Night shift work and stomach cancer risk in the MCC-Spain study

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ABSTRACT

Objectives: Night shift work has been classified as a probable human carcinogen by the International Agency for Research on Cancer based on experimental studies and limited evidence on human breast cancer risk. Evidence at other cancer sites is scarce. We evaluated the association between night shift work and stomach cancer risk in a population-based case-control study.

Methods: A total of 374 incident stomach adenocarcinoma cases and 2,481 population controls were included from the MCC-Spain study. Detailed data on lifetime night shift work was collected including permanent and rotating shifts and their cumulative duration (years). Adjusted unconditional logistic regression models were used in analysis.

Results: A total of 25.7% of cases and 22.5% of controls reported ever being a night shift worker. There was a weak positive, non-significant association between ever having had worked for at least one year in permanent night shifts and stomach cancer risk compared to never having worked night shifts (odds ratio (OR) = 1.2, 95% confidence interval (CI) 0.9-1.8). However, there was an inverse "U" shaped relationship with cumulative duration of permanent night shifts, with the highest risk observed in the intermediate duration category (OR 10-20 years = 2.0, 95% CI 1.1-3.6) (P for trend = 0.19). There was no association with ever having had worked in rotating night shifts (OR = 0.9, 95% CI 0.6-1.2) and no trend according to cumulative duration (P for trend = 0.68).

Conclusions: We found no clear evidence concerning an association between night shift work and stomach cancer risk.

What this paper adds

- Night shift work has been classified as a probable human carcinogen by the International Agency for Research on Cancer based on experimental studies and limited evidence on human breast cancer risk; however evidence at other cancer sites is scarce.

- We evaluated the association between lifetime history of night shift work and stomach cancer risk in a population-based case-control study.

- There was a weak positive, non-significant association with having worked for at least one year in permanent night shifts compared to never having worked night shifts, although there was no clear trend with number of years of permanent night shift work.

- We found no clear evidence concerning an association between night shift work and stomach cancer risk.

INTRODUCTION

Shift work affects a large proportion, approximately 20%, of the labour force worldwide.[1, 2] Shift work, especially night shift work, requires workers to adapt their daily activity-rest cycle and can result in sleepiness, impaired safety, and reduced productivity and quality of life.[3, 4] Increasing evidence suggests that shift work may also lead to a variety of chronic diseases, including high blood pressure, cardiovascular disease, and an increased risk of cancer.[5, 6] In 2007, the International Agency for Research on Cancer (IARC) classified shift work with circadian disruption as a probable human carcinogen (Group 2A) based on sufficient evidence in experimental animal studies on the carcinogenicity of light at night, with limited evidence in humans.[1, 7] Although epidemiological studies have typically focused on risk of breast cancer amongst women [8-12] and prostate cancer amongst men,[13] night shift work may also be associated with cancer at other sites; however, the literature is scarce.[14-17]

One of the main hypotheses for an increased cancer risk associated with night shift work is the 'melatonin hypothesis' which highlights the link between light at night exposure and subsequent decreased melatonin secretion.[18, 19] Experimental studies reported that melatonin, the main hormone of the pineal gland, has direct and indirect anticancer effects including pro-apoptotic, antiproliferative, and antioxidative effects, and regulates the immune system.[18] However there may also be other potentially overlapping mechanisms including phase shift or desynchronization, sleep deprivation impaired immune function, lifestyle disturbances and unhealthy behaviour, as well as lower levels of vitamin D in night shift workers.[19]

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Stomach cancer currently represents the fifth most commonly diagnosed cancer and third leading cause of cancer death worldwide, with an estimated 951,000 new cases and 700,000 deaths in 2012.[20] In Spain, it was estimated there were a total of 7,800 new stomach cancer cases and 5,400 deaths in the same year.[21] Although stomach cancer has been associated with a variety of environmental and behavioral risk factors, including *H. pylori* colonization, cigarette smoking, consumption of nitrates and salted foods, as well as genetic and epigenetic factors,[22] other environmental factors, including occupational exposures may also play an important role in gastric carcinogenesis.

Previous studies of night shift work and stomach cancer risk reported no clear association. Parent et al. [15] examined risk for 10 cancer sites in a population-based case-control study in Montreal, Canada, including 228 incident male stomach cancer cases. There was a weak non-significant association observed for stomach cancer risk among night shift workers (odds ratio (OR) = 1.3, 95% confidence interval (CI) 0.9-2.1). A cohort study of German male chemical workers reported no association between rotating shift work and stomach cancer incidence (hazard ratio (HR) = 1.2, 95% CI 0.5-2.7).[23] A Swedish study evaluated shift work by classifying jobs according to the percentage of shift workers and reported a standardized incidence ratio (SIR) of 1.2% (95% CI 0.6-2.3) for stomach cancer in women and 1.1 (95% CI 1.0-1.2) in men.[16]

We evaluated the association between night shift work and stomach cancer risk in a large population-based case-control study, MCC-Spain which included detailed data

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on lifetime night shift work history as well as a variety of potential confounding factors. The MCC-Spain study has previously been used to examine associations between night shift work and both breast and prostate cancer risk and presents a unique opportunity to examine associations at other cancer sites.[24, 25]

METHODS

Study Population

The MCC-Spain study is a multi-centre, population-based, case-control study designed to examine potential associations between various environmental and genetic factors and risk of five common cancers (breast, chronic lymphocytic leukaemia, colorectal, prostate, and stomach cancer). Detailed data on the study is provided elsewhere.[26] In brief, the study included 12 provinces and 23 public hospitals across Spain. Recruitment of incident cancer cases took place between the years 2008 and 2013 and used the same set of controls for all cancer cases. The MCC-Spain study was reviewed and approved by the Ethics committees of the participating institutions. All participants provided informed consent prior to enrollment into the study.

Newly diagnosed stomach cancer cases were recruited in ten Spanish centres (Asturias, Barcelona, Cantabria, Granada, Huelva, Leon, Madrid, Murcia, Navarra, and Valencia). Cases were defined by the following International Classification of Diseases 10 (ICD-10) codes: C16 and D00.2 representing stomach cancer cases, and C15.5 representing cancer cases of the lower third of the oesophagus. All cancer

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cases were aged 20 to 85 years, confirmed histologically, and lived in the study area for at least six months before diagnosis. Exclusion criteria included having communication difficulties or a physical condition prohibiting them from participation. A total of 459 stomach cancer cases were recruited, with a response rate of 55%. Clinical data was obtained from medical records including tumor histological type, localization, Lauren classification, the 2010 classification of the World Health Organization (WHO), and degree of differentiation.[27, 28] Data on *H. pylori* status was available in 279 cases, with 93% positive. In the remaining cases, data on *H. pylori* status was unknown.

Controls aged 20 to 85 years were selected randomly from the rosters of General Practitioners at the Primary Health Centres (PHC) involved in the study, lived in the same catchment area as cases, and were frequency-matched to all cancer cases by sex and age in 5-year groups. Since the same set of controls was used for all cancer cases in MCC-Spain there was no initial exclusion criteria related to personal cancer history as part of the recruitment process. A total of 3,440 eligible controls were recruited with a response rate of 51%.

Data Collection and Night Shift Work Definition

Detailed data on a range of socio-demographic, lifestyle, and clinical factors was collected in face-to-face interviews by trained personnel. Occupational history data was obtained for all jobs held for more than one year including job title, tasks, start and stop dates, and shift work information (time schedules, hours worked per day, percentage worked in the morning, evening, and night). Ever night shift work was

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defined as working partly or entirely between 12 am and 6 am. Permanent night

shifts consisted of working constantly partly or entirely between 12 am and 6 am.

Rotating night shifts consisted of working at least three night shifts per month, or 10%

of working time. Cumulative duration of night shifts, permanent night shifts, and

rotating night shifts was calculated as the total number of years worked at night.

Statistical Analysis

We analyzed the association between night shift work and stomach cancer risk using

unconditional logistic regression models. We calculated adjusted ORs and 95% CIs

for stomach cancer in relation to ever performing night shift work, permanent night

shift work, or rotating night shift work, as well as categories of cumulative duration

(years). Models were adjusted *a priori* for age, sex, centre, and level of education.

The reference group included subjects who were ever employed but had never

performed night shifts.

We examined the impact of further adjustment for body mass index (BMI), cigarette

smoking status, family history of stomach cancer, physical activity level during

adulthood (from age 16 years, excluding the last 2 years prior to diagnosis or

interview (METS h/week)), current sleep duration (≤ 6, 7-8, ≥ 9 h/day), and ever

sleep problems (for atleast 1 year). Further, in a sub-set of all participants (75% of

cases and 86% of controls) additional data on usual dietary intake during the previous

year was collected using a self-administered modified version of a semi-quantitative

Food Frequency Questionnaire (FFQ), designed to include regional food products.

Adjustment for total energy consumption, and consumption of red-meat, processed-

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meat, cured-meat, fresh fruit and vegetables, and alcohol was also examined among this participant sub-set.

Stratified analyses were conducted by categories of age (<65 vs ≥ 65 years), sex, education (primary or less vs high school/university), family history of stomach cancer (none vs any), cigarette smoking status (non-smoker, former smoker, current smoker), BMI (18-25 vs > 25 kg/m^2), physical activity level (inactive/slightly active vs moderately/very active), sleep duration (≤ 6, 7-8, ≥ 9 h/day), and sleep problems (never vs ever). Potential effect modification was assessed by entering product terms into unconditional logistic regression models and assessing their significance according to the likelihood ratio test. To evaluate the association between night shift work and severity and clinical presentation of the disease, we used multinomial logistic regression to analyse associations according to Lauren classification (intestinal vs diffuse) and tumor localisation (cardia tumors, including the oesophageal junction and lower third of the oesophagus vs non-cardia tumors).

Analyses were conducted using Stata 14.[29]

RESULTS

A total of 374 stomach cancer cases and 2,481 controls were included in the main analysis following the exclusion of participants with no or missing occupational history data (66 cases, 516 controls), participants from study centres with few (<5) cases (Granada and Murcia) (5 cases, 118 controls), controls with a personal history

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of any cancer (n = 204), and participants with missing data on key covariates of interest (14 cases, 121 controls).

There were proportionally more included male cases than controls (Table 1). Cases also tended to be older, have a lower educational level, and reported stomach cancer more frequently in their family history. Cases also reported exercising less during adulthood, having a lower BMI, sleeping more, having a greater total energy and red meat consumption, and a lower alcohol consumption than controls.

Excluded participants tended to be somewhat older (mean (SD) age excluded cases = 73.0 (9.3) years, controls = 68.2 (10.5) years), more likely female (62.4% cases, 49.3% controls), and have a lower level of educational attainment (89.4% cases, 65.9% controls) compared to included participants ($P < 0.01$).

Table 2 summarizes the characteristics of permanent and rotating night shift controls compared to day workers. There were proportionally more male subjects amongst night shift workers. Night shift workers also tended to achieve lower educational levels, report being a current or former smoker more frequently, have a higher BMI, longer sleep duration, and a higher total energy and red meat consumption compared to those who had never worked night shifts. Table 3 provides a listing of the main occupations contributing to permanent or rotating night shift work. These include housekeeping and restaurant services workers (9.6%); motor-vehicle drivers (8.1%); personal care and related workers (6.7%); and domestic and related helpers, cleaners and launderers (4.5%).

The association between ever working night shifts, permanent night shifts, or rotating night shifts and stomach cancer risk is presented in Table 4. A total of 25.7% of cases and 22.5% of controls reported ever working night shifts. Among night shift workers, there were more that had worked in a rotating night shift schedule (13.6% cases, 13.6% controls) than in permanent night shifts (12.0% cases, 8.8% controls). There was no association between ever working night shifts and stomach cancer risk (OR = 1.0, 95% CI 0.8-1.3). There was a weak positive, non-significant association with having had worked for at least one year in permanent night shifts compared to never having worked night shifts (OR = 1.2, 95% CI 0.9-1.8). There was no association with rotating night shifts (OR = 0.9, 95% CI 0.6-1.2).

The exposure-response relationship between cumulative duration of night shifts and stomach cancer risk showed an inverse "U" shape (Table 4). The highest risk for permanent night shift workers was observed in the intermediate duration category (OR 10-20 years = 2.0, 95% CI 1.1-3.6) (*p* trend = 0.19). Analysis according to quartiles of cumulative duration did not result in any meaningful change in the relationship (results not shown). There was also no clear trend according to categories of lifetime cumulative frequency of night shifts with ORs of 1.5 (95% CI 0.8-2.8) and 1.6 (95% CI 0.9-2.8) (*P* = 0.07) observed for categories of < 1,800 and ≥ 1,800 nights worked respectively among the 56.8% of permanent night shift workers with data on frequency of night shifts.

The association between ever, permanent, or rotating night shift work and stomach cancer risk was similar after further adjusting for BMI, cigarette smoking status, family history, and physical activity level (Table 4). Further adjustment for either

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sleep duration or sleep problems also resulted in virtually identical ORs (results not shown). The association between night shift work and stomach cancer risk also did not change upon evaluation of participants with either a reliable or high quality interview, as reported by the interviewer (86.1% of participants) (results not shown).

In analysis of associations among the sub-set of participants who completed the FFQ (279 cases and 2,157 controls), results were somewhat stronger but showed the same general pattern. In the fully-adjusted model, the OR (95% CI) for permanent night shift work was 1.5 (95% CI 1.0-2.4) adjusting for detailed dietary and alcohol consumption data (Table 5). Results according to cumulative duration also revealed a stronger association for participants who worked from 10 to 20 years in permanent night shifts (OR = 3.4, 95% CI 1.7-6.7) and no evidence for a trend ($p = 0.12$).

There was no evidence for effect modification of associations between permanent night shift work and stomach cancer risk according to various demographic and lifestyle factors examined ($P > 0.05$) (results not shown). Associations with permanent night shift work were also similar according to categories of Lauren classification (relative risk ratio (RRR) intestinal = 1.8, 95% CI 1.0-3.2, n = 128 cases; RRR diffuse = 1.4, 95% CI 0.7-2.8, n = 86 cases) and tumor localisation (RRR cardia = 1.3, 95% CI 0.7-2.4, n = 98 cases; RRR non-cardia = 1.3, 95% CI 0.9-2.0, n = 267 cases) where data were available.

DISCUSSION

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Overall, we found equivocal evidence concerning an association between night shift work and stomach cancer risk. Although there was a weak positive, non-significant association with having worked for at least one year in permanent night shifts compared to never having worked night shifts, there was no clear trend with number of years of permanent night shift work, with the highest risk observed in the intermediate duration category of 10-20 years. There was no association with rotating night shifts.

The reason for the observed inverse "U" shape relationship with cumulative duration of night shifts is unclear. Possible explanations may include random variation or a type of healthy worker effect, including adaptation to night shift work in long-term or permanent night shift workers,[30] though this is unlikely as symptoms of stomach cancer are apparent close to its detection. Further, results did not change when stratifying by tumor grade.

The main results of the study are in concordance with the limited number of previous data related to the association of night shift work and stomach cancer risk. Though one study reported a weak positive, non-significant association similar to the one reported here,[15] another study based on personnel records reported no association between rotating shift work and stomach cancer incidence in men.[22] One study that did not evaluate individual information on shift work also reported no clear association.[16]

In previous analyses in MCC-Spain, there was a weak positive association between being a night shift worker and breast cancer risk, particularly amongst premenopausal

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women and for tumors with positive hormonal receptors.[24] Risk was also higher

for women with an evening or morning chronotype (an individual characteristic that

describes the circadian phase and correlates with diurnal preference, the individual

preference for morning or evening activity) compared to the neither type. Night shift

workers, particularly those of long duration and evening chronotype, were also at

higher prostate cancer risk.[25] There was no chronotype information available in

MCC-Spain for stomach cancer cases.

The melatonin hypothesis is one of the most widely accepted pathological pathways

related to increased cancer risk amongst night shift workers though it remains

controversial its relevance for stomach cancer is unclear.[18] Recently, an inverse

association between urinary melatonin levels and prostate cancer was observed

among elderly men.[31] Some studies showed decreased blood or urine melatonin

levels amongst night shift workers, though others showed interpersonal variability

suggesting that some people may be better able to adapt to night shifts than

others.[32, 33]

The current study has several strengths including that it is a population-based multi-

centre study with a considerable number of cases and controls. We obtained detailed

data on night shift work including type of night shifts, their cumulative duration and

frequency. The prevalence of night shift work in this study, 22.5% of controls

reporting ever night shift work, is similar to other European estimates of night

workers (19% of workers in the EU27 overall increasing to 23% among men).[2] A

recent Spanish survey observed that 13% of workers reported night shift work in the

past year, which may be lower than our estimate based on lifetime history among

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controls in larger population centres.[34] Although we defined night shift work as working partly or entirely between 12 am and 6 am, as in previous work in MCC-Spain,[24, 25] it is possible that this definition may have limited our ability to detect an association if work during a particular portion of the night may be more disruptive than another, such as in the early morning period for example, or among workers with greater proportions of the shift at night. However little is known regarding the importance of particular timing or patterns of night shift work.

Although residual confounding cannot be ruled out, there was information available for many recognized risk factors for stomach cancer, though dietary variables were only available in a sub-sample of the total study population and reflected intake during the previous year, which may be affected by the developing cancer. BMI also reflects current BMI at the study interview. Though reported total energy and red meat consumption was slightly greater among ever vs never night shift workers, there may also be other differences in dietary patterns including eating patterns, cooking method, and eating-out for example that were not captured in the study questionnaire here that may be relevant.[35, 36] Results were largely unchanged with adjustment for such detailed demographic and lifestyle data here.

Although some data was available on self-reports of sleep duration and history of sleep problems, such data likely reflect more recent sleep habits and do not necessarily relate with sleeping problems due to shift work. There were also few differences between day, permanent night, and rotating night workers in terms of sleep duration and problems here. Confounding by other occupational exposures is unlikely as few occupational exposures have been related with stomach cancer.[37,

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38] Night shift work is also not relevant for some of the occupations that have been previously linked to stomach cancer (such as coal miners, metal processing, and rubber manufacturing workers for example) (Table 3).[39] Although information was available for *H. Pylori* infection, the high proportion of positive of cases did not allow further evaluation of this factor.

Other potential limitations include the moderate response rate of 55% in cases and 51% in controls. A low response rate among cases is common in studies on stomach cancer because of the poor prognosis of the disease. Proxy respondents were also not permitted as part of MCC-Spain. Population-based studies are also known to have lower response rates for controls than hospital-based studies. The reasons for the low response rate could have differed between cases and controls and could lead to selection bias. For example, people with a higher educational level tended to participate more in MCC-Spain,[26] were less likely to have worked night shifts, and experience a lower risk of stomach cancer than those with a low educational attainment.[40] Also relevant to the current work, there may be selection bias by occupational status with controls currently working night shifts possibly less prone to participate due to their work schedules, which could lead to some spurious association. However, telephone contact was attempted during recruitment a minimum of five different times in the day. There were also no clear differences in findings according to age group, where potential selection bias by occupational status may be minimized in the older age group, or education here, though statistical power was limited. Finally, recruitment was based in the public health system, which would not capture government employees, particularly controls, with private insurance.

In conclusion, our study found no clear evidence concerning an association between night shift work and stomach cancer risk. Further analysis including data on chronotype may contribute to better understanding the relationship between night shift work and stomach cancer risk.

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COMPETING INTERESTS

The authors have no competing interests to declare.

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Table 1. Distribution of participant characteristics, stomach cancer cases and controls, MCC-Spain, 2008-2013.

Characteristic	Controls (N = 2,481) N (%)	Cases (N =374) N (%)	P value[2]
Age (years); mean (SD)	62.4 (11.4)	64.9 (12.5)	*<0.001*
Sex			
Male	1,406 (56.7)	276 (73.8)	
Female	1,075 (43.3)	98 (26.2)	*<0.001*
Educational Level			
Less than high school	1,172 (47.2)	239 (63.9)	
High school or greater	1,309 (52.8)	135 (36.1)	*<0.001*
Centre			
Madrid	633 (25.5)	102 (27.3)	
Barcelona	679 (27.4)	95 (25.4)	
Leon	207 (8.3)	47 (12.6)	
Navarra	305 (12.3)	79 (21.1)	
Cantabria	144 (5.8)	9 (2.4)	
Asturias	107 (4.3)	8 (2.1)	
Valencia	302 (12.2)	24 (6.4)	
Huelva	104 (4.2)	10 (2.7)	*<0.001*
Family History of Stomach Cancer			
None	2,087 (88.3)	282 (79.4)	
Any	277 (11.7)	73 (20.6)	*<0.001*
Cigarette Smoking Status			
Non-smoker	1,002 (40.4)	128 (34.2)	
Former smoker	895 (36.1)	144 (38.5)	
Current smoker	584 (23.5)	102 (27.3)	*0.06*
BMI (kg/m^2); mean (SD)	26.7 (4.2)	25.1 (4.0)	*<0.001*
Physical Activity (METS h/week)			
Inactive / slightly active (0-8)	1,311 (52.8)	236 (63.1)	
Moderately / very active (>8)	1,170 (47.2)	138 (36.9)	*<0.001*
Sleep Duration (h/day); mean (SD)	7.0 (1.4)	7.2 (1.6)	*0.004*
Sleep Problems			
Never	1,548 (67.2)	270 (72.4)	
Ever	754 (32.8)	103 (27.6)	*0.05*
Dietary Habits (Median (IQR))[1]			
Total energy consumption (kcal/d)	1,849.2 (739.8)	2,055.2 (914.6)	*<0.001*
Red meat consumption (g/d)	58.3 (48.3)	73.8 (59.6)	*<0.001*
Vegetable consumption (g/d)	168.1 (133.4)	154.0 (136.6)	*0.05*
Fruit consumption (g/d)	323.6 (282.0)	326.4 (268.4)	*0.92*
Alcohol consumption (g ethanol/d)	4.9 (15.7)	3.3 (17.6)	*0.02*

[1] Subset 2,157 controls / 279 cases.

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[2] Chi-squared test for categorical variables; t-test for continuous with normal distribution; Mann-Whitney test for continuous with non-normal distribution.
Note: Some column totals do not add up to the sum due to missing data.

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Table 2. Distribution of participant characteristics, stomach cancer controls, by night shift history, MCC-Spain, 2008-2013.

Characteristic	Day Worker	Permanent Night Worker	Rotating Night Worker	
	(N = 1,924)	(N =219)	(N =338)	
	N (%)	N (%)	N (%)	P value[2]
Age (years) Mean (SD)	62.2 (11.6)	61.6 (10.9)	63.8 (10.9)	0.03
Sex				
Male	1,011 (52.5)	151 (68.9)	244.0 (72.2)	
Female	913 (47.5)	68 (31.1)	94.0 (27.8)	<0.001
Educational Level				
Less than high school	862 (44.8)	131 (59.8)	179.0 (53.0)	
High school or greater	1,062 (55.2)	88 (40.2)	159.0 (47.0)	<0.001
Centre				
Madrid	540 (28.1)	38 (17.4)	55.0 (16.3)	
Barcelona	481 (25.0)	113 (51.6)	85.0 (25.1)	
Navarra	170 (8.8)	5 (2.3)	32.0 (9.5)	
Leon	249 (12.9)	13 (5.9)	43.0 (12.7)	
Asturias	99 (5.1)	6 (2.7)	39.0 (11.5)	
Huelva	82 (4.3)	7 (3.2)	18.0 (5.3)	
Cantabria	232 (12.1)	23 (10.5)	47.0 (13.9)	
Valencia	71 (3.7)	14 (6.4)	19.0 (5.6)	<0.001
Family History of Stomach Cancer				
None	1,610 (87.6)	188 (91.3)	289.0 (90.3)	
Any	228 (12.4)	18 (8.7)	31.0 (9.7)	0.14
Cigarette Smoking Status				
Non-smoker	829 (43.1)	62 (28.3)	111.0 (32.8)	
Former smoker	653 (33.9)	87 (39.7)	155.0 (45.9)	
Current smoker	442 (23.0)	70 (32.0)	72.0 (21.3)	<0.001
BMI (kg/m^2); mean (SD)	26.5 (4.3)	27.5 (4.2)	27.2 (4.0)	<0.001
Physical Activity (METS h/week)				
Inactive / slightly active (0-8)	1,019 (53.0)	127 (58.0)	165.0 (48.8)	
Moderately / very active (>8)	905 (47.0)	92 (42.0)	173.0 (51.2)	0.10
Sleep Duration (h/day); mean (SD)	6.9 (1.3)	7.0 (1.4)	7.2 (1.4)	0.02
Sleep Problems				
Never	1,201 (67.4)	131 (66.8)	216.0 (66.5)	
Ever	580 (32.6)	65 (33.2)	109.0 (33.5)	0.94
Dietary Habits (Median (IQR))[1]				
Total energy consumption (kcal/d)	1,836.7 (719.9)	1,950.0 (820.5)	1,911.9 (762.8)	0.02
Red meat consumption (g/d)	57.0 (47.9)	59.3 (51.4)	63.7 (50.3)	0.02
Vegetable consumption (g/d)	167.7 (129.2)	168.3 (151.6)	173.1 (148.1)	0.93
Fruit consumption (g/d)	328.0 (277.0)	266.2 (288.8)	325.5 (290.9)	0.06
Alcohol consumption (g ethanol/d)	4.8 (14.6)	4.4 (15.1)	6.5 (21.3)	0.10

[1]1,684 day workers, 180 permanent night workers, 293 rotating night workers.

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[2] Chi-squared test for categorical variables; anova for continuous with normal distribution; Kruskal-wallis test for continuous with non-normal distribution.
Note: Some column totals do not add up to the sum due to missing data.

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Table 3. Main occupations contributing to night shift work (including permanent or rotating night shifts), MCC-Spain, 2008-2013.

ISCO88	Job Title	N (%)
512	Housekeeping and restaurant services workers	80 (9.6)
832	Motor-vehicle drivers	68 (8.1)
513	Personal care and related workers	56 (6.7)
913	Domestic and related helpers, cleaners and launderers	38 (4.5)
223	Nursing and midwifery professionals	34 (4.1)
932	Manufacturing labourers	28 (3.4)
741	Food processing and related trades workers	25 (3.0)
010	Armed forces	22 (2.6)
723	Machinery mechanics and fitters	21 (2.5)
933	Transport labourers and freight handlers	21 (2.5)

Note: Based on 837 jobs and 78 ISCO88 three-digit job titles with reported night shift work. N (%) represents the number (%) of jobs in each category.

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Table 4. Association between night shift work and stomach cancer risk, MCC-Spain, 2008-2011.

	Controls (N = 2,481) N (%)	Cases (N = 374) N (%)	OR (95% CI)[3]	OR (95% CI)[4]
Never night shift[1]	1,924	278	1.0 (ref)	1.0 (ref)
Ever night shift	557	96	1.0 (0.8-1.3)	1.1 (0.8-1.4)
Permanent night shift[2]	219	45	1.2 (0.9-1.8)	1.3 (0.9-1.9)
Rotating night shift	338	51	0.9 (0.6-1.2)	1.0 (0.7-1.4)
Lifetime cumulative duration of night shift work				
Cumulative duration of ever night shift (permanent or rotating workers)				
<10 years	191	28	1.0 (0.6-1.5)	1.1 (0.7-1.6)
10 to 20 years	120	21	1.1 (0.7-1.9)	1.1 (0.7-1.9)
≥ 20 years	246	47	1.0 (0.7-1.5)	1.1 (0.8-1.6)
P for trend			*0.73*	*0.57*
Cumulative duration of permanent night shift				
<10 years	91	14	1.1 (0.6-2.0)	1.1 (0.6-2.1)
10 to 20 years	51	16	2.0 (1.1-3.6)	2.0 (1.1-3.8)
≥ 20 years	77	15	1.1 (0.6-2.0)	1.1 (0.6-1.9)
P for trend			*0.19*	*0.24*
Cumulative duration of rotating night shift				
<10 years	100	14	0.9 (0.5-1.6)	1.0 (0.5-1.8)
10 to 20 years	69	5	0.5 (0.2-1.3)	0.5 (0.2-1.2)
≥ 20 years	169	32	1.0 (0.7-1.5)	1.1 (0.7-1.7)
P for trend			*0.68*	*0.96*

[1]Reference group. Includes day workers and rotating workers (no nights).
[2] Subjects who reported permanent as well as rotating night shift work in their occupational history are included in the permanent workers group.
[3]Adjusted for age, sex, educational level and centre.
[4]Adjusted for age, sex, educational level, centre, BMI, cigarette smoking status, family history, physical activity level.

Table 5. Association between night shift work and stomach cancer risk, dietary questionnaire participants, MCC-Spain, 2008-2011.

	Controls (N = 2,157) N (%)	Cases (N = 279) N (%)	OR (95% CI)[1]	OR (95% CI)[2]
Never night shift	1,684	207	1.0 (ref)	1.0 (ref)
Ever night shift	473	72	1.1 (0.8-1.5)	1.1 (0.8-1.5)
Permanent night shift[3]	180	37	1.6 (1.0-2.4)	1.5 (1.0-2.4)
Rotating night shift	293	35	0.8 (0.5-1.2)	0.8 (0.5-1.2)
Lifetime cumulative duration of night shift work				
Cumulative duration of night shift (permanent or rotating workers)				
<10 years	161	21	1.1 (0.7-1.8)	1.1 (0.6-1.8)
10 to 20 years	98	20	1.5 (0.9-2.5)	1.6 (0.9-2.9)
≥ 20 years	214	31	0.9 (0.6-1.4)	0.9 (0.6-1.4)
p for trend			*0.92*	*0.96*
Cumulative duration of permanent night shift				
<10 years	77	11	1.3 (0.7-2.5)	1.2 (0.6-2.5)
10 to 20 years	41	16	2.9 (1.5-5.4)	3.4 (1.7-6.7)
≥ 20 years	62	10	1.1 (0.5-2.3)	0.9 (0.4-2.0)
p for trend			*0.06*	*0.12*
Cumulative duration of rotating night shift				
<10 years	84	10	0.9 (0.5-1.9)	0.9 (0.4-1.9)
10 to 20 years	57	4	0.5 (0.2-1.5)	0.5 (0.2-1.5)
≥ 20 years	152	21	0.8 (0.5-1.4)	0.9 (0.5-1.5)
p for trend			*0.30*	*0.41*

[1]Adjusted for age, sex, educational level and centre .

[2]Adjusted for age, sex, educational level, centre, BMI, cigarette smoking status, family history, physical activity level, total energy intake, grams of red meat, grams of vegetables, grams of fruit, alcohol consumption.

[3] Subjects who reported permanent as well as rotating night shift work in their occupational history are included in the permanent workers group.

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