Carcinogenicity of night shift work: Data gaps and research challenges

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Executive Summary

Night shift work has been associated with multiple cancers, including breast, prostate, and colorectal cancers. However, evaluations of the overall carcinogenicity of shift work have been inconsistent across organizations that assess hazardous exposures. Generating sufficient evidence to support a robust conclusion regarding whether night shift work causes cancer is important because approximately 1.8 million Canadian worker are exposed. The magnitude of this exposure will not likely change due to our reliance on night shift work in essential services as well as in the manufacturing and service industries.

This report evaluates the state of the research on the carcinogenicity of night shift work and identifies existing data gaps in exposure assessment, epidemiology, and mechanistic data, which make it difficult to properly assess the relationship between night shift work and cancer.

Exposure metrics across studies continue to be variable, making it difficult to compare results across studies. The metrics often lack the detail required to assess the effect of exposure duration, intensity, or specific shift schedule on cancer outcomes. Epidemiological analyses are prone to selection biases (particularly truncation bias and the healthy worker survivor effect) and confounding. They also face challenges with small case numbers and short follow up periods, which lead to inadequate study power. Finally, research into the mechanism of action has revealed the interrelated and overlapping nature of the mode of action, making it difficult to identify the responsible mechanism(s) contributing to the potentially carcinogenic effects of night shift work.

Some well-designed and large-scale studies have been conducted but continued efforts must be made to tackle these challenges. This will help ensure a thorough understanding of the potential relationship between shift work and cancer in humans. Efforts to identify the mechanism(s) of action is of particular importance, as these studies may provide the support needed to effectively assess the carcinogenicity of night shift work.

Purpose

The purpose of this report was to evaluate the current state of the research on the carcinogenicity of night shift work and to identify any existing data gaps.

Context

The carcinogenicity of shift work has been evaluated by multiple organizations, with inconsistent findings. The carcinogenicity of shift work was originally evaluated by the International Agency for Research on Cancer (IARC) in 2007. At that time, the working group

found limited evidence of carcinogenicity in humans and sufficient evidence in experimental animal models. Ultimately, they concluded that shift work involving circadian disruption was a probable human carcinogen (Group 2A) (1).

By April 2014, a large number of new and methodologically-improved epidemiological studies had been published, spurring IARC to re-assess the carcinogenicity of shift work involving circadian disruption (2). As part of the updated evaluation, the Working Group decided that the term 'night shift work' would better reflect the exposure and evidence. Despite incorporating the new and high-quality studies, night shift work remained classified as a Group 2A carcinogen (a probable human carcinogen) (3). More specifically, the Working Group concluded that there was limited evidence in humans that night shift work causes breast, prostate, and colorectal cancer (4).

In August 2018, the National Toxicology Program published a draft monograph on the carcinogenicity of night shift work and light at night (LAN). In part, the NTP selected night shift work and LAN for review due to IARC's 2007 findings that shift work involving circadian disruption is probably carcinogenic to humans. The NTP recommended that persistent night shift work (defined as frequent and long-term, starting in early adulthood) that causes circadian disruption be classified as a known human carcinogen. This conclusion was based on sufficient evidence of carcinogenicity from studies in humans and experimental animals (5).

In November 2019, researchers published a protocol to conduct a Cochrane systematic review. The review will assess the effects of night shift work on cancer risk. More specifically, the proposed study will investigate the relationship of years of night shift work and the incidence of several cancer types, such as bladder, breast, prostate, and colorectal cancers (6).

The extent to which night shift work may contribute to cancer risk is uncertain. However, even if the cancer risk is relatively low, the overall impact may be sizeable due to the sheer number of exposed workers. In Canada alone, approximately 1.8 million, or 12% of the Canadian working force, are exposed to night shift work (7). According to the Burden of Occupational Cancer study, night shift work exposure in Canada could be responsible for 470 to 1,200 new breast cancer cases each year (8). Given our reliance on night shift work (e.g. in essential services such as healthcare and public safety, as well as in manufacturing and the service sector), continued efforts must be taken to assess the carcinogenicity of night shift work.

Approach

The current state of the research on the carcinogenicity of night shift work was evaluated using the literature identified in the NTP's draft monograph (5), as IARC had yet to publish their

monograph at the time of the review. We also used NTP's literature search strategy to identify any new studies published between August 2018 and November 2019.

A review of the NTP's draft monograph and associated literature revealed challenges in three main areas of research: 1) exposure assessment, 2) epidemiology, and 3) mechanistic data. These main challenges are summarized in the sections below.

Results

Challenge #1: Exposure Assessment

IARC held a workshop in 2009 to discuss the limitations and uncertainties of the research included in the 2007 evaluation, including variable definitions of 'shift work' and poor exposure assessments. Recommendations for reducing exposure misclassification were suggested to help guide future studies. These included 1) using a clear and concise definition of 'shift work' and 2) collecting more comprehensive shift details (e.g., start/end time, length, rotating (speed and direction) or permanent, and regularity), years working a non-day shift schedule and cumulative exposure, and system intensity (e.g. time off between shifts) (9).

A clear, concise, and consistent definition of 'night shift work' has yet to be achieved. Recent publications have defined night shift work without providing the specified hours that constituted a 'night shift' (10,11). Other studies defined 'night shift' as work occurring within a specified time period, such as 24:00 to 05:00 (12). However, these specified time periods have varied widely across studies (e.g., 17:00 to 09:00 (13)) and some of these have required a minimum number of working hours between the defined start and end times to be considered exposed (14), while others have not. A minimum number of nights worked over a specified time period has also been used to delineate shift work (e.g. at least one night shift per week (15) or three night shifts per month (16)). Studies have also combined multiple types of shift workers (e.g., evening and night shift workers, as well as permanent night shift workers and rotating shift workers), which has likely led to exposure misclassification (17). Vague terms have been used to describe the timeframe (e.g., 'late evening' (18)). Importantly, poor definitions of 'night shift work' may not allow for proper characterization of night shift work that involves circadian disruption (5).

Some studies have been capturing more aspects of the shift system, but a few recent studies continue to only report ever/never worked nights as an exposure metric (15,19). Exposure metrics such as cumulative duration of night shift work and/or intensity (i.e., time off between night shifts, or the number of night shifts or hours per month [frequency]) are also commonly used. In theory, additional metrics should allow for better differentiation of more 'extensive' exposure. However, differences in how 'extensive' is defined will still exist (e.g., is it more than

10 hours per shift with at least 3 shifts per week for 10 years? (14)). It is important that 'extensive' exposure is properly defined as evidence builds for an increasing breast cancer risk related to high-intensity and long-duration night shift work (5,20).

As shift work is more of an exposure circumstance than a singular exposure, it is inherently more complex to assess exposure to shift work than other more typically addressed agents (e.g. dusts, chemicals, radiation). In an attempt to improve exposure assessment in epidemiology studies, researchers have used biological markers (e.g., melatonin, cortisol, core body temperature) to measure the extent of circadian disruption among shift workers. However, there are individual-specific and external factors that may influence their presence and susceptibility (e.g., age, sex, body mass index) (5). It is not clear how studies may account for individual and population-level differences in biological indicators. It is also expected that personal tolerance and adaptation to night shift work would have implications on the presence of biological markers. So far, there is no defined pattern of personal tolerance and adaptation based on individual variables such as age, gender, and/or chronotype (21).

Despite challenges in assessing exposure to night shift work, some studies have succeeded in effectively capturing numerous, good-quality exposure metrics. Cordina-Duverger and colleagues conducted a pooled case-control analysis of five studies from Canada, France, Germany, Australia, and Spain (14). They were able to capture the type of shift, duration of night work, average frequency of nights per week, and night shift length for all jobs held for greater than 6 months, as well as the last year that a night shift was worked. By gleaning exposure data from five case-control studies, the pooled study had sufficient power (with just under 6,100 breast cancer cases), to detect statistically significant increases in cancer risk among premenopausal women, with the strongest associations among high-intensity, long duration night shift workers. Due to a detailed exposure assessment, Cordina-Duverger et al. were able to find the specific circumstances under which individuals may be at increased risk of breast cancer (14). Their work highlighted the importance of collecting a variety of detailed exposure metrics in order to help ascertain when cancer risk may be highest.

Challenge #2: Epidemiology

Variable study quality has impeded the ability to compare results across studies and to detect potential associations between night shift work and specific cancers. Of particular concern is the potential for selection bias, specifically left- and right-truncation bias and the healthy worker survivor effect. Left truncation occurs when an event of interest (e.g. a period of increased risk, or a developmental milestone) among study subjects has already occurred prior to the study initiation (22). Left truncation can be an issue when studying the association between a specific exposure and cancer if cancer risk wanes over time once the exposure ceases (for example, as with lung cancer risk from smoking) (23). If the study selects

participants who have already past the period of highest risk, the risk estimates will be biased towards the null. There is increasing evidence that the risk of breast cancer due to night shift work is highest in the years immediately following the cessation of night shift work, with cancer risk decreasing over time (11,12,14,24). However, many of the cohorts comprise older women who may not have worked night shifts in the recent past and/or do not collect information on recency or timing of exposure (11,18,19,25,26), making it difficult to accurately assess the impact of night shift work on cancer. Care must also be taken to avoid right-truncation, in which the milestone of interest has not yet passed. Right-truncation can occur if the cohort includes young workers who may not have experienced adequate durations of exposure to be at risk of cancer (e.g. (27)).

Older cohorts are also susceptible to the healthy worker survivor effect, which is the continuous selection process in which workers who are healthiest tend to remain employed (28). In this selection process, workers who are better able to adapt to night work are more likely to remain within the jobs that require shift work, while those who experience negative health outcomes and/or are unable to adapt may leave (i.e. to other jobs or to day shifts) (5). As a result, workers who remain within the occupation experience the longest durations of exposure. Similar to left truncation bias, the healthy worker survivor effect will bias the results towards the null. Potential for this bias exists in studies of breast cancer (e.g. the healthy worker survivor effect was noted as a possibility in approximately a third of the breast cancer studies reviewed in the NTP review (5)) as well as in studies of prostate cancer (10,29,30). Because of the potential for recency effects, the increased likelihood of younger workers doing night shift work, as well as the healthy worker survivor effect, further care must be taken to ensure that the appropriate at-risk group is captured.

In addition to selection biases, study quality has been impacted by small studies, inadequate follow-up, and outcome misclassification. Large numbers of cancer cases are required to obtain sufficient statistical power to detect an effect, particularly if the risk estimates are lower, as expected with shift work and cancer. However, many of the studies have relatively few cases and this is a particular among groups with the highest exposure (e.g. level, duration, or frequency), which is where the greatest effects would be expected (10,12,31–33,16,17,24–27,29,30). Some studies had short follow-up times (mean follow up less than 10 years) (10,18,19,24,25,32) or inadequate exposure periods (some studies assessed exposure only over specific timeframes, and not over individuals' lifetimes (31,34), impacting the ability to detect cases or for cancer to occur. Other studies have assessed the impact of night shift work on cancer mortality (26,35). However, mortality is not an accurate indicator of incidence for cancers with high rates of survival because it underestimates the total number of cases and likely oversamples those with more severe disease. Finally, a major consideration in study quality is how confounding is managed. Workers who engage in night shift work tend to differ

in key ways from day workers. Shift workers are more likely to smoke, be obese, and have lower aerobic capacity compared to day workers, despite having less sedentary time (36,37). Even within night shift workers, differences between occupation groups exist. For example – nurses can be exposed to a number of carcinogenic substances, including formaldehyde, ethylene oxide, radiation, and antineoplastic agents (38). However, studies of nurses, who present the strongest evidence of an association with breast cancer, as well as other worker based studies have often not adequately accounted for co-exposures (e.g. (11,27)). Furthermore, while some epidemiological studies may not have considered all known confounding variables (12,27,34,39–41), which can obscure the relationship between night shift work and cancer, others have unnecessarily included variables that are unrelated to the exposure or are in the causal pathway in the models, which can bias estimates towards the null (11,24,26,42).

Tackling these epidemiological challenges will help studies better ascertain whether an association between night shift work and cancer exists. An example of a particularly well conducted study is the Nurses' Health Study (NHS) (11). The NHS is a prospective cohort of nurses in the United States looking at the association between night shift work and incident breast cancer. It comprised two cohorts - one of women aged between 42 and 67 (NHS1, n=78,516), and the other aged between 24-42 (NHS2, n=114,559). The exposure assessment assessed ever/never exposure to rotating work shifts, as well as the total number of years working rotating shifts for more than 3 nights per month. The wide age range could help to account for truncation bias and healthy worker survivor effects, and the collection of information on life-long exposure was used to assess changes in cancer risk over time. The follow up period was long (24 years), and the study captured a large number of exposed subjects and cases (NHS1, n=5,971; NHS2, n=3,570), ensuring the study had adequate power to detect an association.

Challenge #3: Mechanistic Data

Many biological mechanisms have been proposed to explain how night shift work could increase the risk of cancer. The two main overarching mechanisms are the melatonin hypothesis and the circadian disruption theory (5). These proposed mechanisms are complex and both link shift work, LAN, circadian disruption, and cancer. A brief overview of the mounting research effectively demonstrates the complexity of the mechanistic data.

The melatonin hypothesis focuses on the suppression of melatonin by LAN exposure. Significant LAN exposure may alter the amount of melatonin produced by the pineal gland and the timing of production (known as a "phase-shift"). The suppression of melatonin by LAN is important due to melatonin's ability to impact tumour growth. Melatonin is a well-studied, multi-faceted molecule that influences many functions in most organs. Melatonin's effects have been well

studied in in-vitro and in-vivo models. Melatonin can decrease adverse effects from estrogens (important for hormone-dependent mammary tumours), support the immune system, regulate the cell cycle, and protect against angiogenesis and metastasis. This list is not exhaustive and many other effects of melatonin are described in the literature (5,43–51).

The circadian disruption theory is an extension of the melatonin hypothesis. The circadian disruption theory identifies other pathways through which LAN may impact circadian rhythms, aside from melatonin (5,52). Many studies (e.g., (53–57)) have demonstrated the importance of the undisturbed circadian clock in tumour suppression (5). Evidence suggests that the oscillations of the circadian rhythm are linked to the oscillations of the cell cycle, and a rhythmic disruption may interrupt regulation of the cell cycle, cell proliferation, apoptosis, and DNA damage response. The mechanisms by which the circadian clock controls cell regulation are not fully understood; however, these changes are considered to be prominent hallmarks of carcinogenesis (5,58).

Other factors may also contribute to circadian disruption, such as reduced sunlight exposure, vitamin D deficiency, sleep deprivation, and meal timing (59–63). The influence of these factors on circadian disruption are important considerations as shift workers experience these factors differently than non-shift workers.

It has also been demonstrated that associations between night shift work and LAN exposure and various cancer-relevant biological effects exist. These biological effects are associated with other known human carcinogens and/or important events connected to carcinogenesis. These biological effects include: DNA repair and genomic instability, oxidative stress, epigenetic effects, chronic inflammation and immunosuppression, metabolic alterations, and sex hormones (5).

In summary, since the melatonin hypothesis was first suggested (64,65) there has been a substantial amount of research into the mechanism(s) responsible for the carcinogenicity of night shift work. The mechanistic data is a web of overlapping and interrelated evidence; and so far, scientists have been unable to disentangle the responsible mechanism(s) behind the carcinogenicity of night shift work. In order to pin-point the mechanism(s) responsible within all the possibilities, a complete exploration and understanding will likely be required. Perhaps the greatest mechanistic data gap relates to the mechanisms underlying circadian control of the cell cycle, specifically in the event of circadian disruption. In summary, further exploring the mechanistic data is key to determining whether a causal relationship between night shift work and cancer exists.

Conclusion

Continued efforts must be taken to ensure a thorough understanding of the potential relationship between shift work and cancer in humans. Night shift work is a highly prevalent schedule for workers around the world, and a certain extent of it will always be required. Since the IARC 2007 evaluation, researchers have continued to struggle with mixed findings. Despite the numerous recommendations for reducing exposure misclassification in future studies that stemmed from the IARC workshop in 2009 (9), studies continue to lack the specificity required to effectively compare and combine results across studies. Variability in the exposure metrics collected persist, with the potential for exposure misclassification and attenuation of study results. Epidemiological studies are rifled with challenges, including selection bias (truncation bias and healthy worker survivor effect), small case numbers, inadequate follow up, and confounding. These epidemiologic challenges are compounded by the mechanisms of action, which are complex, overlapping, and still being explored. While the challenges may seem insurmountable, however, some well-designed, large-scale epidemiology studies have been conducted, as evidenced in the NHS cohort and Cordina-Duverger pooled case-control studies. These studies show promise that epidemiological studies may be able to generate sufficient evidence to support a conclusion regarding the carcinogenicity of night shift work. Even so, given that the relative risk of cancer is likely relatively low, efforts to explore the mechanism of action must continue, as the mechanistic findings may support and, ultimately, drive the investigation.

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