

## ACCEPTED VERSION

Wa Mwenga Walasa, Renee N Carey, Si Si, Lin Fritschi, Jane S Heyworth, Renae C Fernandez, Terry Boyle  
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## **The association between shiftwork and the risk of colorectal cancer in females: a population-based case-control study**

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**Keywords:** shiftwork; colorectal cancer; job-exposure matrix; occupation

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**What is already known about this subject?**

Studies of the impacts of shiftwork on human health have reported several adverse health consequences. Few studies have investigated the association between shiftwork and risk of colorectal cancer.

**What are the new findings?**

No evidence of an association between job-exposure matrix assessed shiftwork and risk of colorectal cancer in females was observed in this study.

**How might this impact on policy or clinical practice in the foreseeable future?**

There is increasing evidence that shiftwork is not associated with colorectal cancer risk in females, although further clarification is necessary, ideally from studies with detailed information on shiftwork at an individual level.

## **ABSTRACT**

### **Objective**

Research indicates that shiftwork may be associated with increased risks of adverse health outcomes, including some cancers. However the evidence of an association between shiftwork and colorectal cancer risk is limited and inconclusive. Further, while several possible pathways through which shiftwork might result in cancer have been proposed, few studies have taken these factors into account. We investigated the association between two types of shiftwork (graveyard shiftwork and early morning shiftwork) and six mechanistic shiftwork variables (including light at night and phase shift) and colorectal cancer risk among females in an Australian population-based case-control study. Graveyard shiftwork was the primary exposure of interest.

### **Methods**

Participants (350 cases and 410 controls) completed a lifetime occupational history, and exposure to each of the eight shiftwork variables was assigned to participants through a job-exposure matrix. We used logistic regression to calculate odds ratios (ORs) and corresponding 95% confidence intervals (CI) for the association between different shiftwork variables and the risk of colorectal cancer, adjusting for potential demographic, lifestyle and medical confounders.

### **Results**

Working in an occupation involving long-term exposure (more than 7.5 years) to graveyard shiftwork was not associated with colorectal cancer risk (Adjusted Odds Ratio = 0.95, 95% Confidence Interval = 0.57, 1.58). Similarly, no increased risks of colorectal cancer were seen for any of the other seven shiftwork variables examined.

### **Conclusions**

No evidence of an increased risk of colorectal cancer among females who had worked in occupations involving shiftwork was observed in this study.

**Keywords:** shiftwork; colorectal cancer; job-exposure matrix; occupation

## INTRODUCTION

Colorectal cancer is the third most common cancer in males and the second most common cancer in females worldwide.[1] Colorectal cancer has several known risk factors. Age (50 years and older), family history of colorectal cancer in first degree relatives, certain hereditary factors and inflammatory bowel disease are non-modifiable factors that have been linked to an increased risk of developing colorectal cancer.[2,3] Modifiable risk factors for colorectal cancer include physical inactivity, obesity, high intake of red meat, low intake of fruit and vegetables, tobacco smoking and alcohol consumption.[4,5] Less is known about occupational risk factors for colorectal cancer, although there is some evidence that sedentary work and asbestos exposure may be associated with increased risk.[6,7]

Recent research indicates that shiftwork may be associated with a range of health outcomes, including increased risks of cardiovascular disease and diabetes.[8] Estimates from developed countries indicate that approximately 1 in 6 workers perform shiftwork.[9-11] Given the substantial proportion of workers who perform shiftwork, it is important to investigate its potential health effects.

In 2007, the International Agency for Research on Cancer (IARC) classified 'shiftwork that involves circadian disruption' as being probably carcinogenic to humans.[12] This classification was made on the basis of 'sufficient evidence' in experimental models and 'limited evidence' regarding shiftwork and breast cancer risk in humans. There are a number of possible pathways through which night shiftwork might result in cancer, namely phase shift, light at night, sleep disruption, lifestyle disturbance, and less sunshine.[13] Most epidemiological studies assessing the possible association between shiftwork and cancer have focused on breast cancer, and the evidence on other tumour sites remains scarce.[14,15] While it has been hypothesised that circadian disruption may be implicated in the onset of colorectal cancer,[16] only four studies have investigated this association.[17-20] These studies have had inconsistent results and been criticised for their methodological limitations.[21]

Given the limited and inconsistent evidence to date, we investigated the association between two shiftwork exposures (graveyard shiftwork and early morning shiftwork) and the risk of colorectal cancer among females in Western Australia. We also investigated the association between six mechanistic shiftwork variables (light at night while working night shifts, phase shift while working night shifts, sleep disturbances while working night shifts,

poor diet while working night shifts, lack of physical activity while working night shifts, and lack of vitamin D while working night shifts) and colorectal cancer risk. Each of the mechanistic variables represents a biologically plausible mechanism through which shiftwork may influence cancer risk.[13,22] As there are epidemiological and aetiological disparities between colon and rectal cancer,[23] we also investigated the association between shiftwork and the risk of colon and rectal cancers separately. Graveyard shiftwork was the primary shiftwork exposure of interest. Only females were included as this analysis as the job-exposure matrix used in this study to assess shiftwork is not recommended for use among males.[22]

## **MATERIAL AND METHODS**

### **Study population**

Data from the Western Australia Bowel Health Study (WABOHS) were used in this study. The WABOHS was a population-based case-control study which aimed to investigate environmental and occupational risk factors for colorectal cancer. The design and data collection of WABOHS has been described in detail elsewhere.[24] Briefly, cases in the WABOHS were males and females aged 40-79 years with a confirmed diagnosis of colorectal cancer, notified to the Western Australian Cancer Registry between June 2005 and August 2007. Controls were free of colorectal cancer and randomly selected from the Western Australian electoral roll, and were frequency matched to the cases on age and sex. A questionnaire to collect information on demographics, behavioural factors, medical history and occupation was self-administered to cases and controls. Response fractions were 56% and 46% for female cases and female controls respectively. The WABOHS was approved by the Human Research Ethics Committee of The University of Western Australia and the Confidentiality of Health Information Committee within the Western Australian Department of Health, and the current analysis was approved by the Curtin University Human Research Ethics Committee.

### **Ascertainment of shiftwork**

To capture occupational history, participants in the WABOHS were asked to specify the job title and main tasks for each job they held for more than six months throughout their working life, as well as the age at which the job was started and stopped and whether it was full-time, part-time, casual or seasonal. Each job was coded to the 1968 International Standard Classification of Occupation (ISCO-68) coding system.

We used a Job Exposure Matrix (JEM) to assess exposure to two different types of shiftwork (graveyard shiftwork and early morning shiftwork) and six mechanistic variables (light at night while working night shifts, phase shift while working night shifts, sleep disturbances while working night shifts, poor diet while working night shifts, lack of physical activity while working night shifts, and lack of vitamin D while working night shifts).[22] The definitions of probable exposure to each of the eight variables are outlined in Supplementary Table 1. The JEM predicts the probability that a particular job (based on ISCO-68 code) involved exposure to each of the eight shiftwork variables.[22] As recommended by the creators of the JEM, we used a 30% probability cut-off to classify exposure to each of the shiftwork variables as this cut-off was found to have the most acceptable level of specificity (>75%) without compromising sensitivity (>=70%).[22] We also conducted a sensitivity analysis to assess if using a 50% probability cut-point for all the shiftwork variables resulted in odds ratios further from the null than those observed when using the 30% cut-off, with the rationale that a stricter definition of shift work would result in fewer false positives when assessing possible exposure to each of the shiftwork variables.

The total number of years spent employed in all jobs involving 30% or greater probability of exposure to each shiftwork variable was calculated for each individual. Exposure to each of the shiftwork variables was categorised as a binary (never/ever) variable. Duration of exposure to graveyard shiftwork, and each of light at night, phase shift, poor diet, and lack of physical activity while working night shifts were also categorized as zero years, more than zero but less than 7.5 years, and 7.5 years or above, based on the distribution among controls who ever performed graveyard shiftwork. Duration of exposure to early morning shiftwork, lack of vitamin D, and sleep disturbance were not categorised in this manner due to low prevalence. We also performed a sensitivity analysis to examine the association between longer exposure (i.e., 15 or more years) to graveyard shiftwork was associated with colorectal cancer risk, as has been observed in a previous study.[19]

### **Statistical analyses**

The JEM used to assess the exposure to the shiftwork variables was developed using data from a population-based case-control study of female breast cancer and validated using data from females who participated in a population-based study of the prevalence of occupational exposure to carcinogens. As the distribution of job type varies between males and females, it is recommended that this JEM not be used to assess shiftwork exposure among males.[22] As such, only females were included in this analysis. After excluding four

cases and one control for missing data on occupational history, 760 females (350 cases and 410 controls) were included in our analysis. Logistic regression was used to calculate odds ratios (ORs) and corresponding 95% confidence intervals (CI) for the risk of colorectal cancer, while multinomial logistic regression was used to determine whether the shiftwork variables were differentially associated with the risk of colon cancer (n=244 cases) and rectal cancer (n=106 cases). All analyses controlled for age group because the controls in the WABOHS were age frequency matched to the cases. We adjusted for a number of established colorectal cancer risk factors that we considered to be potential confounder factors, including level of education, socioeconomic status, lifetime cigarette smoking, and alcohol consumption.[3] Level of education was categorized into 3 groups: high school only, vocational qualification, and university qualification. Socio-Economic Indexes for Areas (SEIFA) developed by the Australian Bureau of Statistics was used to classify socioeconomic status based on the postcode of the participant's current address, which was thereafter categorized into quartiles.[25] Self-reported alcohol consumption (grams per day) 10 years ago was categorised based on the quartiles in the controls. Lifetime tobacco smoking was classified into three groups of 0, 1-19, and more than 20 packs per year. Multiple imputation by chained equations was used to impute missing data for highest level of education (4% missing), socioeconomic status (1% missing), cigarette smoking (0.1% missing) and alcohol consumption (4% missing). The multiple imputation model included the main exposure (years employed in an occupation involving graveyard shiftwork), the outcome (control, colon cancer case, rectal cancer case), all the confounders include in the final model, and also country of birth, age left school, body mass index one year ago and at ages 20 and 40 years, maximum body weight, lifetime physical activity, diabetes status, energy intake 10 years ago, and ever used/never used variables for each of hormone replacement therapy, multivitamins, and non-steroidal anti-inflammatory drugs. Twenty imputations were performed, with the estimated associations from each of the imputed datasets averaged to given the overall estimated association, as per Rubin's rules.[26]

Trend tests were conducted by entering ordinal shiftwork variables into the model as continuous variables. A two-sided p-value of <0.05 was considered to be statistically significant. All analyses were carried out using Stata 14.1 (StataCorp LP, College Station, Texas).



## RESULTS

Table 1 shows the distribution of female cases and controls participating in the WABOHS according to selected characteristics. Compared with the controls, the cases were more likely to have ever smoked. Out of a total of 3395 jobs held by cases and controls, 363 (10.7%) were classified as involving exposure to graveyard shiftwork using the 30% probability cut-point. Of these 363 jobs, more than 85% were held by people working in the nursing profession. Of the remaining 15%, medical technician (3%) and prison guard (2%) were the only occupations which made up more than 1%. Prevalence of ever exposure to graveyard shiftwork among the participants was 20%.

When compared with no exposure to graveyard shiftwork, working in an occupation involving short-to-medium term exposure (up to 7.5 years) or long-term exposure (more than 7.5 years) to graveyard shiftwork was not associated with the risk of colorectal cancer (Adjusted OR for 0 < Years < 7.5 = 1.17, 95% CI = 0.73, 1.88; Adjusted OR for 7.5+ Years = 0.95, 95% CI = 0.57, 1.58) (Table 2). Similarly, no increased risk of developing colorectal cancer was seen for early morning shiftwork or for any of the six mechanistic variables.

Examination of colon and rectal cancers separately also found that exposure to neither graveyard shiftwork, early morning shiftwork nor any of the six mechanistic variables were significantly associated with risk (Table 3). While the risk estimates for rectal cancer were all higher than those observed for colon cancer, none of the shiftwork variables were significantly differentially associated with the risk of colon and rectal cancers.

Slightly higher risk estimates were observed in sensitivity analyses in which we investigated the association between exposure to graveyard shiftwork for 15 or more years and colorectal cancer risk (Adjusted OR for colorectal cancer = 1.20, 95% CI 0.64, 2.26; Adjusted OR for colon cancer = 1.03, 95% CI 0.50, 2.11; Adjusted OR for rectal cancer = 1.66, 95% CI 0.68, 4.03).

Similar results for all the shiftwork variables and risk of colorectal cancer were generally observed in sensitivity analyses using a 50% exposure probability cut-off (Supplementary Table 2).

## DISCUSSION

We did not observe any significant associations between JEM-assessed shiftwork and risk of colorectal cancer among females in this Australian population-based case-control study. Null associations were found for the risks of colorectal cancer, colon cancer and rectal

cancer for each of the eight shiftwork variables investigated, namely graveyard shiftwork, early morning shiftwork, light at night, phase shift, sleep disturbances, poor diet, lack of physical activity, and lack of vitamin D.

Only three previous studies have investigated the association between shiftwork and colorectal cancer risk among females (Figure 1). The findings of the present study are consistent with two of these previous studies; a national retrospective cohort study of workers in Sweden and a Spanish case-control study both found no association between shiftwork and risk of colorectal cancer in females (based on JEM-assessed and self-reported shiftwork, respectively).[17,20] Similarly, two studies of colorectal adenomas (a precursor for most colorectal cancers) have found no association between shiftwork and colorectal adenoma risk among females.[27,28] In contrast, data from the Nurses Health Study revealed a 35% increased risk of colorectal cancer among female nurses who reported working 15 or more years of rotating night shifts.[19] Two studies conducted among males have also observed an increased risk of colorectal cancer among shift workers.[17,20]. The Nurses Health Study analysis observed slightly higher risk estimates for rectal cancer than for colon cancer, a pattern which was also observed in the current study.[19] However it is important to note that none of the shiftwork variables were differentially associated with the risk of colon and rectal cancers. Too few studies have been conducted to date to be able to determine whether or not shiftwork increases colorectal cancer risk, and whether the association may differ between males and females, and whether shift work may be differentially associated with the risk of colon and rectal cancers.

The current study has several strengths and limitations. We had information regarding a wide range of demographic, behavioural and medical variables so were able to adjust for a range of potential confounding factors. A further strength was using a JEM specifically designed for the assessment of female workers' exposure to two different types of shiftwork and six different biologically plausible mechanisms through which shiftwork may influence cancer risk. The JEM was also created with data from the same country as the present study and, at the 30% probability cut-off, all metrics except sleep disturbances, lack of vitamin D and early morning shiftwork have a sensitivity and specificity of  $\geq 70\%$  when compared with individual-level exposure determined via job-specific questionnaires.[22] The use of a JEM to categorize exposure to shift work also led to standardization of exposure definition and eliminated reporting bias, which is often associated with self-reporting of job histories.[22]

However, as the JEM assesses graveyard shift on a group level, its use may have led to non-differential exposure misclassification, therefore limiting our ability to find an association if it actually exists.[20] A previous study conducted in a similar study population found use of this shiftwork JEM resulted in a modest (6%) attenuation of risk estimates, when compared with the risk estimates obtained using shiftwork variables based on automated expert assessment of detailed job history information. In addition, the JEM used in this study has only fair sensitivity when assessing sleep disturbances, lack of vitamin D, and early morning shifts,[22] which may have introduced further exposure misclassification for these shiftwork variables. However the general lack of meaningful change in the odds ratios with increasing prevalence in the JEM argues against a major association being masked by misclassification. We were not able to capture the intensity (frequency) of shiftwork at an individual level.[29] It has been hypothesised that workers involved in rotating night shifts have elevated cancer risk as they may not readapt from a previously disrupted circadian rhythm.[30] We also lacked information about chronotype, which has been proposed to potentially alter the effect of shiftwork on cancer risk.[31] It is possible that not taking chronotype into account limited our ability to find an association if one actually existed. A further limitation of this study was the sample size, which limited our ability to detect a small association between shift work and colorectal cancer risk and decreased the precision of the observed odds ratios. Finally, the relatively low response fractions in the WABOHS, particularly among controls, means selection bias may have influenced the results. Among both cases and controls, people who took part in the WABOHS had, on average, higher socioeconomic status and lower comorbidity than those who did not take part in the WABOHS, and controls who were aged 50 years and older were also more likely to take part than controls aged younger than 50 years. However sensitivity analyses in a previous study based on WABOHS data found that selection bias had only a small impact on the observed risk estimates.[24]

In conclusion, in this population-based case-control study we found that JEM-assessed shiftwork was not associated with an increased risk of colorectal cancer among females. Further epidemiological studies, ideally with detailed information on shiftwork at an individual level, are necessary to elucidate the relationship between shiftwork and the risk of colorectal cancer.

**Competing interests:** None declared

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**Ethical approval:** All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study reported in this manuscript comply with the current laws of Australia.

**Table One:** Selected characteristics of the female cases and controls in the Western Australian Bowel Health Study, 2005-2007

	Controls		Cases	
	n	%	n	%
<b>Age Group</b>				
40-49 years	43	10.5	21	6.0
50-59 years	93	22.7	97	27.7
60-69 years	130	31.7	113	32.3
70-79 years	144	35.1	119	34.0
<b>Educational Level<sup>a</sup></b>				
High School Only	212	53.5	183	54.8
Vocational Qualification	135	34.1	103	30.8
University Qualification	49	12.4	48	13.3
<b>Index of Relative Socioeconomic Disadvantage (Quartiles)<sup>b</sup></b>				
1 (most disadvantaged)	100	24.5	104	30.3
2	101	24.8	74	21.6
3	104	25.5	79	23.0
4 (least disadvantaged)	103	25.2	86	25.1
<b>Lifetime Cigarette Smoking<sup>c</sup></b>				
0-0.9 pack-years	266	64.9	218	62.5
1-19.9 pack-years	83	20.2	66	18.9
20+ pack-years	61	14.9	65	18.6
<b>Alcohol Consumption 10 years ago (Quartiles)<sup>d</sup></b>				
0-0.35 grams per day	99	25.1	81	24.3
0.36-2.54 grams per day	99	25.1	77	23.1
2.55-13.99 grams per day	98	24.8	100	30.0
14+ grams per day	99	25.1	75	22.5

<sup>a</sup> Missing for 14 controls and 16 cases

<sup>b</sup> Based on the Socio-Economic Indexes for Areas (SEIFA) developed by the Australian Bureau of Statistics; Missing for two controls and seven cases

<sup>c</sup> Missing for one case

<sup>d</sup> Missing for 15 controls and 17 cases

**Table Two:** Associations between different shiftwork variables and the risk of colorectal cancer among females in the Western Australian Bowel Health Study, 2005-2007

	Controls	Cases				
	n	n	OR <sup>a</sup>	95% CI	AOR <sup>b</sup>	95% CI
<b>TYPES OF SHIFTWORK</b>						
<b>Years in Graveyard Shiftwork</b>						
0 Years (reference)	328	277	1.00		1.00	
0.1 + Years (Ever)	82	73	1.06	0.74, 1.51	1.06	0.73, 1.54
<i>0 &lt; Years &lt; 7.5</i>	41	40	1.16	0.75, 1.84	1.17	0.73, 1.88
<i>7.5+ Years</i>	41	33	0.96	0.59, 1.57	0.95	0.57, 1.58
<b>Years in Shiftwork Involving Early Shifts</b>						
0 Years (reference)	373	317	1.00		1.00	
0.1 + Years (Ever)	37	33	1.04	0.63, 1.71	1.00	0.60, 1.66
<b>MECHANISTIC SHIFTWORK VARIABLES</b>						
<b>Years in Shiftwork Involving Exposure to Light at Night</b>						
0 Years (reference)	329	280	1.00		1.00	
0.1 + Years (Ever)	81	70	1.02	0.71, 1.46	1.02	0.70, 1.48
<i>0 &lt; Years &lt; 7.5</i>	40	38	1.11	0.69, 1.79	1.12	0.69, 1.81
<i>7.5+ Years</i>	41	32	0.93	0.57, 1.52	0.91	0.55, 1.53
<b>Years in Shiftwork Involving Exposure to Phase Shift</b>						
0 Years (reference)	329	281	1.00		1.00	
0.1 + Years (Ever)	81	69	1.00	0.70, 1.44	1.00	0.69, 1.45
<i>0 &lt; Years &lt; 7.5</i>	41	38	1.09	0.68, 1.75	1.09	0.68, 1.76
<i>7.5+ Years</i>	40	31	0.91	0.55, 1.50	0.89	0.53, 1.51
<b>Years in Shiftwork Involving Exposure to Poor Diet</b>						
0 Years (reference)	332	286	1.00		1.00	
0.1 + Years (Ever)	78	64	0.96	0.66, 1.38	0.96	0.65, 1.40
<i>0 &lt; Years &lt; 7.5</i>	39	34	1.02	0.62, 1.66	1.03	0.63, 1.69
<i>7.5+ Years</i>	39	30	0.90	0.54, 1.48	0.88	0.52, 1.50
<b>Years in Shiftwork Involving Exposure to Physical Inactivity</b>						
0 Years (reference)	334	283	1.00		1.00	
0.1 + Years (Ever)	76	67	1.05	0.74, 1.51	1.05	0.71, 1.53
<i>0 &lt; Years &lt; 7.5</i>	37	36	1.15	0.71, 1.88	1.16	0.71, 1.91
<i>7.5+ Years</i>	39	31	0.94	0.57, 1.55	0.93	0.55, 1.57
<b>Years in Shiftwork Involving Exposure to Sleep Disturbance</b>						
0 Years (reference)	400	340	1.00		1.00	
0.1 + Years (Ever)	10	10	1.24	0.50, 3.03	1.19	0.48, 2.95

**Years in Shiftwork Involving Exposure to Insufficient Vitamin D**

0 Years (reference)	368	314	1.00		1.00	
0.1 + Years (Ever)	42	36	1.01	0.63, 1.63	1.00	0.62, 1.61

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AOR, Adjusted Odds Ratio; CI, Confidence Interval; OR, Odds Ratio

<sup>a</sup> Adjusted for age group only

<sup>b</sup> Adjusted for age group, education level, socioeconomic status (assessed by area-level disadvantage score), lifetime cigarette smoking, and alcohol intake 10 years ago

**Table Three:** Associations between different shiftwork variables and the risks of colon and rectal cancers among females in the Western Australian Bowel Health Study, 2005-07

	Colon Cancer			Rectal Cancer		
	n	AOR <sup>a</sup>	95% CI	n	AOR <sup>a</sup>	95% CI
<b>TYPES OF SHIFTWORK</b>						
<b>Years in Graveyard Shiftwork</b>						
0 Years (reference)	197	1.00		80	1.00	
0.1 + Years (Ever)	47	0.94	0.62, 1.43	26	1.38	0.81, 2.33
<i>0 &lt; Years &lt; 7.5</i>	27	1.10	0.65, 1.86	13	1.35	0.68, 2.67
<i>7.5+ Years</i>	20	0.78	0.43, 1.41	13	1.41	0.69, 2.88
<b>Years in Shiftwork Involving Early Shifts</b>						
0 Years (reference)	221	1.00		96	1.00	
0.1 + Years (Ever)	23	1.00	0.57, 1.74	10	1.00	0.47, 2.14
<b>MECHANISTIC SHIFTWORK VARIABLES</b>						
<b>Years in Shiftwork Involving Exposure to Light at Night</b>						
0 Years (reference)	200	1.00		80	1.00	
0.1 + Years (Ever)	44	0.87	0.57, 1.33	26	1.40	0.83, 2.38
<i>0 &lt; Years &lt; 7.5</i>	25	1.01	0.59, 1.74	13	1.38	0.70, 2.74
<i>7.5+ Years</i>	19	0.73	0.40, 1.33	13	1.43	0.70, 2.93
<b>Years in Shiftwork Involving Exposure to Phase Shift</b>						
0 Years (reference)	201	1.00		80	1.00	
0.1 + Years (Ever)	43	0.85	0.55, 1.30	26	1.40	0.82, 2.38
<i>0 &lt; Years &lt; 7.5</i>	25	0.99	0.58, 1.70	13	1.36	0.69, 2.69
<i>7.5+ Years</i>	18	0.70	0.38, 1.28	13	1.45	0.71, 2.98
<b>Years in Shiftwork Involving Exposure to Poor Diet</b>						
0 Years (reference)	205	1.00		81	1.00	
0.1 + Years (Ever)	39	0.79	0.51, 1.22	25	1.42	0.83, 2.43
<i>0 &lt; Years &lt; 7.5</i>	22	0.90	0.52, 1.59	12	1.35	0.67, 2.73
<i>7.5+ Years</i>	17	0.67	0.36, 1.24	13	1.50	0.73, 3.08
<b>Years in Shiftwork Involving Exposure to Physical Inactivity</b>						
0 Years (reference)	203	1.00		80	1.00	
0.1 + Years (Ever)	41	0.86	0.56, 1.34	26	1.53	0.90, 2.62
<i>0 &lt; Years &lt; 7.5</i>	23	1.01	0.58, 1.78	13	1.55	0.77, 3.08
<i>7.5+ Years</i>	18	0.72	0.39, 1.33	13	1.53	0.74, 3.14
<b>Years in Shiftwork Involving Exposure to Sleep Disturbance</b>						
0 Years (reference)	237	1.00		103	1.00	
0.1 + Years (Ever)	7	1.14	0.42, 3.11	3	1.29	0.34, 4.94



**Years in Shiftwork Involving Exposure to Insufficient Vitamin D**

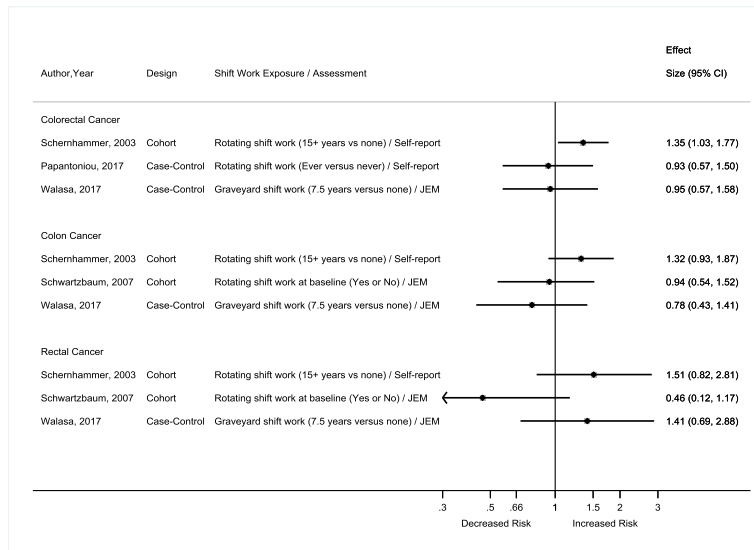
0 Years (reference)	222	1.00		92	1.00	
0.1 + Years (Ever)	22	0.85	0.49, 1.48	14	1.33	0.69, 2.58

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AOR, Adjusted Odds Ratio; CI, Confidence Interval; OR, Odds Ratio

<sup>a</sup> Adjusted for age group

<sup>b</sup> Adjusted for age group, education level, SEIFA disadvantage score, lifetime cigarette smoking, and alcohol intake 10 years ago



**Figure 1: Forest plot of studies of the association between shiftwork and the risk of colorectal cancer among females**

## REFERENCES

- 1 Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015;65:87-108.
- 2 Rosato V, Bosetti C, Levi F et al. Risk factors for young-onset colorectal cancer. *Cancer Causes Control* 2013;24:335-341.
- 3 Potter JD, Hunter D. Colorectal cancer. In: Adami H-O, Hunter D, Trichopoulos D eds. *Textbook of Cancer Epidemiology*, Oxford: Oxford University Press 2008.
- 4 Johnson CM, Wei C, Ensor JE et al. Meta-analyses of colorectal cancer risk factors. *Cancer Causes Control* 2013;24:1207-1222.
- 5 World Cancer Research Fund, American Institute for Cancer Research. WCRF/AICR Systematic Literature Review Continuous Update Project Report: The associations between food, nutrition and physical activity and the risk of colorectal cancer, Washington DC: AICR 2011.
- 6 Aliyu OA, Cullen MR, Barnett MJ et al. Evidence for excess colorectal cancer incidence among asbestos-exposed men in the Beta-Carotene and Retinol Efficacy Trial. *Am J Epidemiol* 2005;162:868-878.
- 7 Boyle T, Fritschi L, Heyworth J, Bull F. Long-term sedentary work and the risk of subsite-specific colorectal cancer. *Am J Epidemiol* 2011;173:1183-1191.
- 8 Itani O, Kaneita Y. The association between shift work and health: a review. *Sleep Biol Rhythms* 2016;14:231-239.
- 9 Australian Bureau of Statistics. Working Time Arrangements, Australia, 6342.0, Canberra: ABS 2013.
- 10 Eurofound. Fifth European Working Conditions Survey, Luxembourg: Publications Office of the European Union 2012.
- 11 McMenamin TM. A time to work: recent trends in shift work and flexible schedules. *Mon Labor Rev* 2007;130:3-15.
- 12 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Painting, firefighting, and shiftwork. *IARC Monogr Eval Carcinog Risks Hum* 2010;98:9-764.

- 13 Fritschi L, Glass DC, Heyworth JS et al. Hypotheses for mechanisms linking shiftwork and cancer. *Med Hypotheses* 2011;77:430-436.
- 14 Ijaz S, Verbeek J, Seidler A et al. Night-shift work and breast cancer;a systematic review and meta-analysis. *Scand J Work Environ Health* 2013;39:431-447.
- 15 Kamdar BB, Tergas AI, Mateen FJ, Bhayani NH, Oh J. Night-shift work and risk of breast cancer: a systematic review and meta-analysis. *Breast Cancer Res Treat* 2013;138:291-301.
- 16 Salavaty A. Carcinogenic effects of circadian disruption: an epigenetic viewpoint. *Chin J Cancer* 2015;34:1-9.
- 17 Papantoniou K, Castano-Vinyals G, Espinosa A et al. Shift work and colorectal cancer risk in the MCC-Spain case-control study. *Scand J Work Environ Health* 2017.
- 18 Parent M-É, El-Zein M, Rousseau M-C, Pintos J, Siemiatycki J. Night work and the risk of cancer among men. *Am J Epidemiol* 2012;176:751-759.
- 19 Schernhammer ES, Laden F, Speizer FE et al. Night-shift work and risk of colorectal cancer in the Nurses' Health Study. *J Natl Cancer Inst* 2003;95:825-828.
- 20 Schwartzbaum J, Ahlbom A, Feychting M. Cohort study of cancer risk among male and female shift workers. *Scand J Work Environ Health* 2007;33:336-343.
- 21 Kolstad HA. Nightshift work and risk of breast cancer and other cancers-a critical review of the epidemiologic evidence. *Scand J Work Environ Health* 2008;34:5-22.
- 22 Fernandez RC, Peters S, Carey RN, Davies MJ, Fritschi L. Assessment of exposure to shiftwork mechanisms in the general population: the development of a new job-exposure matrix. *Occup Environ Med* 2014;71:723-729.
- 23 Jensen OM. Different age and sex relationship for cancer of subsites of the large bowel. *Br J Cancer* 1984;50:825-829.
- 24 Boyle T, Fritschi L, Tabatabaei S, Ringwald K, Heyworth J. Smoking, alcohol, diabetes, obesity, socioeconomic status, and the risk of colorectal cancer in a population-based case-control study. *Cancer Causes Control* 2014;25:1659-1668.
- 25 Australian Bureau of Statistics. Census of Population and Housing: Socio-Economic Indexes for Areas (SEIFA), Australia, State and Territory releases, Canberra: ABS 2003.

- 26 Rubin DB. *Multiple imputation for nonresponse in surveys*: John Wiley & Sons, 2004.
- 27 Devore EE, Massa J, Papantoniou K et al. Rotating night shift work, sleep, and colorectal adenoma in women. *Int J Colorectal Dis* 2017;1-6.
- 28 Thompson CL, Larkin EK, Patel S, Berger NA, Redline S, Li L. Short duration of sleep increases risk of colorectal adenoma. *Cancer* 2011;117:841-847.
- 29 Stevens RG, Hansen J, Costa G et al. Considerations of circadian impact for defining 'shift work' in cancer studies: IARC Working Group Report. *Occup Environ Med* 2011;68:154-162.
- 30 Schernhammer ES, Laden F, Speizer FE et al. Rotating night shifts and risk of breast cancer in women participating in the Nurses' Health Study. *J Natl Cancer Inst* 2001;93:1563-1568.
- 31 Erren TC. Shift work and cancer research: can chronotype predict susceptibility in night-shift and rotating-shift workers? *Occup Environ Med* 2013;70:283.

**Supplementary Table 1: Definition of probable exposure to each of the eight shiftwork variables**

<b>Shiftwork Variable</b>	<b>Definition of Probable Exposure</b>
<b>TYPES OF SHIFTWORK</b>	
Graveyard Shifts	Working between the hours of midnight and 5am
Early Morning Shifts	Working a shift that started between 5am and 7am
<b>MECHANISTIC SHIFTWORK VARIABLES</b>	
Phase Shift	Working two or more nights of forward rotation or three or more nights of backward rotation consecutively
Light at Night	Being exposed to bright or medium light in working areas and/or light in the bedroom when trying to sleep when working night shifts
Poor Diet	Self-rating diet quality (on a four-point scale) as anything less than very healthy when working night shifts
Lack of Physical Activity	Not meeting physical activity guidelines when working night shifts
Lack of Vitamin D	Spending less than one hour outside when working night shifts
Sleep Disturbance	Experiencing decreases in both quantity and quality of sleep when working night shifts

**Supplementary Table 2:** Associations between different shiftwork variables using different exposure probability cut-points and the risk of colorectal cancer among females in the Western Australian Bowel Health Study, 2005-2007

	30% Cut-Off		50% Cut-Off	
	AOR <sup>a</sup>	95% CI	AOR <sup>a</sup>	95% CI
<b>TYPES OF SHIFTWORK</b>				
<b>Years in Graveyard Shiftwork</b>				
0 Years (reference)	1.00		1.00	
0.1 + Years (Ever)	1.06	0.73, 1.54	1.01	0.70, 1.47
<i>0 &lt; Years &lt; 7.5</i>	<i>1.17</i>	<i>0.73, 1.88</i>	<i>1.11</i>	<i>0.69, 1.79</i>
<i>7.5+ Years</i>	<i>0.95</i>	<i>0.57, 1.58</i>	<i>0.85</i>	<i>0.55, 1.52</i>
<b>Years in Shiftwork Involving Early Shifts</b>				
0 Years (reference)	1.00		1.00	
0.1 + Years (Ever)	1.00	0.60, 1.66	0.78	0.37, 1.65
<b>MECHANISTIC SHIFTWORK VARIABLES</b>				
<b>Years in Shiftwork Involving Exposure to Light At Night</b>				
0 Years (reference)	1.00		1.00	
0.1 + Years (Ever)	1.02	0.70, 1.48	0.98	0.67, 1.44
<i>0 &lt; Years &lt; 7.5</i>	<i>1.12</i>	<i>0.69, 1.81</i>	<i>1.11</i>	<i>0.66, 1.75</i>
<i>7.5+ Years</i>	<i>0.91</i>	<i>0.55, 1.53</i>	<i>0.89</i>	<i>0.52, 1.50</i>
<b>Years in Shiftwork Involving Exposure to Phase Shift</b>				
0 Years (reference)	1.00		1.00	
0.1 + Years (Ever)	1.00	0.69, 1.45	0.97	0.66, 1.41
<i>0 &lt; Years &lt; 7.5</i>	<i>1.09</i>	<i>0.68, 1.76</i>	<i>1.02</i>	<i>0.63, 1.64</i>
<i>7.5+ Years</i>	<i>0.89</i>	<i>0.53, 1.51</i>	<i>0.91</i>	<i>0.53, 1.55</i>
<b>Years in Shiftwork Involving Exposure to Poor Diet</b>				
0 Years (reference)	1.00		1.00	
0.1 + Years (Ever)	0.96	0.65, 1.40	1.05	0.65, 1.68
<i>0 &lt; Years &lt; 7.5</i>	<i>1.03</i>	<i>0.63, 1.69</i>	<i>1.08</i>	<i>0.60, 1.84</i>
<i>7.5+ Years</i>	<i>0.88</i>	<i>0.52, 1.50</i>	<i>1.04</i>	<i>0.46, 2.37</i>
<b>Years in Shiftwork Involving Exposure to Physical Inactivity</b>				
0 Years (reference)	1.00		1.00	
0.1 + Years (Ever)	1.05	0.71, 1.53	1.24	0.58, 2.65
<i>0 &lt; Years &lt; 7.5</i>	<i>1.16</i>	<i>0.71, 1.91</i>	<i>1.85</i>	<i>0.70, 4.89</i>
<i>7.5+ Years</i>	<i>0.93</i>	<i>0.55, 1.57</i>	<i>0.56</i>	<i>0.14, 2.25</i>
<b>Years in Shiftwork Involving Exposure to Sleep Disturbance</b>				
0 Years (reference)	1.00		1.00	
0.1 + Years (Ever)	1.19	0.48, 2.95	0.81	0.21, 3.14

**Years in Shiftwork Involving Exposure to Insufficient Vitamin D**

0 Years (reference)	1.00		1.00	
0.1 + Years (Ever)	1.00	0.62, 1.61	1.05	0.29, 3.77

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AOR, Adjusted Odds Ratio; CI, Confidence Interval; OR, Odds Ratio

<sup>a</sup> Adjusted for age group

<sup>b</sup> Adjusted for age group, education level, SEIFA disadvantage score, lifetime cigarette smoking, and alcohol intake 10 years ago