up

were accrued from baseline (June 1988) to the date of death, loss to follow-up, or June 2010, whichever came first. Tests for linear trend across categories of night shift work were performed by assigning the median value of each shift work category. Each endpoint was adjusted for age and regularly updated information throughout follow-up on: alcohol consumption, physical exercise, multivitamin use, menopausal status and postmenopausal hormone use, physical examination in the past 2 years, healthy eating score[37] (without components of multivitamin and alcohol, which were adjusted individually), smoking status, pack-years, and BMI. Information on these covariates was updated at 2–4-year intervals throughout follow-up. Additional adjustment for husbands' education (less than high school, some high school, high school graduate, college, graduate school) was performed as the best indicator of SES; further adjustment for nurses' education left the results virtually unchanged and was therefore not retained in the final models. Sensitivity analyses restricted to women with sleep duration of 6–8 hours were performed. Potential intermediate covariates (e.g., type 2 diabetes (T2D), hypertension, and hypercholesterolemia) were added to multivariable models. The proportional hazards assumption was tested by including interaction terms between duration of night shift work categories and follow-up time.

As smoking and obesity are well-established risk factors for CVD and multiple cancers, stratified analyses were performed by smoking status (never, former, current) and BMI (18.5–24.9, 25.0–29.9, ≥30.0 kg/m$^2$). Interaction *p*-values were calculated by adding interaction terms into the models and performing likelihood ratio tests. To reduce residual confounding, adjustment for pack-years among former and current smokers, and continuous BMI within each BMI stratum, were performed.

## Results

Over 22 years and 1.5 million person-years of follow-up, 14,181 deaths were documented, of which 3,062 were attributed to CVD and 5,413 to cancer. Women who had never worked rotating night shifts accounted for 41% of the person-years of follow up, and those who worked 1–5, 6–4, and ≥15 years on shifts accounted for 41%, 11%, and 7% of person-years, respectively. Table 1 shows that women with longer durations of rotating night shift work tended to be older (mean age, 66.3 years for ≥15 years of shift work vs 63.6–64.6 years for others) and had a higher BMI and were more physically active after standardizing for age. They were also more likely to be current smokers, less likely to use postmenopausal hormones or multivitamins, and of those married, the husbands tended to be less educated. There were no appreciable differences in dietary factors across durations of shift work; however, women who worked night shifts for longer durations tended to drink less alcohol and ate less daily cereal fiber compared to women without night shift work. They also had gained more weight since age 18 years, and were more likely to have a history of diabetes, hypertension, and hypercholesterolemia.

Age- and multivariable-adjusted HRs for the associations between night shift work and all-cause and cause-specific mortality are presented in Table 2. Women working rotating night shifts for >5 years had modest increases in both all-cause and CVD-related mortality, compared to women who never worked rotating night shifts. For all-cause mortality, the multivariable-adjusted HRs for women with 1–5, 6–14, or ≥15 years of rotating night shift

work were 1.01 (95% CI=0.97, 1.05), 1.11 (95% CI=1.06, 1.17), and 1.11 (95% CI=1.05, 1.18; $p_{trend}$<0.001). For CVD mortality, the multivariable-adjusted HRs were 1.02 (95% CI=0.94, 1.11), 1.19 (95% CI=1.07, 1.33), and 1.23 (95% CI=1.09, 1.38; $p_{trend}$<0.001). Women working night shifts for 6–14 or ≥15 years also had higher risk of all-cancer mortality. Compared to women who never worked rotating night shifts, the age-adjusted HRs were 1.10 (95% CI=1.01, 1.20) and 1.20 (95% CI=1.09, 1.32), but these associations were attenuated after multivariable adjustment, with HRs of 1.04 (95% CI=0.95, 1.13) and 1.08 (95% CI=0.98, 1.19), respectively.

Results for specific cancer sites with ≥200 deaths are offered in Table 3. For lung cancer mortality, the age-adjusted HR for ≥15 years of rotating night shift work was 1.44 (95% CI=1.20, 1.73), and 1.25 after multivariate adjustment (95% CI=1.04, 1.51), with smoking as the driving confounder. For colorectal cancer, the age-adjusted HR after ≥15 years of rotating night shift work was 1.42 (95% CI=1.04, 1.94), but was attenuated to 1.33 (95% CI=0.97, 1.83) after multivariate adjustment. Adjusting for current disease status (T2D, hypertension, and hypercholesterolemia) left results largely unchanged (data not shown). Although no increase in breast cancer mortality was observed among women with ≥15 years of rotating night shift work (multivariable HR=0.99, 95% CI=0.74, 1.33), among women with ≥30 years of rotating night shift work, the multivariable HR for breast cancer mortality was 1.47 (95% CI=0.94, 2.32). Cancers with <200 deaths are presented in Appendix Table 1. There was a non-significant increase in mortality from kidney cancer and myeloma among women with 6–14 and ≥15 years of night work: the multivariable HRs were 1.72 (95% CI=1.03, 2.86) and 1.39 (95% CI=0.75, 2.57) for kidney cancer ($p_{trend}$=0.048) and 1.56 (95% CI=0.93, 2.64) and 1.61 (95% CI=0.90, 2.88) for myeloma ($p_{trend}$=0.08). There was no significant association between rotating night shift work and mortality from other cancers.

For mortality from specific types of CVD with >100 deaths (Table 4), increased IHD mortality was observed among women who worked rotating night shifts for 6–14 and ≥15 years (HR=1.22, 95% CI=1.02, 1.46; 1.31, 1.09, 1.59, respectively; $p_{trend}$<0.001). Additional adjustment for current disease status (T2D, hypertension, and hypercholesterolemia) only minimally affected these associations (Table 4). There were no significant associations among women working rotating night shifts for 6–14 and ≥15 years for cerebrovascular disease or any other CVD.

When stratifying by smoking status (Table 5), the association of rotating night shift work appeared to be stronger among current smokers for all-cause mortality ($HR_{\geq 15\ years,}$ 1.21 vs 1.11), but remained statistically significant also among never smokers ($p_{trend}$=0.05). Similarly, for CVD and IHD mortality, HRs were comparable among never smokers and the entire analytic sample. Associations for overall cancer, lung cancer, and colon cancer mortality appeared to vary by smoking status, but there was no statistically significant interaction ($p_{interaction}$>0.05). No significant interaction with BMI was observed for any of the endpoints (Appendix Table 2).

## Discussion

In this large prospective U.S. cohort of nurses, working rotating night shifts for >5 years was associated with a significant increase in all-cause and all-CVD (particularly IHD) mortality. Working ≥15 years of rotating night shift work was associated with a significant increase in lung cancer mortality. There was also a non-significant increase in mortality due to cancer overall, and several specific cancer sites.

Previous studies of shift work and IHD incidence or mortality varied by design and quality, with inconsistent results.[50-53] However, results from two prospective follow-up studies[48,54] and a recent meta-analysis[2] are in line with the present findings. One cohort study of 504 papermill workers observed a significant increase in IHD risk after 10 years of shift work.[30] The other study of the NHS cohort, but with only 4 years of follow-up and many fewer cases (*n*=292), observed an increase in coronary heart disease (both fatal and non-fatal) incidence among night shift workers after both <5 and ≥5 years of rotating night shift work.[48] Moreover, a recent meta-analysis[2] suggested that shift work increases the risk of coronary events (including IHD and other CVD, mixed incidence and mortality data); the association remained when restricted to higher-quality studies and was stronger for night shift work, which disrupts circadian rhythms more than other types of shift work. Of the five studies accounting for duration of shift work,[18,48,54-56] three reported increased risks after longer durations of shift work,[18,48,54] with the exception of two case-control studies.[55,56] Together with previous evidence,[8,10] the current study provides further support for a link between night shift work, especially of longer durations, and increased IHD events.

Several underlying biological mechanisms make such an association plausible: autonomic nervous system activation, an increased inflammatory state, changes in lipid and glucose metabolism, and resulting changes in the risk for atherosclerosis, all of which have previously been described in night shift workers.[57] The finding that women with longer durations of rotating night shift work had a higher BMI and tended to gain more weight since age 18 years may be intermediate conditions subsequent to night shift work, and adjustment for them in multivariable models may underestimate associations. However, analyses stratified by BMI did not alter the results.

The moderately increased lung and colorectal cancer mortality among women with ≥15 years of night shift work is consistent with previous reports on the risk of developing incident lung and colorectal among night shift–working women in the same cohort.[58,59] Relatively few studies have examined associations between shift work and the risk of these two cancers. For lung cancer, two studies[60,61] reported a higher risk among women in nursing, an occupation with a high prevalence of night shift workers, even after adjustment for smoking. A less reliable study[15] found no association between night work and lung cancer risk, but this study was based on registry occupational data, hence possibly underestimating associations, and was not able to account for important confounders or effect modifiers, including smoking. Similarly, the same study found no association between night work and colorectal cancer. Among women with ≥30 years of rotating night shift work, breast cancer mortality was non-significantly increased by 47% in the current study, which is somewhat consistent with a previous report in the same cohort[14] describing a

significant 36% increase in breast cancer incidence. Current results also suggest potentially increased mortality from renal cancer, and myeloma among women with >5 years of rotating night shift work. The number of deaths was <100 for each of these cancers; therefore, power was likely limited in these analyses, warranting additional studies with larger sample sizes.

This study has a few limitations of note. First, night shift work information was not updated after 1988, potentially leading to exposure misclassification because nurses may have changed their night shift work status during the 22-year follow-up. However, much of follow-up was accrued at midlife or around retirement of these nurses, and more detailed job histories in the NHS2 cohort (a similar cohort, which comprised 116,434 younger women, all registered U.S. nurses) suggest that the percentage of nurses working rotating night shifts declines from roughly 40% in their early 20s, to <5% after age 45 years, with only very few women (<2%) starting night shifts midlife or later (unpublished observation). A further limitation of the exposure assessment is that the timing of exposure in earlier adult life is not known (along with the time between exposure and disease diagnosis). Moreover, in the NHS2 cohort, where night shift work history was assessed in much greater detail, <10% of all nurses worked permanent night shifts. A potential concern is that these nurses may not have classified themselves as working rotating night shifts in the current analysis; yet, exclusion of these women did not change results of a prior analysis.[13] Nonetheless, any remaining non-differential misclassification of the exposure assessment could have biased results, albeit likely toward the null in most situations. Another concern relates to multiple comparisons; however, when requiring a *p*-value of 0.01 for significance, the results remain largely unchanged. Lastly, it is difficult to differentiate the effect of night shift work from lack of sleep; however, sensitivity analyses restricted to women who reported 6–8 sleep hours (not including nap times) per day did not change results materially (data not shown).

This study also has considerable strengths. It is one of the largest prospective cohort studies worldwide with a high proportion of rotating night shift workers and long follow-up time. A single occupation (nursing) provides more internal validity than a range of different occupational groups, where the association between shift work and disease outcomes could be confounded by occupational differences. Shift work is more common in people of lower SES, a risk factor for multiple diseases. Using a cohort of nurses with relatively homogeneous SES minimized potential confounding. Furthermore, husbands' education was adjusted to account for residual confounding by SES. Although self-reported duration of rotating night shifts cannot be validated, it is likely that results are accurate, because other self-reports were highly accurate in a similar cohort,[62] and previous validations of similar questions (e.g., electric blanket use)[63] have shown reasonable reproducibility. Moreover, the prospective study design eliminates recall bias. Finally, information on a range of lifestyle factors was prospectively and repeatedly collected and used for multivariable adjustment to minimize potential confounding by these factors.

In summary, this study confirmed associations of rotating night shift work and total and CVD (particularly IHD) mortality, and suggested associations of shift work with multiple cancer sites. These results add to prior evidence of a potentially detrimental effect of rotating night shift work on health and longevity. Future studies are warranted to explore the

potential for residual confounding or effect modification by smoking in relation to lung cancer mortality, and to confirm associations of night shift work with colorectal cancer, kidney cancer, and myeloma. To derive practical implications for shift workers and their health, the role of duration and intensity of rotating night shift work and the interplay of shift schedules with individual traits (e.g., chronotype) warrant further exploration.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Table 1

Age-standardized characteristics of participants in the NHS cohort in 1998, by baseline night shifts (n=71,857).

| | Night shift work duration at baseline in 1988 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Never (n=29,328) | | 1–5 years (n=29,411) | | 6–14 years (n=8,087) | | ≥15 years (n=5,031) | |
| **Characteristics** | **%** | **Mean (SD)** | **%** | **Mean (SD)** | **%** | **Mean (SD)** | **%** | **Mean (SD)** |
| Participants (%) | 41 | | 41 | | 11 | | 7 | |
| Current smoker | 9 | | 10 | | 13 | | 14 | |
| Past smoker | 45 | | 46 | | 45 | | 43 | |
| Physical exam | 92 | | 92 | | 92 | | 92 | |
| Postmenopausal women | 94 | | 94 | | 94 | | 93 | |
| Postmenopausal hormone therapy | 50 | | 50 | | 47 | | 43 | |
| Current multivitamin use | 63 | | 63 | | 62 | | 60 | |
| Family history of breast cancer | 14 | | 14 | | 14 | | 14 | |
| Benign breast disease | 20 | | 20 | | 20 | | 18 | |
| Husband's highest education, college and graduate school | 55 | | 57 | | 50 | | 43 | |
| Diabetes mellitus | 7 | | 7 | | 10 | | 12 | |
| Hypertension | 44 | | 44 | | 47 | | 50 | |
| Hypercholesterolemia | 57 | | 57 | | 58 | | 58 | |
| Age in 1998, y | | 63.6 (7.1) | | 63.8 (7.1) | | 64.6 (7.1) | | 66.3 (6.8) |
| Body mass index, kg/m$^2$ | | 26.4 (5.2) | | 26.5 (5.3) | | 27.4 (5.6) | | 28.0 (5.8) |
| Physical exercise, met-h/wk | | 16.6 (19.9) | | 17.9 (21.6) | | 17.8 (21.8) | | 18.1 (27.3) |
| Walking, met-h/wk | | 6.2 (8.4) | | 6.6 (8.6) | | 6.6 (9.0) | | 6.4 (9.2) |
| Pack-years | | 24.1 (21.4) | | 23.7 (21.0) | | 26.4 (21.8) | | 27.0 (21.7) |
| Alcohol, g/d | | 5.1 (9.2) | | 5.2 (9.2) | | 4.5 (8.7) | | 3.9 (7.9) |
| Red meat, serving/d | | 0.8 (0.4) | | 0.8 (0.4) | | 0.8 (0.4) | | 0.8 (0.4) |
| Vegetables, serving/d, | | 3.1 (1.3) | | 3.3 (1.4) | | 3.3 (1.4) | | 3.3 (1.5) |
| Fruit, serving/d | | 2.3 (1.1) | | 2.4 (1.2) | | 2.4 (1.2) | | 2.3 (1.2) |
| Polyunsaturated fat, g/d | | 10.8 (5.1) | | 10.9 (4.9) | | 10.8 (5.0) | | 10.8 (5.0) |
| Saturated fat, g/d | | 17.9 (8.0) | | 18.1 (8.1) | | 18.4 (8.3) | | 18.7 (8.4) |
| Trans fat, g/d | | 3.0 (1.5) | | 3.1 (1.5) | | 3.1 (1.6) | | 3.1 (1.6) |
| Cereal fiber, g/d | | 6.8 (3.8) | | 6.8 (3.8) | | 6.6 (3.7) | | 6.5 (3.6) |
| Height, Inch | | 64.5 (2.4) | | 64.6 (2.4) | | 64.5 (2.5) | | 64.5 (2.5) |
| Age at first birth, y | | 24.5 (3.7) | | 24.9 (3.7) | | 25.1 (4.6) | | 24.6 (3.9) |
| Weight change from age 18, 1b | | 13.9 (12.9) | | 14.1 (13.0) | | 15.3 (14.0) | | 16.5 (14.6) |

d, day; g, gram; h, hour; kg/m, kilogram per meter; lb, pound; met, metabolic equivalent value; wk, week; y, year.

## Table 2

Association between night shift work and all cause, CVD, and cancer mortality in NHS, 1988-2010 (n=74,862).

| | Night shift work duration | | | | |
|---|---|---|---|---|---|
| **Mortality** | **Never** | **1–5 years** | **6–14 years** | **≥15 years** | **p for trend** |
| **All causes** | | | | | |
| No. of deaths | 5,417 | 5,424 | 1,910 | 1,430 | |
| Age-adjusted HR (95% CI) | 1.00 (ref) | 0.97 (0.94, 1.01) | 1.19 (1.13, 1.25) | 1.24 (1.17, 1.32) | **<0.001** |
| Multivariable HR (95% CI)[a] | 1.00 (ref) | 1.01 (0.97, 1.05) | 1.11 (1.06, 1.17) | 1.11 (1.05, 1.18) | **<0.001** |
| **All cardiovascular disease** | | | | | |
| No. of deaths | 1,128 | 1,128 | 442 | 364 | |
| Age-adjusted HR (95% CI) | 1.00 (ref) | 0.97 (0.90, 1.06) | 1.30 (1.16, 1.45) | 1.45 (1.29, 1.63) | **<0.001** |
| Multivariable HR (95% CI)[a] | 1.00 (ref) | 1.02 (0.94, 1.11) | 1.19 (1.07, 1.33) | 1.23 (1.09, 1.38) | **<0.001** |
| **All cancer** | | | | | |
| No. of deaths | 2,087 | 2,148 | 672 | 506 | |
| Age-adjusted HR (95% CI) | 1.00 (ref) | 1.00 (0.94, 1.06) | 1.10 (1.01, 1.20) | 1.20 (1.09, 1.32) | **<0.001** |
| Multivariable HR (95% CI)[a] | 1.00 (ref) | 1.03 (0.97, 1.09) | 1.04 (0.95, 1.13) | 1.08 (0.98, 1.19) | 0.11 |

Boldface indicates statistical significance ($p<0.05$).

HR, hazard ratio; NHS, Nurses' Health Study; CVD, Cardiovascular diseases.

[a]Multivariable model adjusted for age (continuous), alcohol consumption (none, 0.1-4.9, 5.0-14.9, ≥15.0 g/d), physical exercise (metabolic equivalent values; quintiles), multivitamin use (yes, no), menopausal status (premenopausal, postmenopausal) and postmenopausal hormone use (never, past and current), physical exam in the past 2 years (no , yes for symptoms and yes for screenings), healthy eating score (quintiles), smoking status (never, former, current), pack-years (<10, 10-19, 20-39, ≥40 for former smokers; <25, 25-44, 45-64, ≥65 for current smokers), and BMI ($kg/m^2$; <21, 21-22.9, 23-24.9, 25-27.4, 27.5-29.9, 30-34.9, ≥35) and husband's education (less than high school, some high school, high school graduate, college, graduate school, missing category).

## Table 3

Association between night shift work and cancer-specific (≥ 200 deaths) mortality in NHS, 1988-2010 (n=74,862).

| | | Night shift work duration | | | |
|---|---|---|---|---|---|
| **Mortality** | **Never** | **1–5 years** | **6–14 years** | **≥15 years** | **p for trend** |
| **Lung cancer** | | | | | |
| No. of deaths | 501 | 523 | 168 | 150 | |
| Age-adjusted HR (95% CI) | 1.00 (ref) | 1.02 (0.91, 1.16) | 1.14 (0.96, 1.36) | 1.44 (1.20, 1.73) | **<0.001** |
| Multivariable HR (95% CI)[a] | 1.00 (ref) | 1.05 (0.92, 1.19) | 0.99 (0.83, 1.18) | 1.25 (1.04, 1.51) | **0.05** |
| **Breast cancer** | | | | | |
| No. of deaths | 269 | 293 | 79 | 55 | |
| Age-adjusted HR (95% CI) | 1.00 (ref) | 1.05 (0.89, 1.25) | 1.04 (0.81, 1.34) | 1.08 (0.80, 1.44) | 0.64 |
| Multivariable HR (95% CI)[a] | 1.00 (ref) | 1.07 (0.90, 1.26) | 0.99 (0.76, 1.27) | 0.99 (0.74, 1.33) | 0.83 |
| **Ovarian cancer** | | | | | |
| No. of deaths | 180 | 168 | 47 | 30 | |
| Age-adjusted HR (95% CI) | 1.00 (ref) | 0.92 (0.74, 1.13) | 0.90 (0.65, 1.24) | 0.86 (0.58, 1.27) | 0.41 |
| Multivariable HR (95% CI)[a] | 1.00 (ref) | 0.95 (0.77, 1.18) | 0.89 (0.64, 1.23) | 0.82 (0.55, 1.22) | 0.27 |
| **Pancreatic cancer** | | | | | |
| No. of deaths | 149 | 173 | 52 | 33 | |
| Age-adjusted HR (95% CI) | 1.00 (ref) | 1.12 (0.90, 1.39 | 1.20 (0.88, 1.65) | 1.10 (0.75, 1.60) | 0.47 |
| Multivariable HR (95% CI)[a] | 1.00 (ref) | 1.12 (0.90, 1.40) | 1.14 (0.83, 1.58) | 1.03 (0.70, 1.51) | 0.77 |
| **Colorectal cancer** | | | | | |
| No. of deaths | 180 | 176 | 56 | 52 | |
| Age-adjusted HR (95% CI) | 1.00 (ref) | 0.95 (0.77, 1.17) | 1.07 (0.80, 1.45) | 1.42 (1.04, 1.94) | **0.02** |
| Multivariable HR (95% CI)[a] | 1.00 (ref) | 0.98 (0.79, 1.21) | 1.05 (0.77, 1.42) | 1.33 (0.97, 1.83) | 0.07 |
| **Non Hodgkin's Lymphoma** | | | | | |
| No. of deaths | 103 | 89 | 34 | 26 | |
| Age-adjusted HR (95% CI) | 1.00 (ref) | 0.85 (0.66, 1.09) | 0.94 (0.65, 1.37) | 1.11 (0.74, 1.66) | 0.57 |
| Multivariable HR (95% CI)[a] | 1.00 (ref) | 0.87 (0.67, 1.12) | 0.96 (0.66, 1.40) | 1.06 (0.71, 1.58) | 0.77 |
| **Other cancer (ICD=199)** | | | | | |
| No. of deaths | 146 | 145 | 35 | 32 | |
| Age-adjusted HR (95% CI) | 1.00 (ref) | 0.95 (0.76, 1.20) | 0.80 (0.55, 1.16) | 1.05 (0.72, 1.55) | 0.87 |
| Multivariable HR (95% CI)[a] | 1.00 (ref) | 0.98 (0.77, 1.23) | 0.75 (0.52, 1.09) | 0.94 (0.63, 1.38) | 0.39 |

Boldface indicates statistical significance (p<0.05).

HR, hazard ratio; NHS, Nurses' Health Study.

[a]Multivariable model adjusted for age (continuous), alcohol consumption (none, 0.1-4.9, 5.0-14.9, ≥15.0 g/d), physical exercise (metabolic equivalent values; quintiles), multivitamin use (yes, no), menopausal status (premenopausal, postmenopausal) and postmenopausal hormone use (never, past and current), physical exam in the past 2 years (no, yes for symptoms and yes for screenings), healthy eating score (quintiles), smoking status (never, former, current), pack-years (<10, 10-19, 20-39, ≥40 for former smokers; <25, 25-44, 45-64, ≥65 for current smokers), BMI ($kg/m^2$; <21, 21-22.9, 23-24.9, 25-27.4, 27.5-29.9, 30-34.9, ≥35) and husband's education (less than high school, some high school, high school graduate, college, graduate school, missing category).

## Table 4

Association between night shift work and CVD-specific (>100 deaths) mortality in NHS, 1988-2010 (n=74,862).

| | Night shift work duration | | | | |
|---|---|---|---|---|---|
| **Mortality** | **Never** | **1–5 years** | **6–14 years** | **≥15 years** | **p for trend** |
| **Ischaemic heart disease** | | | | | |
| No. of deaths | 407 | 386 | 170 | 153 | |
| Age-adjusted HR (95% CI) | 1.00 (ref) | 0.92 (0.80, 1.05) | 1.38 (1.15, 1.65) | 1.69 (1.40, 2.04) | **<0.001** |
| Multivariable HR (95% CI)[a] | 1.00 (ref) | 0.97 (0.85, 1.12) | 1.23 (1.03, 1.47) | 1.34 (1.11, 1.61) | **<0.001** |
| Multivariable HR (95% CI)[b] | 1.00 (ref) | 0.96 (0.83, 1.11) | 1.17 (0.98, 1.41) | 1.23 (1.02, 1.49) | **0.006** |
| **Cerebrovascular disease** | | | | | |
| No. of deaths | 319 | 320 | 119 | 90 | |
| Age-adjusted HR (95% CI) | 1.00 (ref) | 0.97 (0.83, 1.14) | 1.24 (1.00, 1.53) | 1.23 (0.97, 1.55) | **0.02** |
| Multivariable HR (95% CI)[a] | 1.00 (ref) | 1.02 (0.87, 1.20) | 1.20 (0.97, 1.48) | 1.12 (0.88, 1.42) | 0.17 |
| Multivariable HR (95% CI)[b] | 1.00 (ref) | 1.01 (0.86, 1.18) | 1.16 (0.94, 1.44) | 1.06 (0.83, 1.34) | 0.36 |
| **Other cardiovascular disease** | | | | | |
| No. of deaths | 402 | 422 | 153 | 121 | |
| Age-adjusted HR (95% CI) | 1.00 (ref) | 1.02 (0.89, 1.16) | 1.28 (1.06, 1.54) | 1.36 (1.11, 1.67) | **<0.001** |
| Multivariable HR (95% CI)[a] | 1.00 (ref) | 1.05 (0.91, 1.20) | 1.18 (0.97, 1.42) | 1.17 (0.95, 1.44) | 0.06 |
| Multivariable HR (95% CI)[b] | 1.00 (ref) | 1.04 (0.90, 1.19) | 1.14 (0.94, 1.38) | 1.13 (0.92, 1.39) | 0.14 |

Boldface indicates statistical significance ($p<0.05$).

HR, hazard ratio; NHS, Nurses' Health Study; CVD, Cardiovascular diseases

[a]Multivariable model adjusted for age (continuous), alcohol consumption (none, 0.1-4.9, 5.0-14.9, ≥15.0 g/d), physical exercise (metabolic equivalent values; quintiles), multivitamin use (yes, no), menopausal status (premenopausal, postmenopausal) and postmenopausal hormone use (never, past and current), physical exam in the past 2 years (no , yes for symptoms and yes for screenings), healthy eating score (quintiles), smoking status (never, former, current), pack-years (<10, 10-19, 20-39, ≥40 for former smokers; <25, 25-44, 45-64, ≥65 for current smokers), BMI ($kg/m^2$; <21, 21-22.9, 23-24.9, 25-27.4, 27.5-29.9, 30-34.9, ≥35) and husband's education (less than high school, some high school, high school graduate, college, graduate school, missingness).

[b]This model was further adjusted for hypertension (yes, no), hypercholesterolemia (yes, no), type 2 diabetes (yes, no),

## Table 5

Association between night shift work and selected endpoints stratified by smoking status, 1988-2010.[a]

| Mortality | | Night shift work duration | | | | p for trend | p-interaction |
|---|---|---|---|---|---|---|---|
| | | Never | 1–5 years | 6–14 years | ≥15 years | | |
| **All causes** | | | | | | | |
| Never smokers | No. of deaths | 1,863 | 1,833 | 638 | 457 | **0.05** | |
| | HR (95% CI) | 1.00 (ref) | 1.04 (0.98, 1.11) | 1.20 (1.10, 1.31) | 1.04 (0.94, 1.16) | | |
| Former smokers | No. of deaths | 2724 | 2728 | 916 | 657 | **0.01** | 0.15 |
| | HR (95% CI) | 1.00 (ref) | 0.98 (0.93, 1.03) | 1.06 (0.98, 1.14) | 1.09 (1.00, 1.19) | | |
| Current smokers | No. of deaths | 670 | 734 | 293 | 243 | **0.02** | |
| | HR (95% CI) | 1.00 (ref) | 1.07 (0.96, 1.19) | 1.08 (0.94, 1.24) | 1.21 (1.04, 1.40) | | |
| **All cardiovascular diseases** | | | | | | | |
| Never smokers | No. of deaths | 411 | 430 | 154 | 139 | **0.01** | |
| | HR (95% CI) | 1.00 (ref) | 1.11 (0.97, 1.27) | 1.25 (1.04, 1.51) | 1.25 (1.03, 1.52) | | |
| Former smokers | No. of deaths | 516 | 521 | 199 | 146 | **0.03** | 0.40 |
| | HR (95% CI) | 1.00 (ref) | 1.00 (0.89, 1.13) | 1.17 (0.99, 1.38) | 1.16 (0.97, 1.40) | | |
| Current smokers | No. of deaths | 169 | 145 | 76 | 57 | 0.24 | |
| | HR (95% CI) | 1.00 (ref) | 0.86 (0.69, 1.08) | 1.10 (0.83, 1.44) | 1.11 (0.82, 1.50) | | |
| **Ischemic heart disease** | | | | | | | |
| Never smokers | No. of deaths | 138 | 143 | 53 | 55 | 0.08 | |
| | HR (95% CI) | 1.00 (ref) | 1.11 (0.88, 1.40) | 1.24 (0.90, 1.71) | 1.31 (0.96, 1.81) | | |
| Former smokers | No. of deaths | 192 | 175 | 71 | 62 | 0.08 | 0.26 |
| | HR (95% CI) | 1.00 (ref) | 0.91 (0.74, 1.12) | 1.08 (0.82, 1.42) | 1.24 (0.93, 1.16) | | |
| Current smokers | No. of deaths | 63 | 57 | 41 | 28 | **0.02** | |
| | HR (95% CI) | 1.00 (ref) | 0.91 (0.63, 1.31) | 1.63 (1.09, 2.43) | 1.41 (0.90, 2.22) | | |
| **All cancer** | | | | | | | |
| Never smokers | No. of deaths | 668 | 672 | 205 | 1357 | 0.77 | |
| | HR (95% CI) | 1.00 (ref) | 1.05 (0.95, 1.17) | 1.10 (0.94, 1.28) | 0.94 (0.78, 1.13) | | |
| Former smokers | No. of deaths | 1085 | 1102 | 339 | 235 | 0.58 | 0.18 |
| | HR (95% CI) | 1.00 (ref) | 0.99 (0.91, 1.08) | 1.01 (0.90, 1.15) | 1.04 (0.90, 1.20) | | |
| Current smokers | No. of deaths | 300 | 342 | 117 | 118 | **0.03** | |
| | HR (95% CI) | 1.00 (ref) | 1.11 (0.94, 1.29) | 1.00 (0.80, 1.24) | 1.35 (1.09, 1.68) | | |
| **Lung cancer** | | | | | | | |
| Never smokers | No. of deaths | 36 | 47 | 12 | 9 | 0.80 | |
| | HR (95% CI) | 1.00 (ref) | 1.31 (0.84, 2.03) | 1.27 (0.65, 2.48) | 1.09 (0.51, 2.33) | | |
| Former smokers | No. of deaths | 314 | 309 | 90 | 66 | 0.57 | 0.17 |
| | HR (95% CI) | 1.00 (ref) | 0.99 (0.84, 1.16) | 0.91 (0.71, 1.15) | 0.96 (0.73, 1.26) | | |
| Current smokers | No. of deaths | 140 | 149 | 60 | 67 | <**0.001** | |
| | HR (95% CI) | 1.00 (ref) | 1.11 (0.86, 1.42) | 1.16 (0.84, 1.61) | 1.88 (1.36, 2.62) | | |
| **Colorectal cancer** | | | | | | | |
| Never smokers | No. of deaths | 64 | 63 | 23 | 20 | 0.13 | |
| | HR (95% CI) | 1.00 (ref) | 1.08 (0.76, 1.53) | 1.30 (0.80, 2.12) | 1.43 (0.85, 2.39) | | |
| Former smokers | No. of deaths | 93 | 92 | 25 | 24 | 0.60 | 0.95 |
| | HR (95% CI) | 1.00 (ref) | 0.98 (0.73, 1.32) | 0.88 (0.56, 1.38) | 1.19 (0.75, 1.89) | | |
| Current smokers | No. of deaths | 20 | 14 | 7 | 6 | 0.89 | |
| | HR (95% CI) | 1.00 (ref) | 0.74 (0.33, 1.67) | 1.07 (0.40, 2.87) | 0.94 (0.32, 2.80) | | |

Boldface indicates statistical significance ($p<0.05$).

HR, hazard ratio; NHS: Nurses' Health Study.

p-values for interaction were obtained by adding interaction terms into the models and performing likelihood ratio tests.

[a] Cox proportional hazard model adjusted for age (continuous), alcohol consumption (none, 0.1-4.9, 5.0-14.9, ≥15.0 g/d), physical exercise (metabolic equivalent values; quintiles), multivitamin use (yes, no), menopausal status (premenopausal, postmenopausal) and post menopausal hormone use (never, past and current), physical exam in the past 2 years (no, yes for symptoms and yes for screenings), healthy eating score (quintiles), smoking status (never, former, current), pack-years (<10, 10-19, 20-39, ≥40 for former smokers; <25, 25-44, 45-64, ≥65 for current smokers), BMI ($kg/m^2$; <21, 21-22.9, 23-24.9, 25-27.4, 27.5-29.9, 30-34.9, ≥35) ) and husband's education (less than high school, some high school, high school graduate, college, graduate school, missingness).