Original article

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Shift work and colorectal cancer risk in the MCC-Spain case–control study

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Objectives Shift work that involves circadian disruption has been associated with a higher cancer risk. Most epidemiological studies to date have focused on breast cancer risk and evidence for other common tumors is limited. We evaluated the risk for colorectal cancer (CRC) in relation to shift work history in a population-based case–control study in Spain.

Methods This analysis included 1626 incident CRC cases and 3378 randomly selected population controls of both sexes, enrolled in 11 regions of Spain. Sociodemographic and lifestyle information was assessed in face-to-face interviews. Shift work was assessed in detail throughout lifetime occupational history. We estimated the risk of colon and rectal cancer associated with rotating and permanent shift work (ever, cumulative duration, age of first exposure) using unconditional logistic regression analysis adjusting for potential confounders.

Results Having ever performed rotating shift work (morning, evening and/or night) was associated with an increased risk for CRC [odds ratio (OR) 1.22, 95% confidence interval (95% CI) 1.04–1.43], as compared to day workers. Having ever worked permanent night shifts (≥3 nights/month) was not associated with CRC risk (OR 0.79, 95% CI 0.62–1.00). OR increased with increasing lifetime cumulative duration of rotating shift work (P-value for trend 0.005) and were highest among subjects in the top quartiles of exposure (3rd quartile, 20–34 years, OR 1.38, 95%CI 1.06–1.81; 4th quartile, ≥35 years, OR 1.36, 95% CI 1.02–1.79).

Conclusions These data suggest that rotating shift work may increase the risk of CRC especially after long-term exposures.

Key terms circadian disruption; colon cancer; lifestyle; night work; prevention; rectal cancer; rotating shift work; shift worker.

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide and among the top three leading causes of cancer death among both men and women (1–3). The adoption of a western lifestyle and diet seem to play an important role in the development of CRC (4). The International Agency for Research on Cancer (IARC) (Group 2A) has classified shift work that involves circadian disruption as a probable human carcinogen (5). Most epidemiological studies have focused on the link between night shift work and breast cancer risk (6) and evidence for other tumor sites is scarce. To date only a few studies have evaluated the association between shift work and CRC, with limited exposure information, and results have been mixed (7–11). In a recent report, shift work was associated with stomach cancer, although the association was weak and not significant (12). Altogether evidence in humans is still very limited and it remains unknown whether shift work is associated with an increased risk of gastrointestinal tumors.

The carcinogenicity of shift work is biologically plausible and a number of underlying mechanisms have been suggested to explain this effect (13, 14). Circadian or clock genes drive the expression of 5–20% of the genome and regulate the timing of basic cell functions, such as DNA damage repair (15). Disruption of the circadian clock may lead to deregulated cell proliferation, which has been implicated in colorectal carcinogenesis. Furthermore a key circadian hormone, melatonin, exhibits direct oncostatic action against gastrointestinal tumors (16) and is suppressed by light in night shift workers (17). Lower melatonin levels have also been described among CRC patients compared to healthy controls (18). Shift work may also lead to a less-healthy lifestyle and diet (19, 20), which are associated with a number of adverse metabolic outcomes such as obesity that may additionally increase CRC risk (19, 21). This hypothesis is of particular importance for disease prevention among shift workers since these are potentially modifiable risk factors.

In the present study, we examined the association between shift work and CRC among men and women enrolled in the multi-case–control (MCC)-Spain study, a population-based case–control study. Shift work was documented in different occupational settings and assessed in detail over lifetime. We evaluated different types of shift work (rotating versus permanent), cumulative lifetime shift work duration and different exposure windows in relation to CRC risk.

Methods

MCC-Spain is a population-based multi-case–control study on frequent tumors (breast, colorectal, prostate, stomach, and chronic lymphocytic leukemia) in Spain with the main aim to investigate environmental and genetic risk factors for such diseases. The study assessed incident cancer cases diagnosed from 2008–2013 in 23 public hospitals distributed around 12 Spanish regions

(Asturias, Barcelona, Cantabria, Girona, Granada, Guipuzkoa, Huelva, León, Madrid, Murcia, Navarra and Valencia) and used the same set of population controls for all cases. Detailed data on the study is provided elsewhere (22).

Cases were men and women, aged 20–85 years old, with a new histologically confirmed diagnosis of CRC living in the catchment area of the participating hospitals for ≥6 months. Controls were selected randomly from the rosters of general practitioners (GP) at the primary health centers (PHC) involved in the study and were frequency-matched to cases by age (in 5-year age groups), sex and region of residence. Controls were free of CRC history and lived in the same catchment area as cases for the same period of time (<6 months). Subjects incapable of participating in the study due to communication difficulties (mental or speaking problems) or excess impairment of physical ability (4 controls and 78 cases) were excluded. In total, 2171 new CRC cases and 4101 population controls were enrolled during the study period. Response rates varied by center and on average were 68% among cases and 54% among controls with valid telephone numbers. Detailed data on occupational history as well as a variety of other demographic, medical, and lifestyle factors was collected through face-to-face interviews performed by trained personnel.

Exposure assessment

Shift work was assessed through lifetime occupational history consisting of all jobs held for at least one year and included information on age at beginning and end of the job, job title, and the main task of the job. Subjects self-classified each job as day, night or rotating. For day and night jobs, we also assessed the exact time-schedules, while this information was not available for rotating jobs. In a follow-up of the MCC-Spain study, we collected this additional information for breast and prostate cancer cases (25) but not for colorectal cases. Therefore, permanent night shift work was defined – by the study investigators – as a fixed schedule that involved working partly or entirely (≥1 hour) between 24:00–06:00 hours, ≥3 times per month. Rotating shift work was defined as any rotation between morning, evening and/or night shifts. Since time-schedules were not available for these jobs, we used the reported nights/month to compare schedules that included ≥3 nights/month (in which case a subject would be classified as "rotating night") versus <3 nights/month (in which case a subject would be classified as "rotating other"). Permanent night shift workers reported on average 20 [standard deviation (SD) 8.5] nights/month whereas rotating shift workers reported 10 (SD 7.2) nights/month. The reference group consisted of subjects who had never worked shift work (ie, only day workers).

A self-administered, validated, semi-quantitative, 140 food-item, food frequency questionnaire (23) was also completed by 85% of participants. Habitual daily consumption of red meat (including processed meat), vegetable, fruit and total energy intake were calculated based on different food items and using food composition tables. Alcohol intake (grams ethanol/day) was calculated for both present and past (at 30–40 years of age) consumption. CRC histological type (adenocarcinoma, mucinous adenocarcinoma, signet ring-cell carcinoma, squamous cell carcinoma, medullary carcinoma, undifferentiated carcinoma, other, type not specified) and tumor localization was available through hospital medical records. Most tumors were adenocarcinomas (92% adenocarcinomas, 5.5% mucinous carcinomas, 1.5% other types, 1% not specified). In the present analysis, tumor anatomical site was analyzed separately for colon (proximal, distal) and rectum and also combined.

The MCC-Spain study followed the national and international directives such as the deontological code and declaration of Helsinki and the Spanish law on confidentiality of data. All subjects that agreed to participate and fulfilled the eligibility criteria signed an informed consent form prior to study participation.

Statistical analyses

In bivariate analysis, we examined the distribution of established or suspected risk factors for CRC in cases and controls and also across shift work profiles. We evaluated the association between shift work and CRC using unconditional logistic regression models and estimated odds ratios (OR) with 95% confidence intervals (95% CI) for different shift work metrics (ever shift work, lifetime cumulative duration, age of first shift work exposure, years since last exposure). We also performed tests for trends across categories of exposure. All statistical tests were two-sided.

Independent variables considered for inclusion in multivariate analysis were selected from the list of CRC risk factors and are shown in the directed acyclic graph (Supplemental figure A, www.sjweh.fi/index.php?page=data-repository). The basic models included age, center, educational level and sex according to the study design. The further-adjusted model also included BMI, family history of CRC in first degree relatives, cigarette smoking, past alcohol consumption (grams ethanol/day), total energy and red meat consumption, leisure-time physical activity [mean metabolic equivalent (METS)/week in the past ten years; inactive (0 METS hours/week), slightly active (0–8 METS hours/week), moderately active (8–16 METS hours/week) and very active (>16 METS hours/week)], aspirin/non-steroid anti-inflammatory (NSAID) use, and sleep duration. A category of missing values was used for each

Table 1. Distribution of characteristics among colorectal cancer cases and controls. Numbers may differ due to missing values. [SD=standard deviation; BMI=body mass index]

Characteristics	Controls (N=3378)				Cases (N=1626)				P-value
	N	%	Mean	SD	N	%	Mean	SD	
Age (years)			65.5	11.7			66.1	10.9	<0.0001
Sex									
Male	1833	54.3			1136	69.9			
Female	1545	45.7			490	30.1			<0.0001
Family history of colorectal cancer [a]									
No	3084	91.3			1320	81.2			
Yes	283	8.4			290	17.8			<0.0001
Educational level									
Less than primary	550	16.3			451	27.7			
Primary	1055	31.2			606	37.3			
High school	1013	30.0			364	22.4			
University	760	22.5			205	12.6			<0.0001
BMI (kg/cm^2)									
<22.5	551	16.3			186	11.4			
22.5–25	739	21.9			319	19.6			
25–30	1386	41.0			708	43.5			
≥30	702	20.8			413	25.4			<0.0001
Tobacco smoking									
Never smoker	1397	41.4			586	36.0			
Ever smoker	1970	58.3			1027	63.2			<0.0001
Physical activity [b]									
Inactive or a little active	1798	53.2			914	56.2			
Moderately or very active	1580	46.8			712	43.8			0.047
Sleep habits									
Sleep duration (hours/day)			7.0	1.3			7.2	6.9	<0.0001
Ever sleep problems	1212	35.9			521	32.0			0.010
Diet habits									
Total energy intake (kcal/day)	1907	640			2035	704			<0.0001
Past alcohol consumption (g ethanol /day) [c]			18.4	27.5			27.1	35.1	<0.0001
All red meat consumption (g/day) [d]			63.5	39.9			73.9	48.5	<0.0001
Vitamin D intake (g/day)			2.8	1.5			2.8	1.7	0.247
Calcium intake (g/day)			913.7	346.2			921.3	349.5	0.498
Drug use									
NSAIDS/aspirin	1045	35.6			344	24.3			<0.0001
Females									
Postmenopausal [e]	1027	66.5			402	82.0			<0.0001
Nulliparouse	302	19.6			72	14.7			0.016
Ever oral contraceptives [e]	781	50.6			164	33.7			<0.0001
Ever hormonal therapy [e]	137	7.5			27	3.7			<0.0001

[a] First degree relatives.
[b] Assessed over the last 10 years excluding 2 years prior to diagnosis.
[c] Assessed at 30–40 years.
[d] Includes red meat (pork, beef, lamb, duck), processed meat and cured meat.
[e] Among females.

categorical confounder that was introduced in the model. In addition a full-case analysis was performed in the population with no missing data which yielded similar results. Wald tests for interaction were used to evaluate possible effect modification by age (<50, 50–70, >70 years), sex, obesity (BMI <30, BMI ≥30) and smoking status (ever versus never smoker).

Results

The present analysis included 1626 cancer cases and 3378 population controls with complete shift work data. Table 1 shows the sociodemographic and lifestyle characteristics of the study population by case–control status. Cases were older (mean 66.1 versus 62.5 years), heavier (BMI>30, 25.4% versus 20.8%) and had family history of CRC reported more frequently (17.8% versus 8.4%) compared to controls. Cases also reported more frequently smoking (63.2 versus 58.3%), physical inactivity (56.2% versus 53.2%), and a higher total energy intake, red meat consumption, and past alcohol consumption (P<0.0001). Cases were less likely to report use of aspirin or NSAIDS drugs (24.3% versus 35.6%) or than controls.

The characteristics of different shift work profiles are presented in table 2. Subjects that had ever performed permanent or rotating shift work were more frequently males, less educated, less physically active and more likely to smoke, compared to never shift workers. They were also more likely to report a higher total caloric intake, red meat consumption and past alcohol consumption. Compared to permanent night workers, subjects with rotating shift work history had a higher educational level, were less likely to smoke but more likely to consume alcohol and red meat. Permanent night work was most commonly found in restaurant services while rotating shift work was most prominent in transportation and commercial drivers (Supplementary table A, www.sjweh.fi/index.php?page=data-repository).

Subjects that had ever worked in rotating work (18% of controls and 24% of cases) had a higher risk for CRC (OR 1.28, 95% CI 1.10–1.49) compared to day workers (table 3). Having ever worked in permanent night work (7.9% of controls and 7.3% of cases) was associated with a borderline lower CRC risk (OR 0.79, 95% CI 0.62–1.00). Risk estimates were slightly attenuated after adjusting for a number of potential confounders, listed under table 3 (OR 1.22, 95% CI 1.04–1.43). The OR for having worked in rotating shift schedules with >3 nights/month (12.2% of controls and 14.9% of cases) was 1.10 (95%CI 0.91–1.32) whereas the respective OR for rotating schedules with <3 reported nights/month (5.9% of controls and 9.1% of cases) was 1.50 (95%

Table 2. Distribution of participant characteristics among different shift work profiles among controls in the MCC-Spain study. Numbers may differ due to missing values. [SD=standard deviation]

Factor	Never shift work (N=2433)			Rotating shift work (N=659)			Permanent night shift work (N=289)		
	%	Mean	SD	%	Mean	SD	%	Mean	SD
Age (years)		62.5	11.7		62.8	11.4		62.2	11.3
Sex									
Male	50.5			62.1			68.2		
Female	49.5			37.9			31.8		
Family history [a]									
No	91.7			90.7			92.3		
Yes	8.3			9.3			7.7		
Educational level									
Less than primary	15.7			14.1			26.1		
Primary	28.7			37.8			37.3		
High school	31.3			27.3			24.7		
University	24.2			20.8			11.9		
BMI (kg/cm^2)									
<22.5	17.7			12.9			12.2		
22.5–25	22.8			21.4			15.3		
25–30	39.9			42.8			46.3		
≥30	19.6			22.9			26.1		
Tobacco smoking									
Never smoker	44.3			36.1			29.8		
Ever smoker	55.7			63.9			70.2		
Physical activity [b]									
Inactive or a little active	52.7			54.8			55.7		
Moderately or very active	47.4			45.5			44.3		
Sleep habits									
Sleep duration (hours/day)		7.0	1.3		7.1	1.4		6.9	1.4
Ever sleep problems	35.0			33.6			35.3		
Diet habits									
Total energy intake (kcal/day)		1892	638		1998	664		1969	678
Past alcohol consumption (g ethanol /day) [c]		17.3	25.8		25.0	34.9		21.9	28.5
All red meat consumption (g/day) [d]		62.5	39.3		70.9	44.4		65.7	42.4
Vitamin D intake (g/day)		2.8	1.5		2.9	1.6		2.6	1.5
Calcium intake (g/day)		908	345		909	334		972	373
Drug consumption									
NSAIDS/Aspirin		33.8			40.8			39.4	
Females									
Postmenopausale		68.9			57.2			59.3	
Nulliparouse		18.4			22.4			26.4	
Ever oral contraceptives [e]		49.6			54.2			56.0	
Ever hormonal therapy [e]		7.4			9.2			5.8	

[a] First degree relatives.
[b] Assessed over the last 10 years excluding 2 years prior to diagnosis.
[c] Assessed at 30–40 years.
[d] Includes red meat (pork, beef, lamb, duck), processed meat and cured meat.
[e] Among females.

CI1.18–1.92). Subjects with histories of both permanent night and rotating shift work (N=129) were classified as permanent shift workers in the main analysis but were also excluded in sensitivity analyses and results were unchanged.

CRC risk increased with increasing (P-value for trend=0.005) lifetime cumulative duration of rotating shift work. Subjects that worked for ≥15 years in rotating shifts showed a higher risk for CRC (OR 1.29, 95% CI 1.06–1.56) compared to day workers (table 4). Analysis according to quartiles of duration revealed the highest OR in the top quartiles of exposure (3rd quartile, 20–34 years, OR 1.38, 95% CI 1.06–1.81; 4th quartile, ≥35 years, OR 1.36, 95%CI 1.02–1.79). Workers exposed earlier in life had a higher CRC risk (<25 years, OR 1.24, 0.99–1.56) compared to those who were exposed later (≥25 years old, 0.95, 0.72–1.25) (table 5). OR tended to decrease with years since last exposure to rotating shift work (≥15 years, 0.97, 95% CI 0.76–1.24). Results based on quartiles among exposed controls were similar (Supplemental table B, www.sjweh.fi/index.php?page=data-repository). The OR for permanent shift work cumulative duration, age at first exposure and years since last exposure were mostly negative or null (tables 4 and 5).

In a stratified analysis by sex, OR for rotating shift work were higher among men (OR 1.32, 95% CI 1.10–1.59) than women (OR 0.93, 95% CI 0.57–1.50) with

Table 3. Ever shift work and colorectal cancer risk in the MCC-Spain study. [OR=odds ratio; 95% CI=95% confidence interval].

	Controls (N=3378)		Colorectal cancer cases (N=1626)		Colon cancer cases (N=1086)		Rectal cancer cases (N=524)					
	N	%	N	%	N	%	N	%	OR [a]	95% CI [a]	OR [b]	95% CI [b]
Colorectal cancer combined												
Never shift work	2432	67.0	1071	60.4					1.00		1.00	
Rotating shift work	659	18.1	426	24.0					1.28	1.10–1.49	1.22	1.04–1.43
Permanent night shift work	287	7.9	129	7.3					0.81	0.64–1.01	0.79	0.62–1.00
Colon cancer [c]												
Never shift work	2432	67.0			721	66.4			1.00		1.00	
Rotating shift work	659	18.1			282	26.0			1.29	1.08–1.53	1.22	1.02–1.46
Permanent night shift work	287	7.9			83	7.6			0.81	0.62–1.06	0.79	0.60–1.11
Rectal cancer [c]												
Never shift work	2432	67.0					339	64.7	1.00		1.00	
Rotating shift work	659	18.1					143	27.3	1.33	1.06–1.67	1.26	0.99–1.58
Permanent night shift work	287	7.9					42	8.0	0.78	0.55–1.23	0.76	0.53–1.11

[a] OR adjusted for age (continuous), center, educational level (less than primary, primary, high school, university) and sex (female, male).

[b] OR adjusted for age (continuous), center, educational level (less than primary, primary, high school, university), sex (female, male), history of colorectal cancer in first degree relatives (yes/no), body mass index (<22.5, 22.5–24.9, 25–29.9, ≥30), smoking status (ever, never), leisure time physical activity (inactive, little active, moderately active, very active), past alcohol consumption (quartiles), total energy intake in grams/day (quartiles), all red meat consumption in grams/day (quartiles), sleep duration in hours/day (<6, 6, 7, 8, >8) and aspirin/ non-steroid anti-inflammatory drug use (yes, no).

[c] The numbers of colon and rectal cancer may not be equal to the total number of colorectal cancers because in some cases the tumor site was unknown.

Table 4. Cumulative years of shift work and colorectal cancer risk in the MCC-Spain study [OR=odds ratio; 95%CI=95% confidence interva]).

	Controls		Cases				P-value for trend [c]			P-value for trend [c]
	N	%	N	%	OR [a]	95% CI [a]		OR [b]	95% CI [b]	
Never shift work	2432	89.5	1071	89.3	1.00			1.00		
Cumulative years of rotating shift work							0.001			0.005
Quartiles										
<8	173	5.6	89	5.9	1.19	0.90–1.57		1.14	0.85–1.51	
8–19	171	5.6	87	5.8	1.17	0.88–1.55		1.12	0.84–1.49	
20–34	158	5.1	119	8.0	1.45	1.11–1.88		1.38	1.06–1.81	
≥35	141	4.6	127	8.5	1.45	1.11–1.89		1.36	1.02–1.79	
Fixed categories (years)										
<15	282	9.2	147	9.9	1.24	1.00–1.56		1.19	0.95–1.49	
≥15	361	11.7	274	18.4	1.35	1.12–1.63		1.28	1.06–1.56	
Cumulative years of permanent night shift work							0.582			0.599
Quartiles										
<4	68	2.5	22	1.8	0.67	0.40–1.10		0.64	0.38–1.08	
4–9	80	2.9	33	2.8	0.78	0.51–1.19		0.71	0.45–1.11	
10–19	73	2.4	33	2.8	0.77	0.50–1.19		0.76	0.49–1.18	
≥20	65	2.4	40	3.3	1.00	0.66–1.51		1.01	0.65–1.55	
Fixed categories (years)										
<15	190	6.9	75	6.3	0.75	0.56–1.00		0.70	0.52–0.96	
≥15	96	3.5	53	4.4	0.91	0.64–1.30		0.91	0.64–1.30	

[a] OR adjusted for age (continuous), center, educational level (less than primary, primary, high school, university) and sex (female, male).

[b] OR adjusted for age (continuous), center, educational level (less than primary, primary, high school, university), sex (female, male), history of colorectal cancer in first degree relatives (yes/no), body mass index (<22.5, 22.5-24.9, 25–29.9, ≥30), smoking status (ever, never), leisure time physical activity (inactive, little active, moderately active, very active), past alcohol consumption (quartiles), total energy intake in grams/day (quartiles), all red meat consumption in grams/day (quartiles), sleep duration in hours/day (<6, 6, 7, 8, >8) and aspirin/non-steroid anti-inflammatory drug use (yes, no).

[c] Two-sided P-value (Wald test) across quartiles of exposure in subjects with rotating shift work history.

Table 5. Age at first shift work and years since last shift work and colorectal cancer risk in the MCC-Spain study [OR=odds ratio; 95% CI=95% confidence interval].

	Controls		Cases		OR [a]	95% CI [a]	OR [b]	95% CI [b]
	N	%	N	%				
Never shift work	2432	89.5	1071	89.3	1.00		1.00	
Age (years)at first rotating shift work								
<25	243	8.5	166	12.4	1.34	1.07–1.67	1.24	0.99–1.56
≥25	200	7.0	99	7.4	0.98	0.75–1.28	0.95	0.72–1.25
Age (years) at first permanent night shift work								
<25	160	5.9	75	6.3	0.81	0.60–1.08	0.80	0.58–1.08
≥25	126	4.6	53	4.4	0.81	0.57–1.14	0.76	0.53–1.09
Years since last rotating night shift work								
<15	142	4.9	89	6.7	1.23	0.93–1.65	1.12	0.83–1.52
≥15	224	7.8	136	10.2	1.05	0.83–1.33	0.97	0.76–1.24
Years since last permanent night shift work								
<15	95	3.5	44	3.7	0.90	0.62–1.33	0.91	0.61–1.34
≥15	150	5.5	72	6.0	0.79	0.58–1.07	0.74	0.54–1.01

[a] OR adjusted for age (continuous), center, educational level (less than primary, primary, high school, university) and sex (female, male).

[b] OR adjusted for age (continuous), center, educational level (less than primary, primary, high school, university), sex (female, male), history of colorectal cancer in first degree relatives (yes/no), body mass index (<22.5, 22.5–24.9, 25–29.9, ≥30), smoking status (ever, never), leisure time physical activity (inactive, little active, moderately active, very active), past alcohol consumption (quartiles), total energy intake in grams/day (quartiles), all red meat consumption in grams/day (quartiles), sleep duration in hours/day (<6, 6, 7, 8, >8), non-steroid anti-inflammatory drug use (yes, no).

a P-value for interaction of 0.065. Risk estimates were different across age groups (<50 years, OR 0.93, 95% CI 0.51–1.69; 50–70 years, 1.43, 95% CI 1.15–1.78; >70 years, 1.02, 95% CI 0.79–1.32). OR of shift profiles were similar across groups of BMI, smoking and menopausal status. The association between night shift work and CRC did not change after subjects with low quality (unsatisfactory and questionable) interviews as reported by the interviewer were excluded. In sensitivity analysis excluding all jobs with shift durations <4 or >12 hours, results remained unchanged (results not shown).

Discussion

In this large case–control study we found an increase in colon and rectal cancer risk related to rotating shift work. We found evidence for increasing CRC risk with longer lifetime cumulative shift work duration. There was no association with permanent night shift work.

The evidence on the association between shift work and CRC is scarce and mixed. This is the first study to present results for different types of shift work and CRC risk. Our findings for rotating shift work are in line with the results from the Nurses' Health Study, the only existing prospective study that described an increased risk for CRC after long-term (>15 years) rotating night shift work (8). Although about 70% of rotating shift workers in our study reported night shifts, in stratified analysis we could not confirm that rotating night shift work is more detrimental compared to other rotating shift schedules, probably due to underreporting of the amount of nights worked per month related to the retrospective nature of exposure assessment. In another case–control study, a higher CRC risk was reported after permanent night shift work, but no dose–response association with cumulative duration of shift work (7). A population based record-linkage study showed no association of night shift work and CRC, although in the later study the control group included a large amount of shift workers, thus, exposure misclassification was high (9). Finally an earlier study on radio and telegraph operators had shown a non-significant increase in risk for colon cancer after evening or night shifts (10). Contrary to our previous work on breast and prostate cancer, permanent night work was not associated with CRC risk (24, 25). However, both these tumors are hormone-dependent and do not fully share carcinogenic mechanisms with CRC.

Several mechanisms such as circadian and sleep disruption as well as lifestyle changes have been suggested for the oncogenic effect of shift work (13). A normal function of the circadian clock and nocturnal melatonin production is essential for colorectal tissue homeostasis (26, 27). Melatonin has well known anticarcinogenic properties including direct effect on colorectal tumor growth and was found to be lower among shift workers and CRC patients (18, 28). In animal studies, downregulation of a number of circadian genes may lead to cell proliferation in colon cancer cell lines and intestinal and colon polyp formation (29). Disruption of the peripheral intestinal circadian clock may contribute to intestinal epithelial transformation of human CRC (30). In a recent case–control study a length polymorphism in the circadian PER3 gene, a core circadian gene associated with morning chronotype, delayed sleep phase syndrome and melatonin secretion was associated with risk of colorectal adenoma, the precursor of colorectal carcinoma (31). Sleep deprivation is associated with impaired immune function and tumor surveillance system and has also been associated with adenoma formation (32). In our study, sleep duration was similar across shift work profiles pointing to other characteristics related to diet and lifestyle to explain the observed associations. Finally a recent cohort study showed no association between rotating night shift work or sleep duration and polyps or adenoma formation, suggesting that circadian disruption may be involved in later stages of carcinogenesis such as tumor promotion (33).

Shift workers differed from non-shift workers in this study in terms of lifestyle, diet and sociodemographic characteristics; for instance they were more frequently obese, ever smokers and less educated. It is possible that subjects with a less healthy lifestyle such as smokers select themselves into shift work (34). More likely, shift workers adopt a less healthy lifestyle and diet due to irregular working hours. Shift workers are at a higher risk for obesity, cardiovascular risk and type II diabetes that are also linked to CRC (21, 35–38). In that case, we might have overestimated the true effect of shift work related circadian disruption on CRC cancer risk. We partly accounted for this potential bias by adjusting OR for a wide range of confounders, but the associations changed slightly in the fully adjusted models. CRC is long considered preventable through effective screening and treatment (4, 39). Lifestyle factors, such as smoking, alcohol and physical activity are potentially modifiable and thus useful for cancer preventive measures in shift workers (40). Risk factors for chronic disease and cancer may vary depending on the age shift work was performed (41). In our study, risks were somewhat higher among subjects that were exposed earlier in life but also attenuated with years since last exposure, even after adjusting for cumulative shift work duration. However these stratified analyses were based on smaller numbers and may represent chance findings. Age at which an individual performed shift work and time since quitting may modulate the effects of shift work on cancer risk and these are new hypotheses that need to be confirmed in future studies. The CRC risk was higher among men although we did not observe a statistically significant interaction. The participation rate was similar in both sexes thus selection bias is not a likely explanation. Alternatively the sex difference might be a chance finding or may indicate the lack of power to describe any association among women because shift work was less frequent among females. While differences in lifestyle such as smoking, alcohol consumption, can partly explain the sex differences, reproductive and hormonal factors are additionally highly plausible factors, since exogen estrogen seems to be protective against CRC.

The strengths of the present study are the histological confirmation of tumors, the large number of cases, the detailed shift work assessment and the careful control for a wide range of potential confounders. The selection of controls through lists of general practitioners provided a representative sample given the universal public coverage of the national health system in Spain, which is another major strength of the study. Shift work was evaluated across a wide range of jobs in a variety of occupational sectors including both sexes which increased the external validity of the study. However, shift work assessment in population-based studies is a big challenge due to the complexity of shift systems across occupations. Although the MCC-Spain study collected detailed shift work information (eg, duration, frequency), in this analysis we lacked the exact time schedules for the rotating shifts. Characteristics of shift rotation such as speed (rapid versus slow) and direction (forward versus backward) were also not available in the present study; therefore we could not compare different rotating schedules in more detail. In addition jobs types varied across shift profiles and between sexes and thus job specific factors might have confounded our risk estimates. Response rates were lower for controls than for cases and differential selection bias might have occurred. We performed stratified analyses by center and also restricted the analyses to centers with the highest response rates among controls and results were similar to the main analysis. Risk estimates varied by center towards both directions, but these estimates were unstable due to small numbers. Subjects working at night, especially permanent night workers, might have been more likely at home during the day when phone calls were performed and if so they might have been overrepresented among controls. However, telephone calls were performed throughout the day and repeated at different time schedules. The questions used to assess shift work are prone to recall bias, especially for past exposures, due to the fact that lifetime occupational information was collected retrospectively. This bias mostly affected our shift work frequency (nights/month) assessment, which had a high amount of missing values (35% of shift workers) compared to duration (<1% missing) and this might explain the differential risk we observed across the groups of increasing rotating night shift work intensity. However, the study had a more general focus on environmental and genetic causes of cancer and not specifically shift work effects, thus, this bias is most likely non-differential and would only attenuate our findings towards the null. Housewives were excluded from this analysis (7% of cases and 8.3% of controls) since we focused on subjects that had ever been employed and provided shift work information. Information on shift work was missing or incomplete in 18% of cases and 12% of controls. However basic sociodemographic characteristics in non-respondents (cases and controls) were similar to respondents. Finally chronotype, an individual characteristic that predicts shift work adaptation and may modify the association between shift work and cancer, was not measured in this subset of the study, and, thus, might have masked some of the true associations in any direction (24, 25).

In this large population based case–control study, long-term rotating shift work in different occupations was associated with CRC. These findings increase the knowledge of the effects of shift work on CRC risk and if confirmed could inform cancer preventive measures such as lifestyle modification and more frequent screening among rotating shift workers.

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Conflicts of interest

The authors declare no conflicts of interest.

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