Carcinogenicity of night shift work

Published Online
July 4, 2019
http://dx.doi.org/10.1016/S1470-2045(19)30455-3

See Comment page 1051

For more on the **IARC Monographs** see http://monographs.iarc.fr/

Upcoming meetings

Nov 5–11, 2019, volume 125: Some industrial chemicals

March 24–31, 2020, volume 126: Opium

May 26 to June 2, 2020, volume 127: Some aromatic amines and related compounds

IARC Monograph Working Group Members

E M Ward (USA)–Meeting Chair; D Germolec (USA); M Kogevinas (Spain); D McCormick (USA); R Vermeulen (Netherlands)–Subgroup Meeting Chairs; V N Anisimov (Russia [unable to attend]); K J Aronson (Canada); P Bhatti (Canada); P Cocco (Italy); G Costa (Italy); D C Dorman (USA); L Fu (USA); A H Garde (Denmark); P Guénel (France); J Hansen (Denmark); M I Härmä (Finland); K Kawai (Japan); E A Khizkhin (Russia), A Knutsson (Sweden); F Lévi (UK); C R C Moreno (Brazil); E Pukkala (Finland [unable to attend]); E S Schernhammer (Austria and USA); R C Travis (UK); M A Waters (USA); M G Yakubovskaya (Russia); H Zeeb (Germany); Y Zhu (USA); S Zienolddiny (Norway)

Declaration of interests
We declare no competing interests.

Invited Specialists
None

Representatives
Y Chen, for Health and Safety Executive (HSE), UK; A Niaudet, for the French Agency for Food, Environmental and Occupational Health and Safety (ANSES)

Declaration of interests
All representatives declare no competing interests.

Observers
R Carel, for Haifa University, Israel; D Clarkson-Townsend, for Emory University, USA; A Forrest, for the United Fire Fighters of Winnipeg, Canada; C E Peters, for the Cumming School of Medicine, University of Calgary, Canada; M Rozenberg, for Centre Léon Bérard, France

In June, 2019, a Working Group of 27 scientists from 16 countries met at the International Agency for Research on Cancer (IARC) in Lyon, France, to finalise their evaluation of the carcinogenicity of night shift work. This assessment will be published in volume 124 of the IARC Monographs.[1]

Night shift work involves work, including transmeridian air travel, during the regular sleeping hours of the general population. The misalignment or disruption of circadian rhythms of normal physiology is the most pronounced effect of night shift work.

Night shift work is essential for guaranteeing round-the-clock production and activities. It is commonly found in health care, manufacturing, transport, retail, and services sectors. About 1 in 5 workers worldwide are engaged in night shift work; however, definitions, quality, and extent of data vary globally. Regulatory approaches for night shift work and their degree of implementation also differ across regions and employment sectors.

In 2007, shift work involving circadian disruption was classified as "probably carcinogenic to humans" (Group 2A), on the basis of sufficient evidence in experimental animals and limited evidence of breast cancer in humans. In this updated evaluation, the Working Group chose the name "night shift work" to better describe the exposure circumstances and to reflect the main evidence base for the human cancer studies. The re-evaluation was motivated by the large number of new, high-quality epidemiologic studies including additional cancer sites. However, the Working Group noted the considerable variability in the detail and quality of exposure information on night shift work reported in these studies. Exposure information was more detailed in case-control studies, including in those nested within cohorts, than in cohort studies. A number of occupational, individual, lifestyle, and environmental factors might mediate, confound, or moderate potential cancer risk in night shift workers.

The Working Group concluded there was limited evidence that night shift work causes breast, prostate, and colorectal cancer. This evaluation was based on comprehensive searches of the literature, screening of the studies using established inclusion criteria, and evaluation of study quality, including a standardised review of exposure assessment. Greater weight was given to the most informative human cancer studies based on methodologic considerations, including study size, potential selection bias, night work assessment quality (most notably, potential for misclassification), and control for potential confounding factors. The largest number of informative studies examined breast cancer, several examined prostate and colorectal cancer, while fewer were done on other cancers.

Most cohort studies, including large cohorts within the general population[2] and among air crew, did not find a positive association with ever versus never working night shifts or by increasing duration of night shift work. The Nurses' Health Study II, a large cohort study that evaluated breast cancer risk across a broad age range, found an elevated risk of breast cancer in long-duration night workers,[3] which was also seen in a Swedish cohort study. The strongest evidence regarding an association of night shift work and breast cancer is provided by cohort-based nested case-control studies and population-based case-control studies. The largest case-control study,[4] including more than 6000 breast cancer cases and corresponding controls from five countries, incorporated an extensive exposure assessment protocol and evaluated detailed exposure metrics on both duration and intensity of exposure (eg, number of night shifts per week). This study provided evidence for positive associations between night shift work and breast cancer risk, particularly among premenopausal women. The associations were strongest for high-intensity, long-duration night shift work. The variation in findings between studies could be attributed to differences in exposure assessment quality or the inclusion of mainly older post-employment women in some cohort studies, such that they might not be able to determine an effect in younger women. A small minority viewpoint was that evidence for breast cancer was inadequate, with studies of sufficient quality available in humans but with inconsistent results. Overall, the Working Group concluded that a positive association has been observed regarding night shift work and breast cancer; however, given the variability in findings between studies, bias could not be excluded as an explanation with reasonable confidence.

Several studies found positive associations between night shift work and prostate cancer risk, particularly in association with longer duration of exposures, but in others there was no, or a very small, increased risk when examining ever versus never exposure to night shift work.[5,6] Several informative studies found some evidence of positive associations between colorectal cancer risk and duration of night shift work. However, these studies had conflicting findings related to colorectal cancer subsites and shift work (night versus rotating) categories.[7] The Working Group concluded that, overall, these studies provide some evidence that night shift work is positively associated with risk of prostate and colorectal cancer; however, because the studies were few in number and the results lacked consistency, chance and bias could not be ruled out.

The Working Group found that there is sufficient evidence in experimental animals for the carcinogenicity of alteration in the light–dark schedule.

The results of several well-designed chronic animal bioassays were key to this evaluation. In one of these studies, male and female mice of three C57BL/6J inbred strains (one wild-type and two genetically engineered) were exposed to repeated 8-h time shifts in the light–dark schedule from 4–90 weeks of age. Increased incidences of hepatocellular carcinoma were seen in all three strains in comparison with control mice maintained at a stable 12-h light and 12-h dark schedule.[8] In another study, exposure to constant light for a lifetime increased the incidences of lung adenocarcinoma, malignant melanoma, and total tumours in female wild-type CBA mice in comparison with control mice maintained at a 12-h light and 12-h dark schedule.[9] The evaluation was further supported by positive results in other studies in rodents exposed to shifts in the light–dark schedule or continuous light using carcinogen-induced or transplantable tumour models.

There is robust evidence in both humans and experimental animals that alteration in the light–dark schedule results in changes in serum melatonin and in the expression of core circadian genes. With respect to key characteristics of carcinogens, the Working Group found that there is strong mechanistic evidence in experimental systems, based on effects consistent with immunosuppression, chronic inflammation, and cell proliferation. Multiple rodent studies of alteration of the light–dark schedule demonstrate immune suppression in nocturnal rats, mice, and Siberian hamsters.[10–12] Enhanced inflammation was seen in rodent studies and models of inflammatory disease. Altered tumour glucose metabolism consistent with the Warburg effect was shown in female nude rats. A few studies of changes in the light–dark schedule directly measured increases in cell proliferation in transplanted tumours. Additional studies using inoculated tumour cells or exposures to carcinogens in rodents showed effects including increased tumour growth consistent with increases in cell proliferation. Mechanistic studies in night shift workers were more disparate regarding the endpoints, study designs, and results. In exposed humans, the Working Group found the mechanistic evidence to be limited, based on suggestive but inconsistent evidence of alterations in oestrogen homeostasis in female night shift workers. In sum, the Working Group classified night shift work in Group 2A, "probably carcinogenic to humans", based on limited evidence of cancer in humans, sufficient evidence of cancer in experimental animals, and strong mechanistic evidence in experimental animals.

IARC Monographs Vol 124 group
International Agency for Research on Cancer, Lyon, France

1 International Agency for Research on Cancer. Volume 124: night shift work. IARC Working Group. Lyon, France; June 4–11, 2019. *IARC Monogr Eval Carcinog Risk Chem Hum* (in press).
2 Travis RC, Balkwill A, Fensom GK, et al. Night shift work and breast cancer incidence: three prospective studies and meta-analysis of published studies. *J Natl Cancer Inst* 2016; **108:** djw169.
3 Wegrzyn LR, Tamimi RM, Rosner BA, et al. Rotating night-shift work and the risk of breast cancer in the Nurses' Health Studies. *Am J Epidemiol* 2017; **186:** 532–40.
4 Cordina-Duverger E, Menegaux F, Popa A, et al. Night shift work and breast cancer: a pooled analysis of population-based case-control studies with complete work history. *Eur J Epidemiol* 2018; **33:** 369–79.
5 Behrens T, Rabstein S, Wichert K, et al. Shift work and the incidence of prostate cancer: a 10-year follow-up of a German population-based cohort study. *Scand J Work Environ Health* 2017; **43:** 560–68.
6 Barul C, Richard H, Parent ME. Nightshift work and prostate cancer risk: results from the Canadian case-control study PROtEuS. *Am J Epidemiol* (in press).
7 Papantoniou K, Devore EE, Massa J, et al. Rotating night shift work and colorectal cancer risk in the Nurses' Health Studies. *Int J Cancer* 2018; **143:** 2709–17.
8 Kettner NM, Voicu H, Finegold MJ, et al. Circadian homeostasis of liver metabolism suppresses hepatocarcinogenesis. *Cancer Cell* 2016; **30:** 909–24.
9 Anisimov VN, Baturin DA, Popovich IG, et al. Effect of exposure to light-at-night on life span and spontaneous carcinogenesis in female CBA mice. *Int J Cancer* 2004; **111:** 475–79.
10 Logan RW, Zhang C, Murugan S, et al. Chronic shift-lag alters the circadian clock of NK cells and promotes lung cancer growth in rats. *J Immunol* 2012; **188:** 2583–91.
11 Castanon-Cervantes O, Wu M, Ehlen JC, et al. Dysregulation of inflammatory responses by chronic circadian disruption. *J Immunol* 2010; **185:** 5796–805.
12 Bedrosian TA, Fonken LK, Walton JC, Nelson RJ. Chronic exposure to dim light at night suppresses immune responses in Siberian hamsters. *Biol Lett* 2011; **7:** 468–71.

Declaration of interests
A Forrest declares that his airfare and hotel costs for the IARC meeting were paid for by the Manitoba Professional Firefighters. All other observers declare no competing interests.

IARC Secretariat
L Benbrahim-Tallaa; V Bouvard; W R Diver; F El Ghissassi; J Girschik; Y Grosse; K Z Guyton; A L Hall; Z Herceg; C Marant Micallef; N Olson; E G Rowan; H Rumgay; M K Schubauer-Berigan; M C Turner

Declaration of interests
All secretariat declare no competing interests.

For the **Preamble to the IARC Monographs** see https://monographs.iarc.fr/wp-content/uploads/2019/01/Preamble-2019.pdf

For **IARC declarations of interests** see https://monographs.iarc.fr/wp-content/uploads/2019/05/124-Preliminary-list-Participants.pdf

Disclaimer
The views expressed are those of the authors and do not necessarily represent the decisions, policy, or views of their respective institutions.