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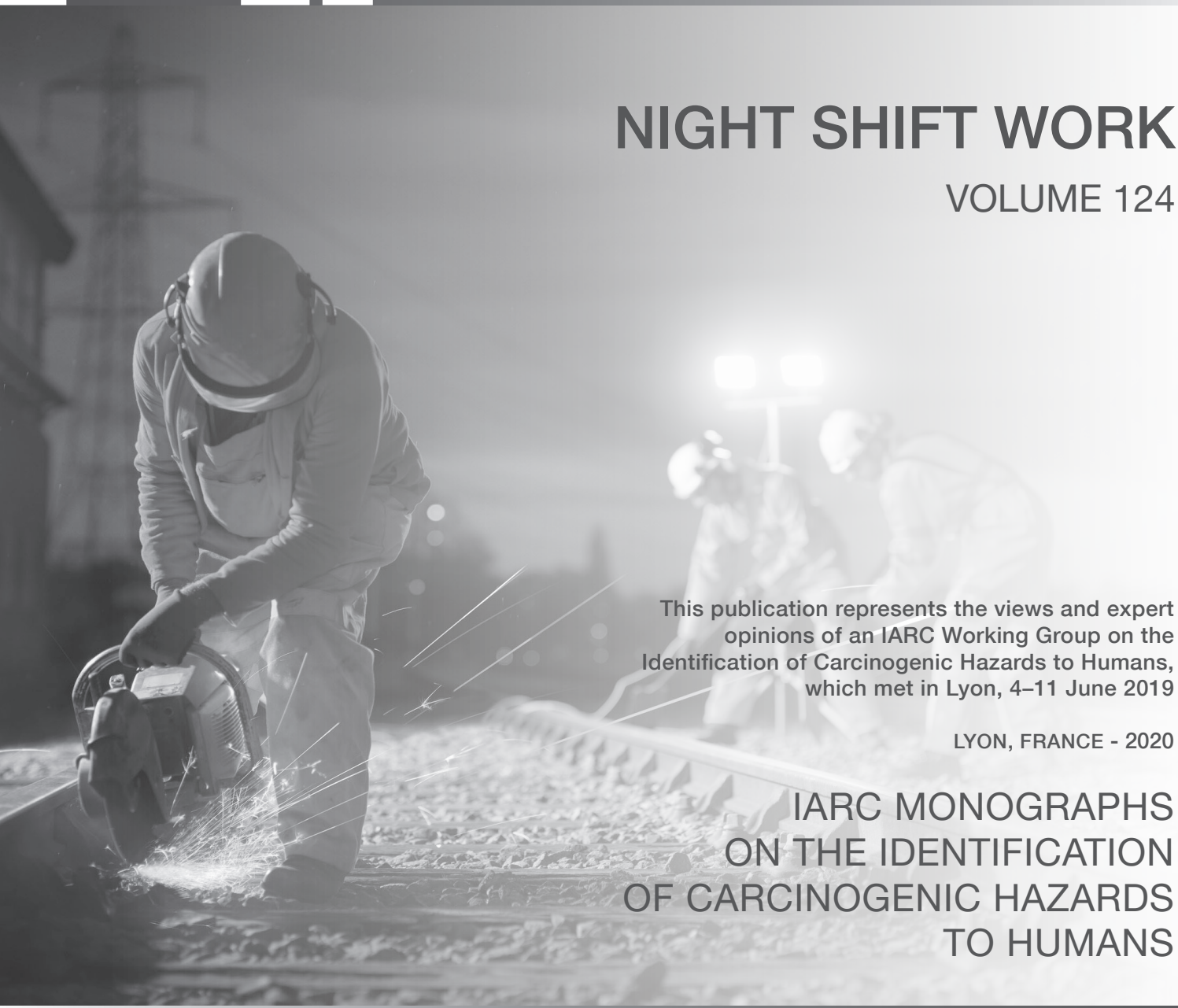

NIGHT SHIFT WORK

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IARC MONOGRAPHS ON THE IDENTIFICATION OF CARCINOGENIC HAZARDS TO HUMANS

International Agency for Research on Cancer

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5. SUMMARY OF DATA REPORTED

5.1 Exposure characterization

"Night shift work" involves work, including transmeridian travel, during the regular sleeping hours of the general population. The disruption of circadian rhythms of body functions as a result of alterations in the environmental light–dark schedule is the most pronounced effect of night shift work.

Night shift work is essential for guaranteeing round-the-clock production and activities. In the modern "24/7 society" (24 hours per day, 7 days per week) the nature of night shift work is changing as a result of the diversification of working time patterns. Its prevalence differs between sectors, and occurs most commonly in health care, manufacturing, transport, retail, and services. It is estimated that 1 out of 5 workers worldwide are engaged in night shift work, although definitions, quality, and extent of statistical data vary. Globalization of the labour market has led to increasing use of night shift work in low- and middle-income countries. Regulatory approaches for night shift work and their degree of implementation vary widely across regions and sectors.

Night shift workers may be occupationally co-exposed to biological, chemical, and physical carcinogens (e.g. cosmic radiation exposure in aircrew). In addition, several individual, lifestyle, and environmental factors may mediate, confound, or moderate the potential risk of cancer in night shift workers.

Exposure to night shift work and flying over time zones may be assessed in epidemiological studies with questionnaires, interviews, or diary methods, as well as registry (e.g. payroll) or work schedule data of actual working hours (e.g. flight history records of aircrew). The amount of detail and quality of exposure information on night shift work in epidemiological studies varies considerably between individual studies.

5.2 Cancer in humans

There have been several informative cohort, case–cohort, nested case–control, and case–control studies conducted in specific occupational groups (most predominantly, nurses, and also including aircrew) exposed to night shift work, as well as in the general population. Since the publication of the previous monograph on the subject of night shift work (*IARC Monographs* Volume 98), the number of such studies has grown considerably. The most important development within the body of research has been the refinement and expansion of exposure assessment metrics.

Many of the available studies were of high quality. The largest number of studies examined cancer of the breast, several examined cancer of the prostate and cancer of the colon and rectum, while fewer were conducted on most other cancers, including common cancers such as of the lung or hormone-related cancers such as of the ovary and endometrium.

For cancer of the breast, the majority of the informative cohort studies did not find a positive association with duration of night shift work. The informative nested case–control studies provided support for a positive association between night shift work and risk of cancer of the breast. Findings from the informative case–control studies, including a large, pooled case–control study that incorporated many of the more detailed exposure metrics, provided evidence for positive associations between various exposure metrics of night shift work and risk of cancer of the breast.

The variation in findings between studies could be attributed to differences in exposure assessment or to the inclusion of only older women in some studies, such that they may not be able to determine an effect in younger women.

In summary, there is now a large body of evidence to assess the potential association between night shift work and risk of cancer of the breast. A small minority of the Working Group held the viewpoint that a positive association has not been observed in this body of evidence. The Working Group consensus was that a positive association between night shift work and cancer of the breast has been observed in the body of evidence; however, given the variability in findings between studies, the Working Group were unable to exclude with reasonable confidence bias as an explanation.

Studies on cancer of the prostate include several studies in the general population, industrial cohort studies, population-based case–control studies, and one study in airplane cockpit crew. Several of these studies found positive associations between exposure to night shift work and the risk of cancer of the prostate, particularly in association with longer durations of exposure; however, other studies reported no, or a very small, increased risk when examining ever versus never exposure to night shift work. Overall, the Working Group found that there is suggestive evidence that risk of cancer of the prostate is positively associated with night shift work; however, because of the relatively small number of studies and lack of consistent results with the same exposure metrics, chance and bias could not be ruled out with reasonable confidence.

Several cohort and case–control studies of night shift work and cancer of the colon and rectum have been conducted. The majority of the well-designed and informative studies found positive associations between exposure to night shift work and risk of cancer of the colon and rectum, particularly in association with longer durations of exposure. However, the elevated risks observed with longer durations of exposure were moderate in magnitude, and some findings were not consistent between studies. Overall, the Working Group found that there is some evidence suggesting that the risk of cancer of the colon and rectum is positively associated with exposure to shift work involving night work; however, because of the small number of studies and lack of consistency in their results, chance and bias could not be ruled out with reasonable confidence.

The Working Group determined that no conclusions could be made for any of the other cancers, because of either the small number of studies reporting results, inconsistencies in the findings, or the use of weak methods for assessing exposure to night shift work.

5.3 Cancer in experimental animals

In one article reporting on a series of well-designed lifetime studies using both male and female mice (and considered key to the evaluation of alteration in the light–dark schedule), shifts in the light–dark schedule significantly increased the incidence of hepatocellular carcinoma in wildtype and two different knockout mouse models. In one well-designed lifetime study in female mice exposed to continuous light (and considered key to the evaluation of

alteration in the light–dark schedule), significant increases in the incidence of malignant lymphoma, lung adenocarcinoma, and total tumours were observed.

Shifts in the light–dark schedule increased mammary tumour weight in one study and decreased tumour latency in another study in cancer-prone transgenic mice. A lifetime study in female rats exposed to shifts in the light–dark schedule gave negative results.

In a lifetime study in female transgenic mice prone to cancer of the mammary gland and exposed to continuous light, the multiplicity of adenocarcinoma of the mammary gland was significantly increased.

In two lifetime studies, one in male and female rats and one in female rats, the animals were exposed to natural light–dark alterations, with light durations ranging from 4 hours in winter to 24 hours (continuous light) in summer. In the study in male and female rats, significant increases in the incidence of benign mammary gland tumours and of total tumours were observed in female rats exposed to natural light–dark alterations. A significant increase in the incidence of benign tumours (mainly mammary gland tumours) was observed in the study in female rats exposed to natural light–dark alterations.

In one of two studies with limited experimental details, female mice exposed for life to continuous light demonstrated an increase in the incidence of tumours of the mammary gland. No increase was observed in the second study in another mouse strain. One lifetime study in female mice and one lifetime study in male and female rats exposed to continuous light gave negative results.

Studies have been reported in which the effects of continuous light were evaluated in rats or mice exposed to a chemical carcinogen. In most studies, tumour incidence and/or multiplicity were compared in carcinogen-treated groups exposed to either continuous light or to a normal light–dark schedule. Studies reported in nine publications were performed to investigate the effects of continuous light on the induction of mammary tumours in carcinogen-treated female rats. Exposure to continuous light increased the incidence and/or multiplicity of mammary tumours in four out of nine studies; the other five studies gave negative results, and one reported decreased incidence of mammary tumours in rats exposed to continuous light. The effects of continuous light on carcinogen-induced tumorigenesis in other organs were evaluated in a total of three studies. In a two-generation study in rats, continuous light enhanced the induction of tumours of the peripheral nervous system and of the kidney. In two studies in male rats, effects on hepatocarcinogenesis and colon carcinogenesis were less convincing; no significant differences in tumour incidence were observed in either study.

Seven of eight studies in transplantable or carcinogen-induced tumour models provide evidence that shifts in the light–dark schedule increase the rate of tumour growth in mice and rats. In a first study, shifts in the light–dark schedule significantly increased the growth rate of 3-methylcholanthrene-induced tumours in male mice. In a second study, significantly increased multiplicity of diethylnitrosamine-induced liver tumours was observed in male mice. In a third study, a significantly increased rate of syngeneic sarcoma growth was observed in male mice. In two other studies, significantly increased osteosarcoma growth rates were observed in male mice. In a sixth study, significantly increased growth rates of syngeneic lung carcinoma were observed in male mice; a significant increase in lung metastases was also observed. In a seventh study, significantly increased incidence of lung metastases of a syngeneic mammary tumour was observed in male rats.

Studies have been reported in which the effects of continuous light were evaluated in mice

or rats injected with tumour cells. In one study in mice injected subcutaneously with tumour cells, continuous light accelerated tumour progression. In two studies in male mice subcutaneously injected with human cervical adenocarcinoma cells or human prostatic carcinoma cells, and exposed to continuous light, there was a significant increase in tumour growth. In a study in immunodeficient female rats inoculated with human breast cancer cells and in a study in male rats inoculated with rat glioma cells, there were significant increases in tumour growth rate, tumour volume, and tumour weight in rats exposed to continuous light. In a study in male rats transplanted with syngeneic hepatocarcinoma and in a study in immunodeficient female rats inoculated with human breast cancer cells, significant increases in tumour growth were observed in rats exposed to continuous light. In two studies in immunodeficient female rats exposed to dim light during the dark phase and inoculated with human breast cancer cells, there were significant increases in tumour growth. In a study in male rats transplanted with syngeneic hepatocarcinoma and exposed to standard light regimen, dim light during the dark phase, or constant light, a significant positive linear relationship was observed between light intensity and tumour growth.

5.4 Mechanistic evidence

With respect to the key characteristics of carcinogens, available evidence comprised end-points relevant to whether night shift work induces oxidative stress; is immunosuppressive; induces chronic inflammation; is genotoxic; induces epigenetic effects (including on clock genes); modulates receptor-mediated effects (i.e. relevant to endocrine hormones); alters cell proliferation, cell death, and nutrient supply; and causes immortalization. Considerations included the consistency of results across studies of similar end-points and designs, and coherence across studies of similar end-points. Some studies of night shift work reported elevated levels of oxidative stress markers or decreased antioxidant capacity, while some reported null findings, and positive results were not always replicated for the same end-points across studies. Many of the available studies had limitations, including small sample sizes and insufficient descriptions of exposure. Studies in experimental systems also had mixed findings, which may be due in part to the use of different exposure scenarios and experimental end-points. Many of these studies evaluated short-term responses and relied on the measurement of outcomes at single time-points.

Several studies demonstrated an increased occurrence of self-reported infectious disease in shift workers, suggestive of immunosuppression. Results for markers of immune function and inflammation were mixed, and the studies had several limitations, including small sample sizes, lack of adjustment for potential confounding factors, and issues around timing of biospecimen collection. Multiple studies in rodents exposed to alterations in the light–dark schedule demonstrated immune suppression in nocturnal rats, mice, and hamsters, and immune enhancement in a diurnal rodent. Experimentally induced alteration in the light–dark schedule has been shown to enhance inflammation in studies in rodents and in models of inflammatory disease. Overall, these studies provide consistent and coherent evidence that alteration of the light–dark schedule modulates the immune response in experimental systems.

Studies of genotoxicity in night shift workers, including those providing positive findings, were available only for aircrew, and these studies were uninformative due to confounding by exposure to ionizing radiation. No studies were available in experimental systems. A few studies in humans and several in experimental animals showed epigenetic effects; however, they covered a narrow range of end-points and the results were inconsistent.

A number of studies evaluated the effect of night shift work on blood levels of estrogens, providing suggestive evidence. There was a set of five studies with positive results, including two large studies nested in cohorts of nurses. There were also studies with negative results, one of which was from a large and well-controlled study of nurses. In a few studies, night shift workers showed an increased risk of hypothyroidism. For hormones other than melatonin, estrogen, and thyroid, the studies were few in number and the results were inconsistent. In experimental systems, estrogen levels were evaluated in multiple species in response to alteration in the light–dark schedule, but the results were inconsistent.

No data on alterations in cell proliferation, cell death, or nutrient supply were available from studies in humans. In experimental animals, a few studies that directly measured cell proliferation showed that it increased in transplanted tumours after alterations in the light–dark schedule. Additional studies using inoculated tumour cells or exposures to carcinogens in rodents exposed to changes in the light–dark schedule showed increased tumour growth consistent with cell proliferation. One study in female nude rats showed an impact of alteration in the light–dark schedule on tumour glucose metabolism (Warburg effect in tumours).

Studies in night shift workers were mostly consistent in showing telomere shortening, but they were few in number. One study in a diurnal rodent model showed telomere shortening in response to an alteration in the light–dark schedule.

With regard to other relevant evidence, melatonin is an important regulator of circadian rhythms and a biomarker of circadian disruption in both humans and animals. There is consistent evidence that night shift work suppresses melatonin levels in humans, from multiple cross-sectional studies across different occupations. This is consistent with evidence that light at night decreases melatonin production in most of the studies in experimental animals.

Few studies in humans of night shift work and clock gene expression and methylation were identified, and results varied across the studies. This may be attributable, at least in part, to differences in study design, including genes evaluated, sample sizes, eligibility criteria, and the shift work schedules under consideration. Studies in experimental systems show that the expression of clock genes is altered in response to shifts in the light–dark schedule, and are associated with cell proliferation or tumour growth.

To summarize, the mechanistic evidence is consistent and coherent with respect to the key characteristics of carcinogens on the basis of effects consistent with immunosuppression, chronic inflammation, and cell proliferation in experimental systems. In exposed humans, there is suggestive evidence for effects on estrogen levels in female night shift workers. In humans and in experimental systems, there is robust and consistent evidence of changes in melatonin in response to alterations in the light–dark schedule.