

Night shift work and colorectal cancer risk

Austrian Society for Occupational Medicine Conference
Innsbruck, 20 September 2019

Kyriaki Papantoniou, MD PhD

Associate Professor

Department of Epidemiology

Medical University of Vienna

kyriaki.papantoniou@meduniwien.ac.at



MEDICAL UNIVERSITY
OF VIENNA



HARVARD
MEDICAL SCHOOL



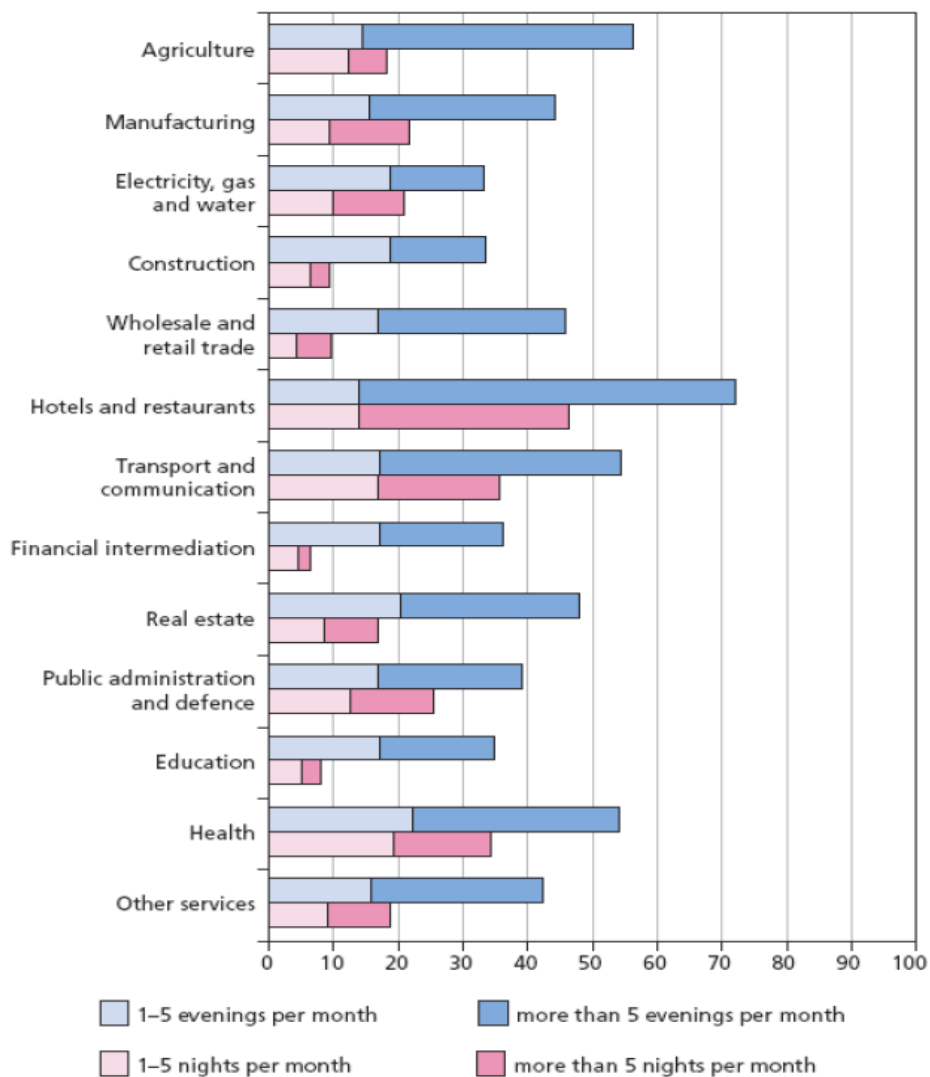
BRIGHAM HEALTH
BRIGHAM AND
WOMEN'S HOSPITAL

Egmont-Baumgartner Preis 2019

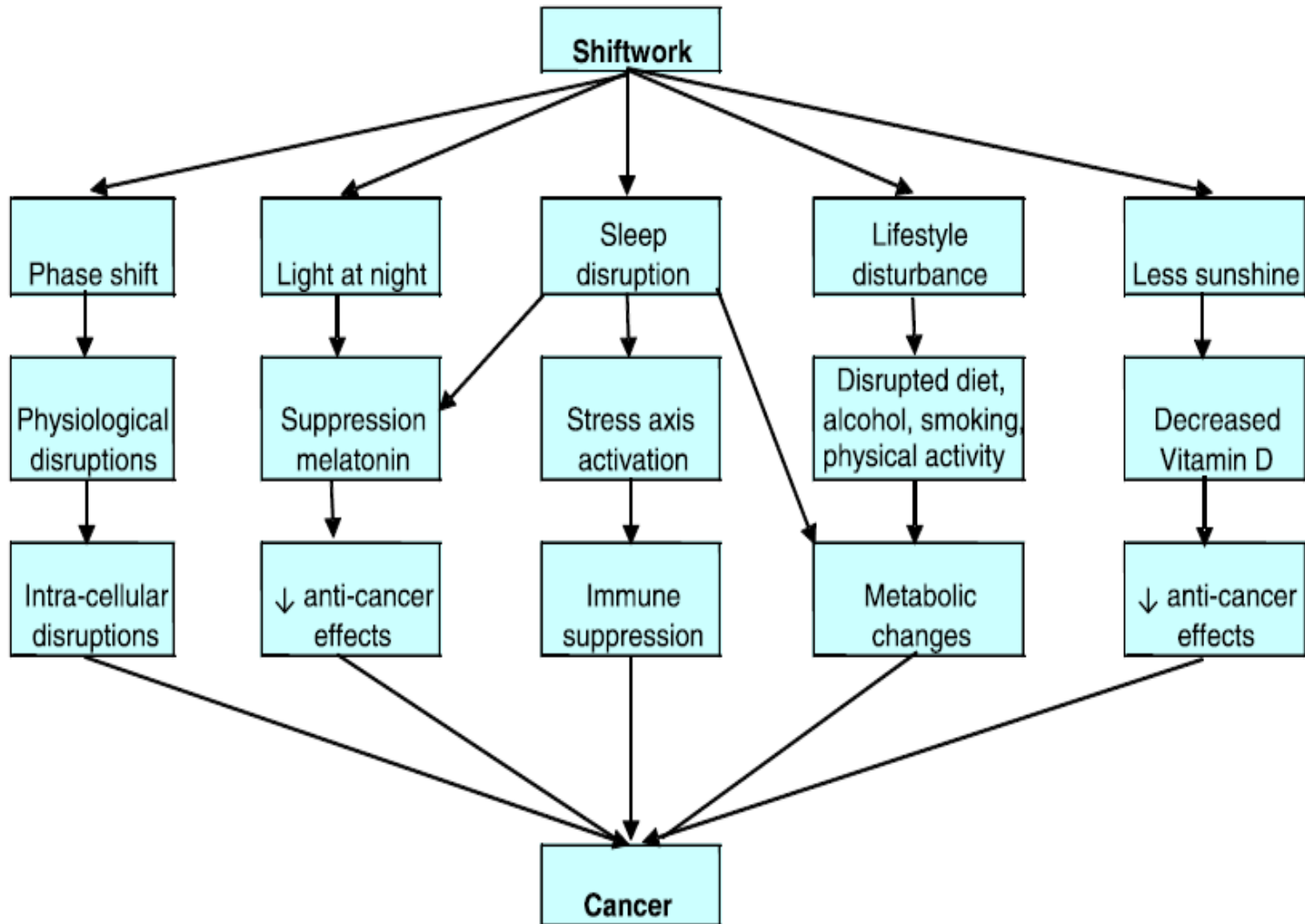
1. Papantoniou K, Castaño-Vinyals G, Espinosa A, Turner MC, Alonso-Aguado MH, Vicente M, Nuria Aragonés N, Pérez-Gómez B, Pozo BM, Gómez-Acebo I, Ardanaz E, Altzibar JM, Peiro R, Tardon A, Lorca JA, Chirlaque MD, García-Palomo A, Jimenez-Moleon JJ, Dierssen T, Ederra M, Amiano P, Marina Pollan M, Moreno V, Kogevinas M. **Shift work and colorectal cancer risk in the MCC-Spain case-control study.** *Scand J Work Environ Health.* 2017 May 1;43(3):250-259

2. Papantoniou K, Devore E, Massa J, Strohmaier S, Vetter C, Yang L, Yan S, Giovannucci E, Speizer F, Schernhammer E. **Rotating night shift work and colorectal cancer risk in the Nurses' Health Studies with 24 years of follow-up.** *Int J Cancer.* 2018 Dec 1;143(11):2709-2717.

Night shift work



Mechanisms



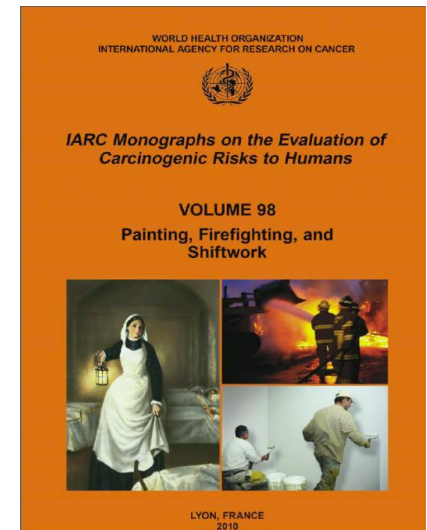
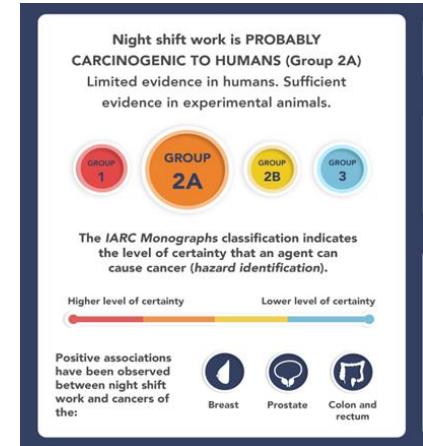
Carcinogenicity of shift work

IARC (WHO), 2007

“Shift work involving circadian disruption is probably carcinogenic to humans” (**Group 2A**)

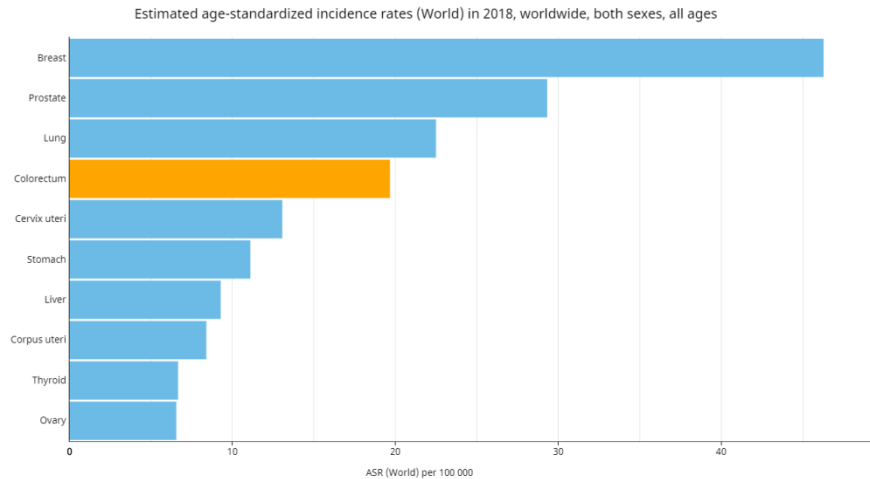
based on...

- Sufficient evidence from (>20) animal studies showing the carcinogenicity of light during night
- Limited evidence from epidemiological studies showing higher risks for **breast** cancer among female night workers & flight attendants

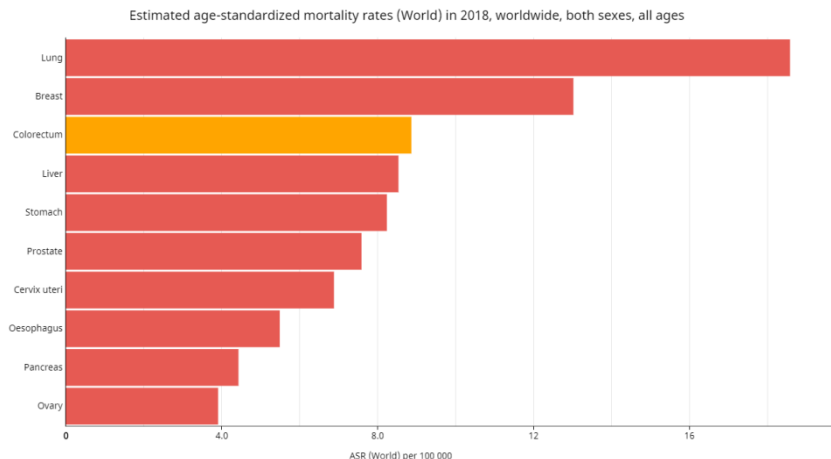


Colorectal Cancer Epidemiology

• Incidence



• Mortality



• Etiology

- Age (>50 yrs)
- Family history
- Inflammatory bowel disease
- Physical inactivity
- Obesity
- Smoking
- Alcohol consumption
- High intake of red and processed meat
- Low intake of fruit and vegetables
- Occupational/Environmental risks
 - Night shift work?
 - Light at night?

Night work & Colorectal cancer

2003: Schernhammer et al JNCI: 35% increase in risk with 15+ years shift work in women

2007: Schwartzbaum et al SJWEH: null finding, JEM-based exposure, both sexes

2013: Parent et al AJE: 2-fold increase in risk of colorectal cancer in men

Objectives

1. To evaluate night shift work in relation to colorectal cancer risk in a large population based case-control study: the **MCC-Spain** study
2. To evaluate rotating night shift work and colorectal cancer risk in two prospective cohorts of female nurses, the **NHS** and **NHS II**

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

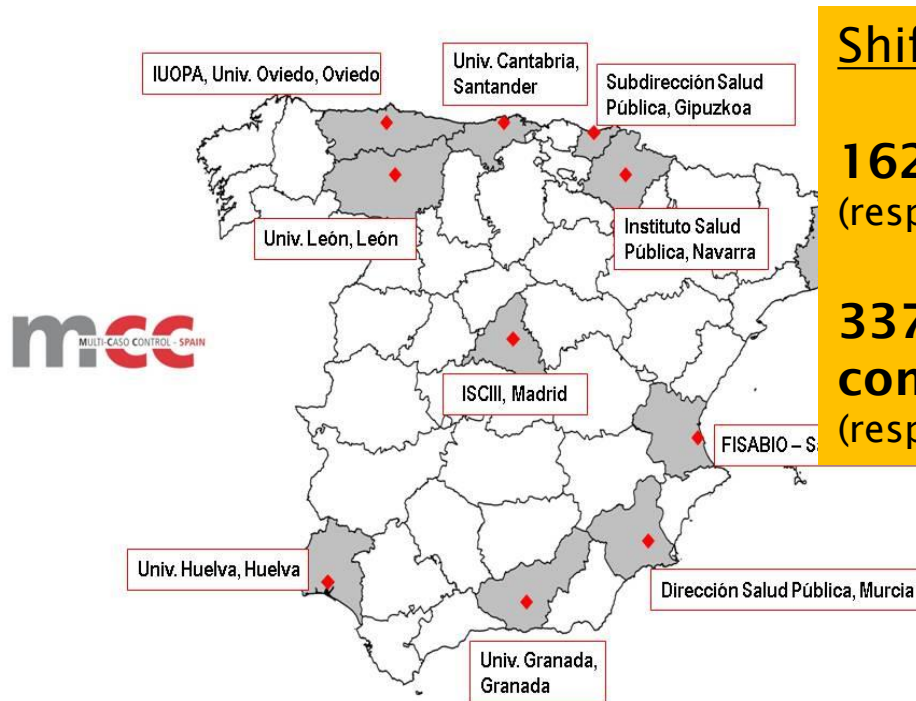
by Kyriaki Papantoniou, PhD,^{1, 2, 27} Gemma Castaño-Vinyals, PhD,^{1, 3, 4, 27} Ana Espinosa, PhD,^{1, 3, 4, 27} Michelle C Turner, PhD,^{1, 4, 5, 27} Maria Henar Alonso-Aguado, PhD,^{6, 7, 27} Vicente Martin, PhD,^{8, 27} Nuria Aragonés, PhD,^{9, 10, 27} Beatriz Pérez-Gómez, PhD,^{9, 10, 27} Benito Mirón Pozo, PhD,^{11, 27} Inés Gómez-Acebo, PhD,^{12, 27} Eva Ardanaz, PhD,^{13, 14, 27} Jone M Altzibar, PhD,^{15, 16, 27} Rosana Peiro, PhD,^{17, 27} Adonina Tardon, PhD,^{18, 27} José Andrés Lorca, PhD,^{19, 20, 27} Maria Dolores Chirlaque, PhD,^{21, 22, 27} Andrés García-Palomo, PhD,^{23, 27} Jose Juan Jimenez-Moleon, PhD,^{24, 27} Trinidad Dierssen, PhD,^{12, 27} Maria Ederra, PhD,^{13, 14, 27} Pilar Amiano, PhD,^{15, 16, 27} Marina Pollan, PhD,^{9, 10, 27} Victor Moreno, PhD,^{6, 7, 26, 27} Manolis Kogevinas, PhD^{1, 3, 4, 27}

Papantoniou K, Castaño-Vinyals G, Espinosa A, Turner MC, Alonso-Aguado MH, Martin V, Aragonés N, Pérez-Gómez B, Pozo BM, Gómez-Acebo I, Ardanaz E, Altzibar JM, Peiro R, Tardon A, Lorca JA, Chirlaque MD, García-Palomo A, Jimenez-Moleon JJ, Dierssen T, Ederra M, Amiano P, Pollan M, Moreno V, Kogevinas M. Shift work and colorectal cancer risk in the MCC–Spain case-control study. *Scand J Work Environ Health*. 2017;43(3):250–259. doi:10.5271/sjweh.3626

MCC-Spain Case-Control Study



Design: A population based multi case-control study on 5 common cancers using population controls (N \approx 10000)



Shift work analysis

1626 incident colorectal cancer cases
(response rates 68%)

3378 randomly selected population controls
(response rates 54%)

21 hospitals
12 regions

Recruitment: 2008 2014

Exposure definition

What kind of job was it in terms of shift type?

1. day 2. night 3. rotating

Shift work type:

- Permanent night
- Rotating

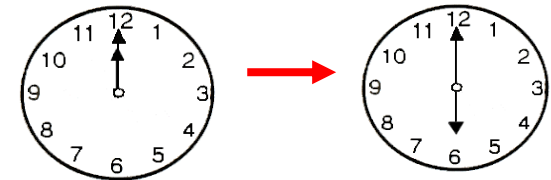
What was your habitual working schedule?

De __ : __ A __ : __

How many hours did you work/day?

__ __ hours

Night work: at least 1
hour between



≥3 nights/month

How many nights did you work per month? |_|_|

How old were you at the beginning of the job?

How old were you at the end of the job?

Cumulative duration
(total years)

Shift work and colorectal cancer risk

	Colorectal (N=1626)
	OR (95% CI)
Never shift work	1.0 (Ref)
Ever permanent night work	0.79 (0.62-1.00)
Ever rotating shift work	1.22 (1.04-1.43)

Shift work and colorectal cancer risk: **by anatomical site**

	Colorectal (N=1626)	Colon (N=1086)	Rectum (N=524)
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Never shift work	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Ever permanent night work	0.79 (0.62-1.00)	0.79 (0.57-1.03)	0.76 (0.53-1.11)
Ever rotating shift work	1.22 (1.04-1.43)	1.22 (1.02-1.46)	1.26 (0.81-1.48)

Duration of rotating shift work and colorectal cancer

	Controls/Cases	OR (95% CI) ^b
Never shift work	2432/1071	1 (Reference)
<8 yrs	173/89	1.14 (0.85-1.51)
8-19 yrs	171/87	1.26 (0.84-1.49)
20-34 yrs	158/119	1.38 (1.06-1.81)
≥35 yrs	141/127	1.36 (1.02-1.79)
p-trend***		0.005

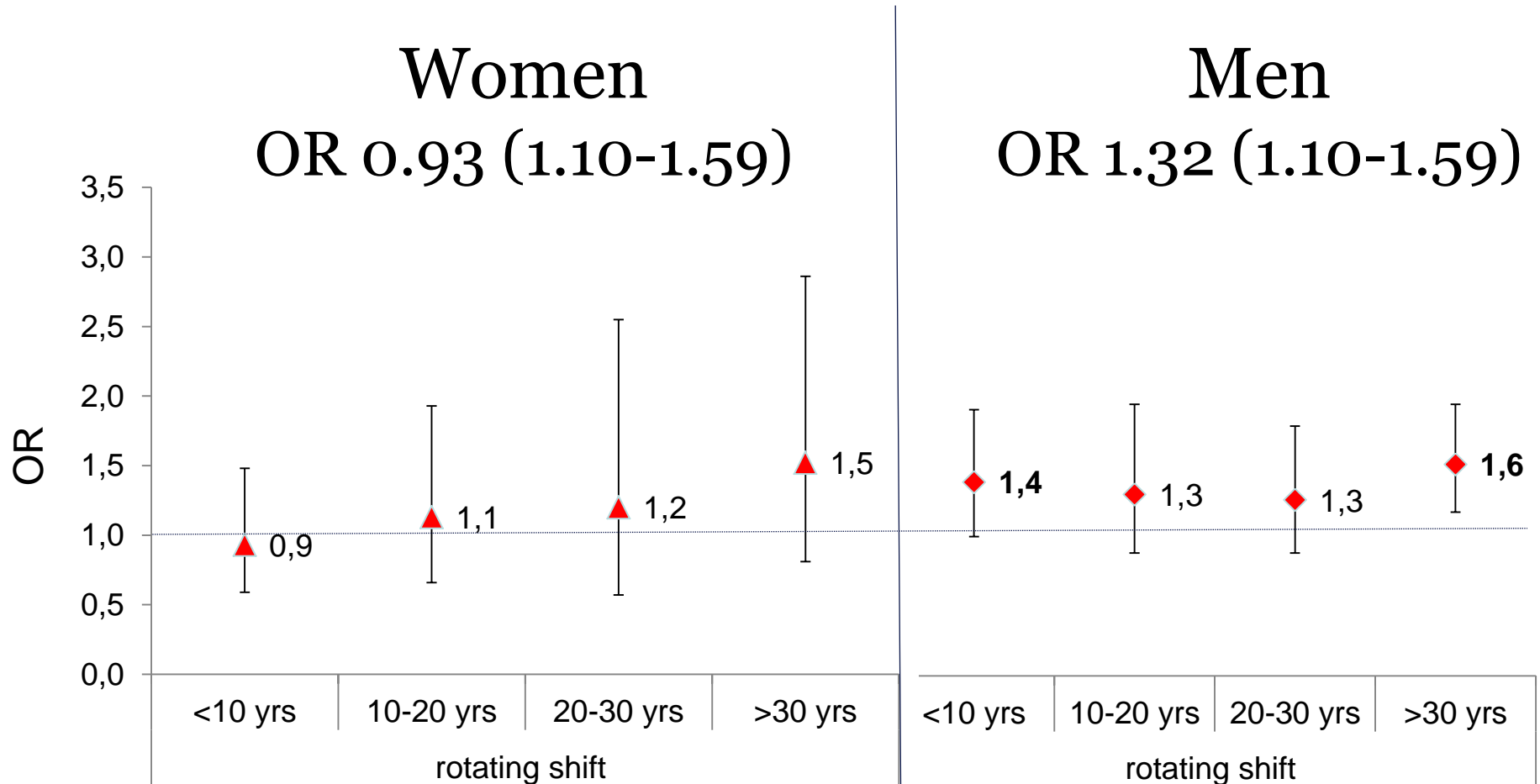
^bOR adjusted for age (continuous), center, educational level (less than primary, primary, high school, university), sex (female, male), history of colorectal cancer in first degree relatives (yes/no), body mass index (<22.5, 22.5-24.9, 25-29.9, ≥30), smoking status (ever, never), leisure time physical 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/nonsteroid anti-inflammatory drug use (yes, no).

Age at first rotating shift work exposure and colorectal cancer

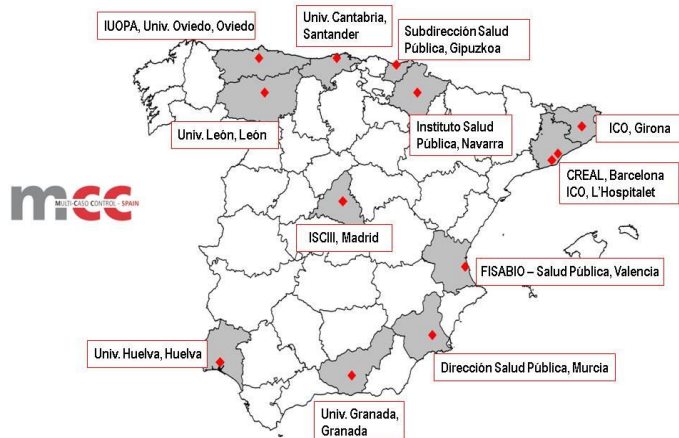
	Controls/Cases	OR (95% CI)^b
Never shift work	2432/1071	1 (Reference)
<25 years	243/166	1.24 (0.99-1.56)
≥25 years	200/99	0.95 (0.72-1.25)

^bOR 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/nonsteroid anti-inflammatory drug use (yes, no).

Duration of rotating shift work and colorectal cancer, by sex



Summary of findings



Original article

Scand J Work Environ Health – online first. doi:10.5271/sjweh.3626

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

by Kyriaki Papantoniou, PhD,^{1, 2, 27} Gemma Castaño-Vinyals, PhD,^{1, 3, 4, 27} Ana Espinosa, PhD,^{1, 3, 4, 27} Michelle C Turner, PhD,^{1, 4, 5, 27} Maria Henar Alonso-Aguado, PhD,^{6, 7, 27} Vicente Martin, PhD,^{8, 27} Nuria Aragonés, PhD,^{9, 10, 27} Beatriz Pérez-Gómez, PhD,^{9, 10, 27} Benito Mirón Pozo, PhD,^{11, 27} Inés Gómez-Acebo, PhD,^{12, 27} Eva Ardanaz, PhD,^{13, 14, 27} Jone M Altzibar, PhD,^{15, 16, 27} Rosana Peiro, PhD,^{17, 27} Adonina Tardon, PhD,^{18, 27} José Andrés Lorca, PhD,^{19, 20, 27} Maria Dolores Chirlaque, PhD,^{21, 22, 27} Andrés García-Palomo, PhD,^{23, 27} Jose Juan Jimenez-Moleon, PhD,^{24, 27} Trinidad Dierssen, PhD,^{12, 27} Maria Ederra, PhD,^{13, 14, 27} Pilar Amiano, PhD,^{15, 16, 27} Marina Pollan, PhD,^{9, 10, 27} Victor Moreno, PhD,^{6, 7, 26, 27} Manolis Kogevinas, PhD^{1, 3, 4, 27}

- 22% increase of CRC risk with ever rotating shift work in a variety of occupations
- CRC risk increased with longer (20+ years) cumulative shift work duration
- No association with permanent night work

Rotating night shift work and colorectal cancer risk in the nurses' health studies

Kyriaki Papantoniou¹, Elizabeth E. Devore², Jennifer Massa³, Susanne Strohmaier², Céline Vetter^{2,4}, Lin Yang¹, Yan Shi⁵, Edward Giovannucci^{3,6}, Frank Speizer² and Eva S. Schernhammer^{1,2,6}

¹Department of Epidemiology, Center of Public Health, Medical University of Vienna, Vienna, Austria

²Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

³Department of Nutrition, Harvard T. H. Chan School of Public Health, Boston, MA

⁴Department of Integrative Physiology, University of Colorado, Boulder, CO

⁵Department of Medical Oncology, Chinese PLA General Hospital, Beijing, China

⁶Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, MA

Animal and human data have suggested that shift work involving circadian disruption may be carcinogenic for humans, but epidemiological evidence for colorectal cancer remains limited. We investigated the association of rotating night shift work and colorectal cancer risk in two prospective female cohorts, the Nurses' Health Study (NHS) and NHS2, with 24 years of follow-up. In total, 190,810 women (NHS = 77,439; NHS2 = 113,371) were included in this analysis, and 1,965 incident colorectal cancer cases (NHS = 1,527; NHS2 = 438) were reported during followup (NHS: 1988–2012, NHS2: 1989–2013). We used Cox proportional hazards models adjusted for a wide range of potential confounders. We did not observe an association between rotating night work duration and colorectal cancer risk in these cohorts (NHS: 1–14 years: Hazard Ratio (HR) 1.04, 95% CI: 0.94, 1.16; 15+ years: HR 1.15, 95% CI: 0.95, 1.39; $P_{\text{trend}} = 0.14$ and NHS2: 1–14 years: HR 0.81, 95% CI: 0.66, 0.99; 15+ years: HR 0.96, 95% CI: 0.56, 1.64 and $P_{\text{trend}} = 0.88$). In subsite analysis in NHS, rectal cancer risk increased after long-term (15+ years) rotating night shift work (proximal colon cancer: HR 1.00, 95% CI: 0.75, 1.34, $P_{\text{trend}} = 0.90$; distal colon cancer: HR 1.27, 95% CI: 0.87, 1.85, $P_{\text{trend}} = 0.32$; rectal cancer: HR 1.60, 95% CI: 1.09, 2.34, $P_{\text{trend}} = 0.02$). We found no overall evidence of an association between rotating night shift work and colorectal cancer risk in these two large cohorts of nurses. Risk for rectal cancer significantly increased with shift work duration, suggesting that long-term circadian disruption may play a role in rectal cancer development.

The Nurses' Health Studies

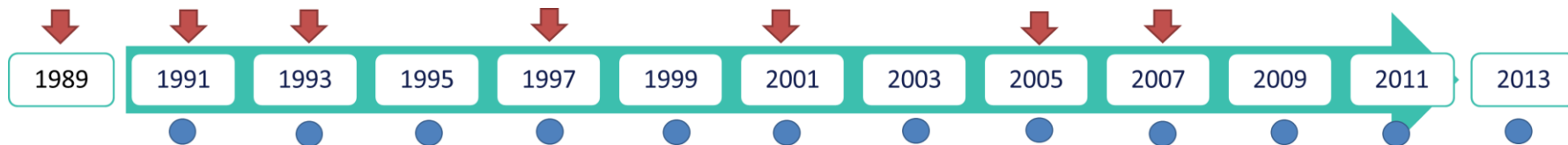
NHS:

121,700 female US registered nurses (1976), aged 30 to 55 years → **77,470** in analysis



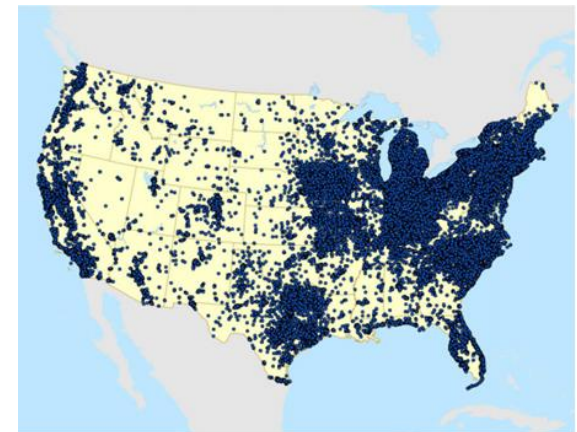
NHS II:

116,430 female US registered nurses (1989), aged 25 to 42 years → **113,371** in analysis



Shift work assessment ↓ : total years of rotating night shifts at **baseline (NHS/NHS II)** and **updated** during follow up (**NHS II**)

Colorectal cancer ascertainment ● : **1,527 (NHS)** and **438 (NHS II)** incident colorectal cancer cases



Statistical analyses

Cox proportional hazard models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CI)

Main analyses:

- **Baseline** shift work history and colorectal cancer risk (NHS)
- **Baseline** shift work history and colorectal cancer risk (NHS II)
- **Updated** shift work history and colorectal cancer risk (NHS II)

Secondary analyses:

- Stratified analyses by **anatomical site**: colon vs rectum (NHS)

Rotating night shift work duration and colorectal cancer risk in the NHS, 1988-2012

	Cases	Person-yrs	HR (95%CI) ^a	HR (95% CI) ^b
Rotating night shift work duration				
Never	571	63,5313	Ref	Ref
1-2 yrs	340	37,7113	1.03 (0.90, 1.18)	1.04 (0.91, 1.19)
3-4 yrs	263	25,7436	1.05 (0.91, 1.22)	1.05 (0.91, 1.22)
5-9 yrs	111	10,4210	1.10 (0.89, 1.35)	1.08 (0.88, 1.32)
10-14 yrs	71	69,589	1.04 (0.81, 1.33)	1.00 (0.78, 1.28)
15-19 yrs	43	42,288	1.03 (0.76, 1.41)	1.00 (0.73, 1.36)
20-29 yrs	57	41,997	1.32 (1.00, 1.74)	1.24 (0.94, 1.63)
30+ yrs	39	24,748	1.24 (0.90, 1.72)	1.19 (0.86, 1.66)
	1495	1,552,202	p-trend=0.04	p-trend=0.16

^aAdjusted for age (months) and follow-up cycle

^bAdjusted for age (months), height (continuous in inches), BMI (<18.5, 18.5-24.9, 25.0-29.9, 30+ kg/m²), educational level (RN license, bachelor's degree, masters or doctoral degree), menopausal status (premenopausal, postmenopausal), menopausal hormone therapy (never, past, current), first-degree family history of colorectal cancer (yes, no), alcohol consumption (0, 0.1-4.9, 5-14.9, ≥15g/day), physical activity (≤8, 8.1-16, 16.1-24, ≥24 MET-hrs/week), colonoscopy/sigmoidoscopy in the previous 2 years (yes, no), current regular aspirin or NSAIDs use (>2 tablets/week), daily energy intake (kcal/day), red or processed meat (servings/day) and folate consumption in quintiles.

Baseline night shift work history and colorectal cancer risk in the NHS II, 1989-2013

	Cases (N)	Person-yrs	HR (95%CI) ^a	HR (95% CI) ^b
Baseline rotating night shift work duration				
Never	160	893,405	Ref	Ref
1-2 yrs	81	683,208	0.67 (0.51, 0.88)	0.67 (0.51, 0.88)
3-4 yrs	72	464,040	0.88 (0.67, 1.17)	0.88 (0.67, 1.17)
5-9 yrs	35	200,991	0.97 (0.67, 1.40)	0.95 (0.66, 1.38)
10-14 yrs	20	81,264	1.25 (0.78, 1.99)	1.24 (0.77, 1.98)
15+ yrs	7	24,711	1.17 (0.55, 2.52)	1.10 (0.51, 2.38)
	375	2,347,619	p-trend=0.28	p-trend=0.35

^aAdjusted for age (months) and follow-up cycle

^bAdjusted for age (months), height (continuous in inches), BMI (<18.5, 18.5-24.9, 25.0-29.9, 30+ kg/m²), educational level (RN license, bachelor's degree, masters or doctoral degree), menopausal status (premenopausal, postmenopausal), menopausal hormone therapy (never, past, current), first-degree family history of colorectal cancer (yes, no), alcohol consumption (0, 0.1-4.9, 5-14.9, ≥15g/day), physical activity (≤8, 8.1-16, 16.1-24, >24 MET-hrs/week), colonoscopy/sigmoidoscopy in the previous 2 years (yes, no), current regular aspirin or NSAIDS use (>2 tablets/week), daily energy intake (kcal/day), red or processed meat (servings/day) and folate consumption in quintiles.

Updated night shift work duration and colorectal cancer risk in the NHS II, 1989-2013

	Cases (N)	Person-yrs	HR (95%CI) ^a	HR (95% CI) ^b
Updated rotating night shift work duration				
Never	131	722,745	Ref	Ref
1-4 yrs	156	1,163,704	0.73 (0.58, 0.92)	0.72 (0.57, 0.91)
5-9 yrs	59	300,937	0.87 (0.63, 1.21)	0.84 (0.61, 1.17)
10-14 yrs	25	109,653	1.08 (0.70, 1.67)	1.04 (0.67, 1.60)
15-19 yrs	9	37,375	1.04 (0.53, 2.05)	0.98 (0.50, 1.94)
20+ yrs	4	13,206	1.08 (0.40, 2.92)	0.97 (0.36, 2.65)
	375	2,347,619	p-trend=0.34	p-trend=0.51

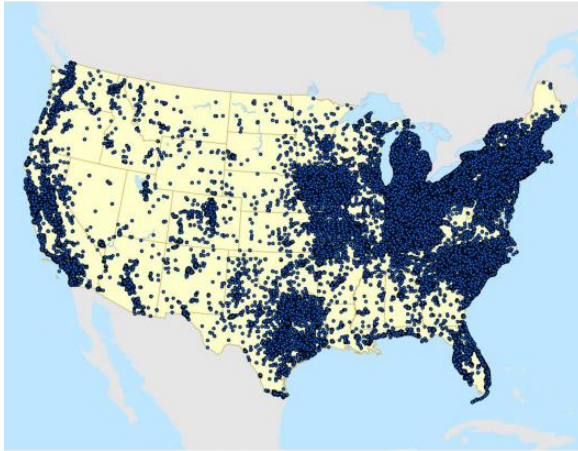
^aAdjusted for age (months) and follow-up cycle

^bAdjusted for age (months), height (continuous in inches), BMI (<18.5, 18.5-24.9, 25.0-29.9, 30+ kg/m²), educational level (RN license, bachelor's degree, masters or doctoral degree), menopausal status (premenopausal, postmenopausal), menopausal hormone therapy (never, past, current), first-degree family history of colorectal cancer (yes, no), alcohol consumption (0, 0.1-4.9, 5-14.9, ≥15g/day), physical activity (≤8, 8.1-16, 16.1-24, >24 MET-hrs/week), colonoscopy/sigmoidoscopy in the previous 2 years (yes, no), current regular aspirin or NSAIDs use (>2 tablets/week), daily energy intake (kcal/day), red or processed meat (servings/day) and folate consumption in quintiles.

Night shift work duration & colorectal cancer risk by anatomical site (NHS)

	Cases (N=1495)	HR (95%CI) ^a	HR (95% CI) ^b	P-for-trend
Rotating night shift work duration				
Proximal colon (N=637)	637			
Never	259	Ref	Ref	
1-14 yrs	323	0.95 (0.81, 1.12)	0.95 (0.80, 1.12)	
15+ yrs	55	1.02 (0.76, 1.37)	0.99 (0.74, 1.33)	>0.05
Distal colon (N=356)				
Never	130	Ref	Ref	
1-14 yrs	191	1.11 (0.88, 1.39)	1.12 (0.89, 1.40)	
15+ yrs	35	1.30 (0.89, 1.89)	1.25 (0.85, 1.83)	>0.05
Rectum (N=293)				
Never	109	Ref	Ref	
1-14 yrs	150	1.04 (0.81, 1.33)	1.03 (0.80, 1.32)	
15+ yrs	34	1.62 (1.09, 2.39)	1.55 (1.05, 2.30)	0.03

Summary of findings



Rotating night shift work and colorectal cancer risk in the nurses' health studies

Kyriaki Papantoniou¹, Elizabeth E. Devore², Jennifer Massa³, Susanne Strohmaier², Céline Vetter^{2,4}, Lin Yang¹, Yan Shi⁵, Edward Giovannucci^{3,6}, Frank Speizer² and Eva S. Schernhammer^{1,2,6}

¹Department of Epidemiology, Center of Public Health, Medical University of Vienna, Vienna, Austria

²Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

³Department of Nutrition, Harvard T. H. Chan School of Public Health, Boston, MA

⁴Department of Integrative Physiology, University of Colorado, Boulder, CO

⁵Department of Medical Oncology, Chinese PLA General Hospital, Beijing, China

⁶Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, MA

- **No overall** evidence of an **association** between ever **rotating night shift work** and **CRC risk** in these two large cohorts of nurses.
- **Long-term** night **shift work** exposure might be associated with an **increased CRC risk**, and in particular **rectum** cancer.

Strengths

NHS & NHS II	MCC-Spain study
The largest analysis to date (N=1900 cases)	Large study (N=1626 cases)
Physician confirmed diagnosis of CRC	Physician confirmed diagnosis of CRC
Analyses adjusted for a wide range of potential confounders	Analyses adjusted for a wide range of potential confounders
Prospective design, temporality	Case-control design with population controls
Duration of shift work updated through follow-up (NHSII)	Detailed shift work exposure - lifetime occupational history
Among nurses	Across a variety of occupational sectors

Limitations

NHS & NHS II	MCC-Spain study
NHS: exposure was only assessed at baseline	Selection bias : response rates were lower among controls than cases
NHS II: low power for secondary analyses (e.g anatomical site)	Recall bias : retrospective shift work assessment (non-differential misclassification)
Only females/single occupational group	Job specific confounders might be unevenly distributed across shifts
No information on intensity of shift work	Shift work frequency: 35% missings Shift work duration: <1 % missings

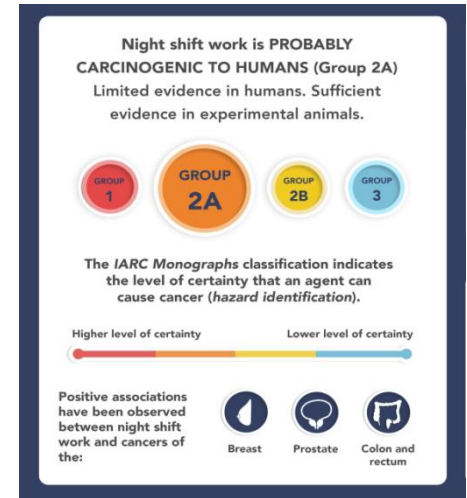
Updated carcinogenicity of shift work

IARC (WHO), 4-11 June 2019

“**Night shift work** is probably carcinogenic to humans” (Group 2A)

based on...

- **Sufficient** evidence from experimental animal studies (alteration in light-dark schedule) and strong mechanistic evidence
- **Limited** evidence from epidemiological human studies showing positive associations between night work and **breast**, **prostate** and **colorectal** cancer risk



Acknowledgements



And its research centres



Eva Schernhammer

Céline Vetter

Vicente Martin Sanchez

Manolis Kogevinas

Lin Yang

Elizabeth Devore

Inés Gómez Acebo

Gemma Castaño

Florian Rorher

Susanne Strohmaier

Marina Pollán

Ana Espinosa

Anna Kosheleva

Jennifer Massa

Jose-Juan Jimenez

Mariona Bustamante

Moleón,

Victor Moreno

Walter Willet

Eva Ardanaz

Frank Speizer

Jone M Altzibar

Rosana Peiro

Edward Giovannucci

Adonina Tardón

Charles Fuchs

Juan Alguacil

Carmen Navarro

