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CLINICAL REVIEW

# Shift work and cancer risk: Potential mechanistic roles of circadian disruption, light at night, and sleep deprivation

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SUMMARY

Shift work that includes a nighttime rotation has become an unavoidable attribute of today's 24-h society. The related disruption of the human circadian time organization leads in the short-term to an array of jet-lag-like symptoms, and in the long-run it may contribute to weight gain/obesity, metabolic syndrome/type II diabetes, and cardiovascular disease. Epidemiologic studies also suggest increased cancer risk, especially for breast cancer, in night and rotating female shift workers. If confirmed in more controlled and detailed studies, the carcinogenic effect of night and shift work will constitute additional serious medical, economic, and social problems for a substantial proportion of the working population. Here, we examine the possible multiple and interconnected cancer-promoting mechanisms as a consequence of shift work, i.e., repeated disruption of the circadian system, pineal hormone melatonin suppression by exposure to light at night, sleep-deprivation-caused impairment of the immune system, plus metabolic changes favoring obesity and generation of proinflammatory reactive oxygen species.


## Introduction

Invention of the light bulb by Edison in 1879 and subsequent development of electric generating and distribution systems significantly changed the lifestyle of human beings through extension of activity into the night, thereby making prevalent night work (NW), involving today some 15–20% of the workforce of industrialized countries. In fact, surveys indicate only ~25% of the workforce is employed in "regular" daytime (±08:00 to ±17:00 h) Monday to Friday schedules.[1] The nocturnal activities demanded by shift work (SW) schedules disrupt the natural sleep-wake cycle and circadian time organization; expose workers to artificial light at night (LAN), an abnormal biological time of light exposure; cause irregular eating patterns; and alter social and family life routines.[2] Apart from performance decrements and elevated vulnerability to accidents, NW and SW are associated with increased risk for various long-term health effects, ranging from sleep disorders to metabolic conditions and cardiovascular disease (CVD), among others.[3–5]

Of particular concern are the findings during the past decade of several epidemiologic studies revealing slightly to moderately increased risk for breast, prostate, colon, and endometrial epithelial malignancies plus non-Hodgkin's lymphoma in long-time NWers (night workers) and SWers (shift workers).[6–8] These suggestive, but not yet conclusive, epidemiologic findings are bolstered by extensive laboratory animal research. i) Laboratory animal studies simulating rotating SW schedules and transmeridian flights that cause repeated disruption of the circadian time organization favor development of breast cancer in female animals and also accelerated growth of transplanted non-endocrine tumors.[9,10] ii) Experimental manipulations – pinealectomy[11,12] or bright light during the subjective night[13] – that suppress the pineal hormone melatonin (MEL) promote the development and growth of malignancies, while experimental manipulations that elevate MEL – by its administration at certain circadian times, exposure to prolonged dark spans,[14] blinding,[12] and up-regulation of melatonin receptor type 1 (MT1)[15] – favor decrease in breast cancer rate and growth of transplanted tumors in animal models, which is consistent with the observation of decreased breast cancer rate in blind women.[16] Against this background of laboratory animal and human epidemiologic findings, in October 2007 the World Health Organization International Agency for Research on Cancer (IARC) convened in Lyon, France a working group of 24 scientists to critically address the concern of the potential association between shift work and cancer risk. The conclusions of the working group summarized in Monograph 98[8] were: i) evidence is limited in humans for the

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**Abbreviations List**

| | |
|---|---|
| 13-HODE | 13-hydroxyoctadecadienoic acid |
| aMT6s | 6-sulphatoxymelatonin |
| *ATM* | ataxia teleangiectasia mutated |
| Bmal1 | brain and muscle aryl hydrocarbon receptor nuclear translocator [ARNT]-like |
| BMI | body mass index |
| BRAC1 | breast cancer1, early onset human caretaker gene |
| $CD8^+$ | cytotoxic and memory T-cells |
| CDC2 kinase | cell division cycle 2 kinase |
| CLOCK | circadian locomotor output cycles kaput |
| c-Myc | myelocytomatosis viral oncogene human recombinant |
| CpG | cytosine bound by phosphodiester bond to guanine |
| CRP | C-reactive protein |
| Cry | cryptochrome genes |
| CVD | cardiovascular disease |
| D | dark |
| DNA | deoxyribonucleic acid |
| DW | day work |
| DWers | day workers |
| E2 | estradiol |
| ERα | estrogen receptor α |
| ERλ | estrogen receptor λ |
| ESR1 | ERα encoding gene |
| G0/G1 | transition from resting phase to phase G1 of the cell cycle |
| G1/S | transition from G1 to DNA synthesis of the cell cycle |
| G2/M | transition from G2 phase of mitotic cycle to mitosis |
| Gadd 45α | growth arrest and DNA damage-inducible, alpha protein |
| h/d | hours/day |
| HER2/neu | human epidermal growth factor receptor 2 |
| hPER2 | human period 2 clock gene |
| IARC | International Agency for Research on Cancer |
| IFNγ | interferon-gamma |
| IL | interleukin |
| L | light |
| LAK | lymphokine activated killer cell |
| LAN | light at night |
| LD | light-dark |
| MCF-7 | Michigan Cancer Foundation − 7 |
| Mdm2 | murine double minute oncogene |
| MEL | melatonin |
| min/d | minutes/day |
| $mPER2^{m/m}$ | Per2 mutation |
| MT1 | melatonin receptor type 1 |
| MT2 | melatonin receptor type 2 |
| MTCL | murine breast cancer-derived cell line |
| NF-kB | nuclear factor kappa-light-chain-enhancer of activated B cells |
| NK | natural killer cell |
| NSs | night shifts |
| NW | night work |
| NWers | night workers |
| p53 | protein 53 or tumor protein 53 |
| Per | period genes |
| RASSF1A | Ras association domain-containing protein 1 |
| Rev-erbα | nuclear receptor subfamily 1, group D, member 1 |
| RNA | ribonucleic acid |
| RORα | retinoid-related orphan receptor, alpha |
| SCN | suprachiasmatic nucleus |
| SEEM | selective estrogen enzyme modulator |
| SERM | selective estrogen-receptor modulator |
| sICAM | soluble intercellular adhesions molecule |
| siRNA | small interfering RNA |
| SW | shift work |
| SWers | shift workers |
| Th1 | T-helper1 cells and proinflammatory Type 1 |
| Th2 | T-helper2 cells and anti-inflammatory Type 2 |
| TNFα | tumor necrosis factor alpha |
| Wee1 | nuclear kinase belonging to the Ser/Thr family of protein kinases |

carcinogenicity of SW that involves NW; ii) there is sufficient experimental evidence in laboratory animals for the carcinogenicity of LAN; and iii) SW that involves circadian disruption is probably carcinogenic in humans (as a group 2A carcinogen).

The potential mechanism of SW-associated cancers is complicated, involving many biological processes and systems, among others, sleep disruption, LAN, circadian disruption, and lifestyle factors. The purpose of this article is to review and integrate the relevant findings of several different biological disciplines − chronobiology, sleep medicine, immunology, endocrinology, nutrition/biochemistry, and molecular biology − relative to the possible mechanisms underlying increased cancer risk, particularly breast cancer, of female SWers.

## Circadian timekeeping

An understanding of the mechanisms of biological timekeeping is necessary to discuss the disrupting and detrimental effects of NW and rotating SW. Circadian (~24-h) rhythms are orchestrated by cellular oscillators found in most, if not all, nucleated cells of the body that regulate practically every biological process and function in a time-specific manner via various clock-controlled genes.[17–19] In mammals, in which the expression of 2–10% of all genes is circadian rhythmic,[20] the circadian system is organized in a hierarchical manner: a master oscillator, the paired suprachiasmatic nucleus (SCN) of the hypothalamus, regulates downstream peripheral oscillators via humoral, endocrine, and neural signals, resulting in a coherent time organization of bodily processes for optimal performance.[17,18,21] The central oscillator is paced, i.e., externally synchronized, with the periodic-astronomic surrounding mainly by time cues provided by the environmental light (L)–dark (D) cycle, conveyed through non-visual, photic retinal ganglion cells[22] most sensitive to the blue-violet (446–484 nm) spectrum. The predictable-in-time alteration of environmental L and D every 24 h provides circadian time information, and the duration of the daily L relative to the D span over the course of the year conveys circannual (seasonal) time information. Some peripheral oscillators, in addition, are responsive to non-photic synchronizers, e.g., time pattern of food uptake, which under certain circumstances may become dominant.[23]

Clock mechanisms in the SCN and peripheral organs are similar at the molecular level. Circadian oscillators consist of a network of transcriptional-translational feedback loops that drive ~24-h rhythmic expression patterns of the core clock components.[17,18] In the primary feedback loop, the driving elements are the transcription factors CLOCK (circadian locomotor output cycles kaput) and Bmal1 (brain and muscle aryl hydrocarbon receptor nuclear translocator [ARNT]-like), which heterodimerize and initiate