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Shift work and cancer – considerations on rationale, mechanisms, and epidemiology

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This paper summarizes the rationale for, possible mechanisms of, and problems related to risk assessment of the association between shift work and cancer. The mechanisms by which circadian disruption may favor the induction and/or promotion of malignant tumors are complex and multifactorial. The multilevel endocrine changes caused by circadian disruption with melatonin suppression through light at night (LAN) lead to the oncogenic targeting of the endocrine-responsive breast in women and possibly the prostate in men. Repeated phase shifting with internal desynchronization may lead to defects in the regulation of the circadian cell cycle, thus favoring uncontrolled growth. Sleep deprivation leads to the suppression of immune surveillance that may permit the establishment and/or growth of malignant clones. The epidemiological studies published so far, although dealing with large cohorts and controlling for several personal confounders, have defined the exposure to shift and/or night work rather loosely and consequently do not allow for the proper assessment of the risk connected with circadian disruption.

Key terms breast cancer; circadian rhythm disruption; light at night; LAN; melatonin; night work; occupational exposure; prostate cancer; risk assessment; sleep deprivation.

Shift work is the organization of working time by different teams in succession to cover more than the usual 8-hour day, up to and including the whole 24-hour period. Its prevalence is increasing in today's 24-hour society enabling round-the-clock activities, not only in relation to technological requirements and necessary social services, but also in order to support productive and economic choices in industry as well as commerce and leisure.

According to the data collected in the third EU Survey on Working Conditions in 2000, 76% of the working population (73% of employed and 92% of self-employed workers) are engaged in working hours other than normal daytime work, (ie, shift and night work, compressed week, Saturday and/or Sunday work, irregular or flexible working hours, split shifts) (1). The fourth EU survey (2005) revealed quite large differences among countries as concerns weekly working hours and evening and night work. Evening work ranged from 36–58% and night work from 18–24% on average. In general, 21.9% of men and 10.7% of women work on shifts that include night work. Seven percent (7%) of shift workers work permanently at night (2). In the United States, according to the Bureau of Labor Statistics, in 2004 almost 15% of full-time salaried workers usually worked on shifts that included nights (16.7% of men and 12.4% of women); African Americans were more likely to do so than Caucasians, Hispanics/Latinos, or Asians; but shift work decreases progressively with age (3).

Most studies and reports carried out in the last decades refer to shift work that includes night work as the most disruptive of the biological homeostasis and a relevant risk factor for workers' health as it causes a mismatch between the endogenous circadian timing system and the environmental synchronizers (the light–dark cycle in particular), with consequent disturbances of the normal circadian rhythms of psychophysiological functions, beginning with the sleep–wake rhythm. Besides the short-term effects that can be summarized as a form of "jet-lag" syndrome (including sleeping and digestive troubles, sleepiness and weakness, poorer mental agility, and reduced performance efficiency), the long-term effects most often reported deal with chronic sleep, gastrointestinal, neuropsychic, and cardiovascular disorders, as well as negative interference with pregnancy (4–7).

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In recent years, several studies have been published that show an increased incidence or prevalence of cancer, in particular breast cancer, among shift workers. The epidemiologic evidence of a relationship between shift work and breast cancer among women is based on nine studies (8–16), six of which suggest a moderately increased risk of developing breast cancer after prolonged exposure to shift work. More limited observations are available in other studies, some of which posed a warning also for cancers of the prostate (15, 17, 18) and colon-rectum (8, 15, 19), endometrium cancers (20), and non-Hodgkin's lymphoma (21) (see table 1).

In 2007, the International Agency on Research on Cancer (IARC) established an ad-hoc working group that classified "shift work that involves circadian disruption" as "probably carcinogenic to humans" (Group 2A) on the basis of "limited evidence in humans for the carcinogenicity of shift work that involves night work", and "sufficient evidence in experimental animals for the carcinogenicity of light during the daily dark period (biological night)" (22).

According to the IARC evaluation method, the "limited evidence of carcinogenicity in humans" means that "a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias, or confounding could not be ruled out with reasonable confidence". Such an assessment with its possible implications, both at medical and socioeconomic levels, instigated a large debate in the scientific and social communities, with different and somewhat contrasting positions about the validity of some studies and reliability of related outcomes.

This paper aims to enable a better understanding of this important issue by highlighting the rationale for risk assessment, the possible mechanisms involved, and open questions that need prompt and appropriate responses from a biological as well as organizational point of view.

Light at night as a cancer risk factor

The first suggestion that the globally increasing use of electric lighting at night (LAN) might contribute to the breast cancer pandemic was made in 1987 (23). Since then, an increasing number of researchers have conducted studies of various predictions of the theory. The biological rationale was originally based on the nocturnal suppression of melatonin that might lead to a putative elevation of estrogen (24), a known cause of breast cancer (25). As the science on the molecular genesis of circadian rhythms has advanced rapidly in recent years, a variety of other mechanisms have been suggested (26, 27). These are discussed elsewhere in this paper. This section provides a brief overview of the epidemiological studies done to date.

The high and increasing risk of breast cancer in the industrialized world over the past half century has presented a profound mystery. The rise or fall of most other major cancers have readily apparent explanations: smoking and lung cancer, hepatitis viruses and liver cancer, and *Helicobacter pylori* and stomach cancer. For breast cancer, reproductive factors and gender hormone levels are well-established risk factors, and recent reductions in the use of hormone replacement therapy have had a rapid impact on risk among post-menopausal women (28). However, the known risk factors, including the reproductive ones, cannot explain the bulk of breast cancer cases (29, 30). The only dietary factor that has shown a reproducible association with breast cancer risk is alcohol consumption (31). It may turn out that a multitude of risk factors playing small individual roles are working together to have a cumulatively large impact or a major factor has so far been entirely overlooked.

It is easy to speculate about electric lighting and breast cancer as the prevalence of both has increased together in the modern world. But every other feature of modernization has also increased contemporaneously with breast cancer incidence. To take the large idea and derive testable hypotheses requires predictions to be made on the basis of the theory. Evidence in support of any one of the predictions could easily have alternative explanations. However taken together, evidence in support of a wide variety of predictions that apparently have only one common thread – electric light – could at some point constitute proof of a causal relation. The predictions that have been made, and for which at least some evidence exists, are: (i) non-day shift work would increase risk; (ii) blind women would be at lower risk; (iii) long sleep duration would lower risk; (iv) higher ambient nighttime bedroom light level would increase risk; and (v) community nocturnal light level as measured by satellite would codistribute with breast cancer incidence. Not one of these studies, or even category of studies can "prove" that LAN increases the risk of breast cancer. For each prediction, the exposure metrics are crude and confounding is possible. For example, some blind persons can perceive LAN for their circadian system, sleep duration is a very crude metric and timing of sleep may also be important, and community-light level at night may or may not be meaningful for individuals. However, each of these considerations would lead to exposure misclassification and tend to reduce the ability of epidemiological studies to detect the true impact of LAN should it exist. Given the disparate nature of these predictions, the consistency of observations so far supports the LAN theory.

The strongest evidence base exists for a higher risk among women with a history of working non-day shifts.

Tokumaru and colleagues (32) conducted a meta-analysis of studies of flight attendants who had elevated breast cancer risk. These studies were not originally done as tests of the shift work prediction. They were motivated by the possibility that cosmic radiation was the problem. However, flight attendants also work non-day shifts, in addition to travelling across times zones and experiencing jet lag, all of which could disrupt circadian rhythms. Later, a series of studies designed specifically to test the shift work prediction mostly supported an association (8–12, 14); however, two studies did not – one was a case–control study (13) and the other was very weak due to a debilitating level of exposure misclassification (15). The IARC used this evidence, both from the studies of flight attendants and non-day shift workers, in its evaluation of shift work as a probable human carcinogen, 2A (7). Kolstad (33) later reviewed these studies.

The other predictions so far articulated have more limited evidence. Blind women have been reported to be at lower risk in several studies (34–38), but the numbers of cases have been small in some of these studies. Long sleep duration has been associated with lower risk in three (39–41) out of four (42) prospective studies. High nighttime light in the bedroom is very difficult to study in real-world epidemiological studies. In case–control studies, the potential for recall bias is large, but two such studies reported an association with two different methods for estimating LAN in the bedroom (9, 13). Finally, one study examined the codistribution of light level at night and breast cancer incidence in 147 communities in Israel (43). After adjustment for a few population-level variables that may act as confounders (ie, per capita income, birth rate), the incidence in the town with the highest LAN level was 73% higher than that of the town with the lowest level.

The epidemiological predictions and evidence described above, coupled with the very fast-moving basic biology on the functioning of the circadian system offers a compelling argument to accelerate the pace that new evidence on breast cancer is generated. For unknown reasons, breast cancer incidence and mortality both increase dramatically as societies industrialize. If electric LAN plays a role, then specific intervention and mitigation strategies can be developed and deployed.

Circadian disruption and cancerogenesis – mechanistic considerations

Circadian rhythms in cell and organ physiology are driven and controlled by an autoregulatory transcription–translation feedback loop that regulates the expression of rhythmic (clock) and clock-related genes, which are present in virtually all metabolizing nucleated cells of the body in a time-specific manner (44–46). In the mammalian organism, the circadian system is organized in a hierarchical way so that a master oscillator in the suprachiasmatic nuclei (SCN) in the hypothalamus regulates the downstream peripheral oscillators via humoral, endocrine, and neural signals (47–49) into a coherent time organization favoring optimal function (38, 50, 51). The central pacemaker is kept in step with our periodic-astronomic surrounding by non-vision-related photic stimuli from retinal ganglion cells (52, 53) with high sensitivity to light as shown by the suppression of melatonin (54, 55), and by initiating circadian phase shift (56). An abrupt shift in synchronizer phase, as experienced in shift work with several hours change in working time, is followed by a gradual phase adaptation over several transient cycles with transient uncoupling of the molecular events within the oscillators with intra-oscillator desynchronization.

The central oscillator in the SCN shifts faster than the oscillators in peripheral tissues and organs with transient uncoupling of the peripheral oscillators from the central oscillator (the circadian pacemaker) in the SCN, leading to internal desynchronization of circadian periodic physiologic variables within the body. The duration of this time of internal desynchronization differs from variable to variable (57, 58). The phase shift of the central and peripheral oscillators in human subjects is faster after a phase-delay than a phase-advance, which is of importance for the design of shift work rotas (50, 59–63). A circadian phase shift is a complex phenomenon that affects all metabolizing and proliferating cells in the human body and, depending upon the extent of the shift, requires time (days) for complete adjustment, which limits the possibility of a rapid adaptation to changes in shift.

In the mammalian time structure, the circadian rhythms are superimposed upon infradian rhythms of lower frequency, some of which apparently also represent endogenous oscillations and may in their interaction alter the impact of schedule changes upon the organism. The infradian rhythms to be considered are of about 3–4 day period lengths (circasemiseptan), 1 week (circaseptan), and the “menstrual” frequency range (20–30 days). Also seasonal variations or circannual rhythms (if endogenous in nature) alter the process of circadian phase adaptation. Among shift workers studied under comparable conditions during different seasons, the pattern of phase adaptation may be markedly different (64).

Circadian clock and cell cycle

Circadian clock genes regulate cell proliferation and apoptosis at multiple sites and by a number of different mechanisms. Defects in some core clock genes are associated with the risk of developing certain forms of malignancies. Structural variations in clock genes Period homolog 3 (Per3) and non-synonymous polymorphisms in the circadian gene NPAS2 (neuronal PAS domain protein 2) are associated with an increased risk of developing breast cancer, especially among younger women (65, 66). Single nucleotide polymorphisms in several core circadian genes are associated with the risk of developing prostate cancer among men (67). Cryptochrome (Cry) 2 is a core circadian gene and transcriptional repressor. Three single nucleotide polymorphisms of Cry 2 were significantly associated with the risk of developing non-Hodgkin's lymphoma (68). In contrast, some polymorphisms in NPAS2 appeared to be protective against the disease (69).

Circadian clock genes control numerous cell-cycle-related genes, cell-cycle check points and tumor-suppressor genes, which mediate DNA damage response and modulate transcription factors such as Cyclin B1, Cdc2 kinase and cell division (70–72). Clock-controlled genes include the tumor-suppressor genes c-Myc, tumor protein 53 (p53), Mdm2, and Gadd45α and genes that encode caspases, cyclins, and numerous other transcription factors (70, 73, 74). In human-proliferating tissues, such as skin and oral mucosa, circadian clock gene expression was found to be associated with the timing of cell-cycle phases (75). In animal models, Per1 has a tumor suppressor function that, however, is exerted only at certain circadian stages. Down-regulation of Per1 leads to augmented tumor growth through an increase in the amplitude of the circadian peaks in tumor cell proliferation (76).

The CLOCK-BMAL1 arm of the circadian oscillator directly regulates the cell-cycle genes Wee1 involved in G2/M transitions (71), c-Myc involved in GO/G1 transitions, and cyclin D1 involved in G1/S transitions (77). Wee1 transcription is activated by the CLOCK-BMAL1 heterodimer and suppressed by Per/Cry proteins (71). Cyclin D1, which is expressed under circadian clock control, associates with estrogen receptor alpha (ERα), enhances its activity, and antagonizes the mediated suppression of ERα of the breast cancer suppressor gene BRACA1 (breast cancer 1). Over-expression of Cyclin D1 induces mammary tumorigenesis in mice and is associated with a poor prognosis for human breast cancers (77, 78).

Per2 acts as a tumor-repressor gene in breast cancer (77, 79). Per2 is endogenously expressed in human breast epithelial cells but is reduced or absent in human breast cancer cell lines. The expression of Per2 significantly inhibits the growth of MCF-7 human breast cancer cells, an effect which was further increased when Per2 was co-expressed with cytochrome (79). Per2 links the circadian oscillator system to the function of ERα in endocrine-responsive mammary cells. The Per2 gene in mammary cells induces estradiol. Per2 expression reduces the ERα response to estradiol, while Per2 inhibition by siRNA (small interfering ribonucleic acid) enhances estradiol activation of ERα target genes (80).

Per2-deficient mice show a deregulation of cell proliferation and the tumor suppressor genes c-Myc, Cyclin D1, Cyclin A, Mdm2, and Gadd45α (77). Per2 gene dysfunction activates the c-Myc signaling pathway, and impairs p53-mediated apoptosis leading to genomic instability and cell proliferation, with an accumulation of damaged cells serving as a source for tumor development (72). When examining Per2 knockout mice, Fu et al (77) observed a neoplastic growth phenotype with increased sensitivity to gamma (γ) radiation favoring tumor development. Down-regulation of Per2 by RNA interference leads to an accelerated growth of a murine breast cancer-derived cell line (MTCL) in vitro and accelerated MTCL tumor growth in vivo with a doubling of the daily amplitude of the tumor growth rhythm (81).

Apart from the endocrine-responsive mammary cell lines and tumors, among adenoma-prone mice, Per2 mutations also favor the development of colonic adenomas (a precursor of human colon cancer) and deregulation of Per2 increased the cell proliferation in human colonic cell cancer cell lines (82).

Endocrine target tissues, like the breast and prostate, appear to be especially prone to tumor development after circadian disruption from LAN (the subjective dark span), a process in which the suppression of melatonin may play an important role (12, 14, 17). But also non-endocrine transplantable or carcinogen-induced tumors in rodents were found to exhibit accelerated development after a carcinogenic stimulus (83) and/or accelerated growth after repeated phase shift (84) or SCN alteration (85) suggesting circadian cell-cycle-related mechanisms of carcinogenesis and/or promotion.

Melatonin suppression by light at night

Cellular melatonin receptors are widely distributed and found in most tissues of the human body (86). In addition, melatonin can enter cells and function as reactive oxygen and a nitrogen scavenger independently of receptors (87).

Melatonin may act on initiation, promotion, and progression of tumors. In endocrine-dependent tumors, melatonin effects on hypothalamic centers may be of importance. A decrease in melatonin production favors an upregulation of the gonadal axis – as seen among female shift workers who had an increase in circulating estrogen after prolonged exposure to shift work (88). Prolonged exposure and/or increased cellular response to estrogens during a woman's lifetime is an important risk factor for breast cancer (89, 90).

At the cellular level, melatonin may protect cells from DNA damage by carcinogenic agents through its ability to act as a free radical scavenger directly or indirectly via activation of the glutathione or related antioxidative pathways. In addition to protecting DNA by suppressing the formation and accumulation of altered DNA, melatonin may also help to promote DNA repair (15, 91–93).

Melatonin acts as a response modifier to estrogens especially estradiol. Melatonin exerts an anti-estrogenic effect via interaction with ERα (94–95) and counteracts the effects of estradiol on breast cancer cell proliferation, invasiveness, and telomerase activity (96–100). Melatonin down-regulates both the expression of protein growth factors and proto-oncogens stimulated by estrogen (101, 102) and the epidermal growth factor receptor 2 (HER2/neu), the expression of which is associated with increased malignancy in some forms of human breast cancer (103). Melatonin modulates local estrogen biosynthesis (which is of special importance in post-menopausal breast cancer) by reducing aromatase expression and activity (104, 105). It inhibits telomerase activity (98–100) and the transcription of Cyclin D1 expression. Cyclin D1 over-expression is associated with tumorigenesis and metastases formation. Melatonin exerts oncostatic action by regulating the uptake and metabolism of linoleic acid, which is a promoter of both human and murine mammary tumorigenesis via multiple pathways (91–93). Blask et al (106) provided an example of the direct effect of melatonin on human breast cancer xenografts in nude rats. These grafts were connected with the host by one artery and one vein. Perfusion of the grafts with melatonin-depleted blood from women exposed to LAN stimulated the tumor growth in comparison to blood with the physiologic nighttime level of melatonin, which had an inhibitory effect.

Sleep deprivation and the promotion of cancer

Night and shift workers on early-morning shift sleep 2–4 hours/day less than their daytime counterparts (107–109). Sleep deprivation and accumulation of a sleep deficit have a marked impact on the worker that may have a bearing on the moderately increased cancer rate reported among shift workers. Already a modest amount of sleep loss even during a single night leads to genomic effects along multiple pathways with a wide spectrum of potential pathology and alterations in immune reactivity. Numerous endocrine rhythms are altered by sleep deprivation. If there is light exposure during the night, as is the case during night work, melatonin suppression will occur and exert effects on numerous peripheral circadian rhythms. During the normal "quiet-period" of the pituitary-adrenal axis in the late afternoon and evening, cortisol concentrations tend to be increased, the evening rise of growth hormone among men is suppressed while, among women (who do not show this single peak), growth hormone values drop in a less conspicuous fashion. The nocturnal surge in prolactin is decreased. Insulin shows an increased acute response to glucose challenge and insulin resistance develops (110–112). There is a decrease in the nocturnal level of leptin (at the circadian peak time) that may be related to the obesity reported after prolonged night and shift work (113, 114). Plasma norepinephrine is elevated during sleep deprivation and the sympathovagal balance is altered (112, 113). Genetic variants of the human CLOCK gene have been associated with increased energy intake (115); Englund et al (116) have found variants of Per2 and NPAS2 to be associated with high-fasting blood glucose and hypertension, respectively, suggesting circadian clock-related mechanisms in the development of the metabolic syndrome, the incidence of which has been found to be increased among shift workers (117).

Sleep deprivation alters the function of the immune system, which in part may be a consequence of the depression of melatonin and prolactin. Immune-competent cells in animals and human subjects express membrane (MT1) and nuclear (RZR/ROR) melatonin receptors that allow a direct melatonin action on the immune system (86, 118, 119). A reduction in endogenous melatonin production by pinealectomy (120, 121) or functional depression by light (122) during the subjective night (dark span) leads to immune suppression that may favor the establishment and growth of abnormal cell clones (118, 119). These defects in immune function could be reversed by the administration of melatonin. The immune suppression is the result of a number of related mechanisms including a reduction in the number of natural killer (NK) cells and cytotoxic lymphocytes and a decrease in TH1-cell-produced pro-inflammatory cytokines such as interleukin IL-2, IL-12, and interferon γ and tumor necrosis factor (TNF) γ. IL-2 plasma concentrations and activity per 10^5 T-cells, which show a high amplitude circadian rhythm under the usual regular sleep–wakefulness alteration are depressed during the daily peak time of these variables with a marked decrease in circadian amplitude. This change extends in part over the following night of recovery sleep (123). Changes in the production of TH2 anti-inflammatory cytokine IL-10 have been observed during sleep deprivation (124). The balance between TH1 cytokines (eg, IL-2, IL-12, interferon γ), which under the usual diurnal sleep–wakefulness patterns predominate during day time, is shifted in favor of TH2 cytokines (eg, IL-4, IL-10) that usually predominate during night time sleep. This shift decreases the immune surveillance and cellular immune response favoring the persistence of abnormal cell clones (125, 126). Melatonin stimulates the production of IL-6 from monocytes that act on some malignant cell growth (127).

Even partial sleep deprivation (early or late) was found to lead to a decrease in the number and activity of NK cells (128) with a lowering of immune surveillance.

Considerations on exposure assessment

As mentioned earlier, to date several epidemiological studies have considered a possible association between shift work and cancer. They deal with: breast cancer [9 studies (8–16), 6 positive], prostate cancer [3 studies (15, 17, 18), 2 positive], colo-rectal cancer [3 studies (8, 15, 19), 1 positive]; endometrium cancer [(20) positive study] and non-Hodgkin's lymphoma [(21) positive study]; and all cancers [4 studies (8, 15, 129, 130) all negative]. Some extensive and critical reviews on most of these studies have been recently carried out (33, 131–133). The main characteristics and findings of these studies are summarized in table 1.

In this section, our aim is to highlight some issues that seem to be relevant for a proper assessment of the relationship between shift work and cancer, both in terms of the causal relation and the strength of the association.

Two main problems arose in examining the epidemiological studies, namely the very rough exposure estimates used and the unclear assessment of concurrent risk factors, other confounders, or mediating factors.

As concerns the studies on breast cancer, for which evidence of an association appears to be most plausible, both the cohort and case–control studies based their

Table 1. Study characteristics and risk of cancer among shift workers in chronological order. [RF=radio frequency; ELF=extremely low frequency; 95% CI= 95% confidence interval]

Study and country	Study	Subjects and cases	Period	Exposure to night work	Duration of exposure	Ratio or risk	95% CI
Breast cancer							
Tynes et al, 1996 (8), Norway	Nested case–control within cohort	2169 naval radio-telegraph operators, 50 cases	Follow-up 1961–1991	Presence both at night and during day work, with possible exposure to light at night, RF and ELF fields	Overall	1.5 [a]	1.1–2.0
					Age <50 (<3.1 years)	0.3	0.1–1.2
					Age <50 (>3.1 years)	0.9	0.3–2.9
					Age >50 (<3.1 years)	3.2	0.6–17.3
					Age >50 (>3.1 years)	4.3	0.7–26.0
Davis et al, 2001 (9), USA	Case–control	813 cases, 792 controls	1992–1995	≥1 graveyard shift per week in the 10 years before diagnosis	<1 year	1.2 [b]	0.6–2.3
					1–3 years	1.4	0.7–2.8
					3–4.6 years	0.6	0.3–1.5
					>4.6 years	2.3	1.2–4.2
Hansen, 2001 (10), Denmark	Population-based, nested case–control	7035 cancer patients	Follow-up 1964–1994	≥6 months at work in sectors with >60% shift/night work (reference <40%)	All night work	1.5 [b]	1.3–1.7
					>6 years night work	1.7	1.3–1.7
Schernhammer et al, 2001 (11), USA	Prospective cohort	78 562 nurses, 2441 cases	Follow-up 1988–1998	Rotating night shifts, ≥3 nights per month in addition to days and evenings	>0–14 years	1.08 [c]	0.99–1.18
					15–29 years	1.08	0.90–1.30
					≥30 years	1.36	1.04–1.78
Lie et al, 2006 (12), Norway	Nested case–control within cohort	44 835 nurses, 537 cases	1960–1982	Night work from national registers of nurses	>0–14 years	0.95 [b]	0.67–1.33
					15–29 years	1.29	0.82–2.02
					≥30 years	2.21	1.10–4.45
O'Leary et al, 2006 (13), USA	Case–control	487 cases, 509 controls	1996–1997	Evening and overnight shifts, light-at-night exposure at home	Night & evening shifts	1.04 [b]	0.79–1.38
					Evening shifts	1.08	0.81–1.44
					Night shifts	0.55	0.32–0.94
Schernhammer et al, 2006 (14), USA	Prospective cohort	115 022 nurses, 1352 cases	1989–2001	Rotating night shifts, ≥3 nights/ month in addition to days and evenings	1–9 years	0.98 [c]	0.87–1.10
					10–19 years	0.91	0.72–1.16
					≥20 years	1.79	1.06–3.01
Schwartzbaum et al, 2007 (15), Sweden	Retrospective cohort	1 148 661 women, 70 cases among 3057 shift workers	1971–1989	Job sectors with ≥40% rotating shift workers (reference <30%)	Shift work in 1970	0.94 [a]	0.74–1.18
					Shift work in 1960 &1970	0.97	0.67–1.40
Pesch et al, 2008 (16), Germany	Case–control	857 cases, 892 controls	2000–2004	Ever worked in night shift for ≥1 year	Ever in night shift work	0.91 [b]	0.55–1.49
					>0–4 years	0.65	0.28–1.48
					5–9 years	0.93	0.31–2.82
					10–19 years	0.83	0.27–2.60
					≥20 years	2.48	0.62–9.99

(continued)

Table 1. Continued

Study and country	Study	Subjects and cases	Period	Exposure to night work	Duration of exposure	Ratio or Risk [a]	95% CI
Prostate cancer							
Kubo et al, 2006 (17), Japan	Prospective cohort	14 502 men, 31 cases	1988–1997	Fixed nightwork and rotating night/day work	Fixed night shifts Rotating shifts	2.3 [c] 3.0	0.6–9.2 1.2–7.7
Conlon et al, 2007 (18), Canada	Case–control	760 cases, 1632 controls	1995–1998	Full-time rotating shift work (questionnaire retrospective)	All workers ≤7 years 7.1–22 years 22.1–34 years >34 years	1.19 [b] 1.44 1.14 0.93 1.30	1.00–1.42 1.10–1.87 0.86–1.52 0.70–1.23 0.97–1.74
Schwartzbaum et al, 2007 (15), Sweden	Retrospective cohort	1319 cases in 69 759 shiftworkers	1971–1989	Job sectors with at least 40% rotating shiftworkers (reference <30%)	Shift work in 1970 Shift work in 1960 &1970	1.04 [a] 1.02	0.99–1.10 0.95–1.10
Colo-rectal cancers							
Tynes et al, 1996 (8), Norway	Nested case–control within cohort	2169 female naval radio-telegraph operators	1961–1991	Both night and day work, with possible exposure to light at night, and to RF and ELF	Colon (9 cases) Rectum (6 cases)	1.3 [a] 1.8	0.6–2.6 0.7–3.9
Schernhammer et al, 2003 (19), USA	Prospective cohort	78 586 nurses, 347 colon cancers, 103 rectal cancers	1988–1998	Rotating night shifts, ≥3 nights per month in addition to days and evenings	Colo-rectal (1–14 years) Colo-rectal (≥15 years) Colon (≥15 years) Rectum (≥15 years)	1.00 [c] 1.35 1.32 1.51	0.84–1.19 1.03–1.77 0.93–1.87 0.82–2.81
Schwartzbaum et al, 2007 (15), Sweden	Retrospective cohort	69 759 male shift workers, 3057 female shift workers, 465 colon cancers, 330 rectum cancers	1971–1989	Job sectors with ≥40% rotating shiftworkers (reference <30%)	Shift work in 1970 Colon (men) Colon women Rectum (men) Rectum women	 1.03 [a] 0.94 1.02 0.46	 0.94–1.13 0.54–1.52 0.91–1.13 0.12–1.17
Endometrium cancer							
Viswanatham et al, 2007 (20), USA	Retrospective cohort	53 847 nurses, 449 cases	1988–2004	Rotating night shifts, ≥3 nights per month in addition to days and evenings	1–9 years 10–19 years ≥20 years	0.89 [c] 1.06 1.47	0.74–1.08 0.76–1.49 1.03–2.10
Non-Hodgkin's lymphoma							
Lahti et al, 2008 (21), Finland	Retrospective cohort	1 666 272 persons, 6307 cases	1971–1995	Cumulative index of nighttime work (regular/irregular 3-shift work, regular night work) in various occupations.	10 years (men) 10 years (women)	1.10 [c] 1.02	1.03–1.19 0.94–1.12
All cancers							
Taylor & Pocock, 1972 (129), UK	Retrospective cohort (many sectors)	4188 shift workers, 219 cases / 189 expected	1956–1968	Shift work (any system other than regular day work) since 1946	>10 years, all neoplasms	1.16 [d]	
Rafnsson et al, 1990 (130), Iceland	Retrospective cohort (fertilizers plant)	603 men workers, 70 cases	1954–1985	3-shift work	Overall <1 year 2–5 years 6–15 years ≥16 years	1.40 [d] 4.12 2.02 1.71 0.59	
Tynes et al, 1996 (8), Norway	Nested case–control within cohort	2169 naval radio-telegraph operators, 140 cases	1961–1991	Both night and day work, with possible exposure to light at night, and to RF and ELF	Overall	1.2 [a]	1.0–1.4
Schwartzbaum et al, 2007 (15), Sweden	Retrospective cohort (all sectors)	69 759 male shift workers, 3057 female shift workers, 6792 cancers	1971–1989	Sectors with 40% rotating shiftwork (reference <30%)	Shift work in 1970 (men) Shift work in 1970 (women) Shift work in 1960 & 1970 (men) Shift work in 1960 & 1970 (women)	1.02 [a] 1.00 1.01 1.00	1.00–1.05 0.89–1.13 0.98–1.05 0.82–1.21

[a] Standardized incidence ratio (SIR)
[b] Odds ratio (OR)
[c] Relative risk (RR)
[d] Standardized mortality ratio (SMR)

exposure assessment on either very simple questions about being or not being involved in shift work (including nights) or a rough attribution to jobs involving shift work reported by national registers or census. For example, in the first nurses' health study, a moderate but significant increase of the relative risk (RR=1.36) for breast cancer was observed among women who worked as nurses ≥30 years (11), whereas no association was found with colo-rectal cancer (19). The authors asked the participants, only once in 1988, a single question: "How many years in total have you worked rotating night shifts with at least three nights per month in addition to days or evenings in that month?" In the second nurses' health study (14), covering 12 years (1989–2001) and where a significant relative risk (RR=1.79) was reported for those who worked ≥20 years, the same question on lifetime history of rotating night shift work was repeated in a mailed questionnaire in 1991, 1993, 1997, and 2001.

In the case–control study carried out by Davis et al (9), concerning various work sectors in which night work was significantly (OR=2.3) associated with breast cancer in the group with ≥4.6 years of work, exposure was estimated by an in-person interview about hours per week worked during the graveyard shift, based on a weighted average of all jobs in the ten years before diagnosis. Also O'Leary et al (13), who found no association between shift work and cancer, carried out a retrospective interview and ascertained the type of shift [in terms of late evening (until 02.00 hours) and overnight shifts] worked for each of the jobs held during the 15-year period prior to the reference date.

A slightly more detailed assessment of night work has been made in another very recent case–control study, carried out in the framework of the German GENICA study (16), where both shift and night work were not associated with breast cancer (OR=0.96 and OR=0.91, respectively). Exposure was retrospectively assessed by a telephone interview recalling information on having ever done night work for ≥1 year, its duration, the cumulative number of night shifts, the first incidence of night work, and time since last night work.

On the other hand, the studies based on national cancer registers ascribed exposure according to shift work prevalence in various working sectors, adopting different cut-off points to account for shift work percent in the "exposed" and "not exposed" subjects, with consequent poor specificity and a high chance of misclassification in both groups.

In the study by Hansen (10), who recorded a significant OR=1.5 for all night work combined, women were considered to work predominantly at night if they had been employed "for at least half a year in one or more of the trades in which at least 60% of the female responders had nighttime schedules", whereas the control groups included work sectors with <40% women involved in nighttime schedules. Besides, finding no evidence of an association, Schwartzbaum et al (15) defined shift workers "as those who had a rotating schedule with three or more possible shifts per day or had work hours during the night at least one day during the week preceding the interview", according to the annual Swedish Survey of Living Conditions. The authors then classified the shift workers as people employed in jobs and industry combinations where at least 40% are normally shift workers, and they compared these with occupations in which less than 30% were shift workers. This estimate of the prevalence of shift work was very different from any other national survey, thus making comparison of exposure classification impossible.

Based on the Finnish Cancer Registry and 1970 census file, Lahti et al (21) found non-Hodgkin's lymphoma to be rather modestly associated with nighttime work among men with high exposure (RR=1.28); a job-exposure matrix was created to provide estimates of the proportion of exposed persons and the mean level of exposure according to the prevalence of nighttime work in all occupations. This was assessed on the basis of responses to the question: "How is your working time arranged?'' as presented in the 1990 Quality of Work Life Survey.

In the Norwegian study on nurses (12) that reported a significantly increased risk (OR=2.21) among those who worked nights for >30 years, the reconstruction of total work history and number of years with night work was based on individual information from the Norwegian Board of Health's registry of nurses, and census data from 1960, 1970, and 1980. Moreover, the authors "assumed that work sites other than infirmaries only involved daytime work", whereas "all work at infirmaries was assumed to include night work, except for managerial jobs, teaching, and work at physiotherapy- or out-patients' departments".

On the other hand, in the study by Tynes et al (8), dealing with a large cohort of Norwegian radiotelegraph operators working on ships between 1920–1980, in which an association was found between breast cancer, shift work and women ≥50 years, shift work and travel across time zones were classified for each ship by a shipping journalist and a researcher with detailed knowledge of the recent (1945–1990) history of Norwegian merchant ships, according to four categories on frequent presence in the radio room (day and night).

Also as concerns prostate cancer, in the prospective cohort study on Japanese shift workers covering a period of ten years (17) that recorded a significant higher risk among those working rotating shifts (RR=3.0), a self-administered questionnaire carried out at baseline asked participants which work schedule they had previously undertaken the longest: daytime work, fixed-night work, or rotating night and day work. In the study by

Conlon et al (18), in which having worked full-time rotating shift work was also associated with a modestly increased risk of prostate cancer (OR=1.2), the authors say generically that the 25-page mailed questionnaire included a question about "usual work time (daytime, evening/nightshift, rotating shift, other)".

On the other hand, in a negative study on the excess of mortality of English industrial shift workers by Taylor & Pocock (129), "shift work" included any system of working hours other than regular day work (eg, 3-shift rotas at weekly or more frequent rotation, alternate day and shift work, double days, rotating 12-hour shift, regular night work).

Therefore, the information concerning shift work was mainly based either on (i) sporadic self-reported assessment on shift work including nights (mainly rotating) or (ii) affiliation to a job sector in which, according to nationwide databases and registries, a somewhat high percentage of workers were shift workers. This certainly led to the misclassification of some workers and even to the paradox of including permanent night workers in the control group, as in the case of studies that considered only rotating shift workers as the target group. This might even have underestimated the actual weight of night work as compared to day work. Non-differential exposure misclassification will obscure any real effect should it exist.

Exposure quantification (ie, years spent doing shift work) was also quite mixed. For example, the minimum time period considered for inclusion in various studies' target groups was: (i) "at least one night shift per week in the last 10 years" (9, 13); (ii) "at least three nights per month" (11, 14); (iii) "frequent presence in radio room both at night and day" (8); (iv) "at least half a year in one or more trades with 60% or more workers who had nighttime schedules" (10), or (v) "ever worked in night shift for ≥1 year" (16). Also the cut-off point used for comparing the different groups of shift workers was mainly based on the subsample numerical content. The longest exposure assessed in the different studies ranged >3.1 years (8), to >4.6 years (9), >10 years (129), ≥20 years (14, 16, 19–21, 130), and ≥30 years (11, 12, 18).

Another difference between the studies was how night work was defined. For example, Davis et al (9) defined the graveyard (or night) shift as "beginning work after 19:00 hours and leaving work before 09:00 hours"; O'Leary et al (13) referred to it as "starting as early as 19:00 hours and continuing until the following morning"; while Schwartzbaum et al (15) defined night work as "any hour between 01.00–04.00 hours" and Pesch et al (16) used "working the full-time period between 24.00–05.00 hours".

No study has considered other main organizational factors characterizing the different shift systems that are known to affect biological adjustment and tolerance and have negative consequences for health. These include: length of shift cycle, direction (forward/backward) and speed of rotation (fast/slow), number of nights worked in succession, start time of the work shifts, associated overtime, number and position of rest days, and regularity/irregularity of shift schedules. Only a few studies have considered the amount of nights worked per month, while no study made a distinction between continuous and semi-continuous shift systems.

Moreover, it was a common finding that, during their working life, shift workers often change their shift schedules, having different characteristics and structure, due to organizational strategies/changes and/or career development; in some cases, they may also move from shorter or longer periods to day work, and vice versa. As a general trend over the recent years, there has globally been a progressive change from the traditionally slow-rotation shift systems – based on weekly or fortnightly rotation – to faster rotating shift schedules (ie, every one, two or three days). This has resulted in a significantly different impact on the organization of the biological rhythm in terms of phase shift, circadian desynchronization, and re-adjustment, as well as sleep deprivation and recovery.

As concerns circadian disruption, apart from the amount of night shifts, two other factors are of paramount importance, namely, direction and speed of shift rotation. In other words, we know that slow-rotating shift systems imply longer sequences of night shifts in a row, thus causing higher phase-shifts and circadian misalignments or desynchronization of many biological functions. On the other hand, backward rotation may also represent a higher risk in this sense if there are no sufficient rest periods between shifts, enabling a prompt sleep recovery and circadian readjustment (134–137).

However, in the case of shift work and cancer studies, circadian disruption has never been measured directly but has been only postulated according to the data of other studies on shift workers' circadian adjustments (138–144).

There is still some discussion on the definition of "circadian disruption" (26) and, particularly, the criteria used to characterize and quantify it according to reliable biomarkers (ie, should these be melatonin, cortisol, core temperature, sleep, or clock genes?) Melatonin may be the most reliable (145), but some promising methods, based on genome-wide expression profile and blood metabolomics, able to detect internal body time and circadian rhythm disorders, have recently been proposed (146, 147).

Using overnight or morning-void urine sampling, four studies (148–151) examined the association between excretion of 6-sulphatoximelatonin (aMT6-s) and the risk of developing breast cancer among shift workers. No statistically significant differences were found in a

Table 2. Risk of breast cancer among female flight attendants (FA). [95% CI= 95% confidence interval]

Authors	Subjects	Ratio or risk	95% CI
Pukkala et al (156), Finland	1577 FA, 20 cases	1.87 [a]	1.15–2.23
	With 15–19 years of employment	3.4 [a]	1.5–6.8
Lynge (157), Denmark	915 FA	1.61 [a]	0.90–2.70
Wartenberg & Stapleton (158), USA	287 retired FA	2.0 [a]	1.0–4.3
Haldorsen et al (159), Norway	3105 FA	1.1 [a]	0.8.1.5
Rafnsson et al (160), Iceland	1532 FA, >5 years employment	5.24 [b]	1.58–17.38
Blettner et al (161), Germany	114 706 FA	1.28 [c]	0.72–2.20
Reynolds et al (162), USA	6107 FA	1.42 [a]	1.09–1.83
	On international routes	1.79 [a]	1.21–2.54
Linnersjo et al (163), Sweden	2324 FA	1.30 [a]	0.85–1.74
Zeeb et al (164), EU	33 063 FA	1.11 [c]	0.82–1.48
Kojo et al (165), Finland	44 cases/ 517 non-cases	1.52 [b]	0.49–4.74

[a] Standardized incidence ratio (SIR)
[b] Odds ratio (OR)
[c] Standardized mortality ratio (SMR)

Table 3. Risk of prostate cancer among male pilots and crew members. [95% CI= 95% confidence interval]

Authors	Subjects	Ratio or risk	95% CI
Band et al (168), Canada	913 pilots	1.54 [a]	0.70–3.00
Band et al (169), Canada	2680 pilots	1.87 [b]	1.38–2.49
Irvine & Davies (170), UK	6209 pilots	1.11 [a]	0.62–1.84
	1153 flight engineers	0.92 [a]	0.19–2.69
Gundestrup & Storn (171), Denmark	3790 pilots	0.8 [b]	0.2–2.2
Haldorsen et al (172), Norway	3701 pilots	1.0 [b]	0.7–1.5
Rafsson et al (173), Iceland	458 pilots	1.28 [b]	0.41–2.98
Blettner et al (174), EU	27 797 cockpit crew	0.94 [a]	0.71–1.26
Hammar et al (175), Sweden	1490 civil pilots	1.24 [b]	0.74–1.97
	2808 military pilots	1.17 [b]	0.84–1.49
Zeeb et al (176), Germany	6061 pilots	1.26 [a]	0.53–2.59
Zeeb et al (164), EU	11 079 pilots & cabin crew	1.09 [a]	0.35–2.68
Pukkala et al (177), Scandinavia	10 211 pilots	1.21 [b]	0.93–1.54
	With >10 000 hours long-haul flights, age >60 years	3.88 [b]	1.26–11.9

[a] Standardized mortality ratio (SMR)
[b] Standardized incidence ratio (SIR)

8-year follow-up study (148). An inverse association was recorded in a nested case–control study included in part II of the nurses' health study (149); in part I of the study, a similar finding was made (150). In the Ordet study from Italy, an inverse association was also found between pre-diagnosis urinary melatonin and subsequent breast cancer risk (151). In another study, Schernhammer et al (14) also found higher aMT6-s levels in women who had never worked rotating night shifts as compared with those who had ≥15 years of rotating night shifts. Most probably it will be necessary to have multiple, periodical dosages over the years to understand the real meaning and implications of transient and/or permanent disruption of the circadian patterns on cancer risk, both *per se* or in association with other mechanisms.

Although several studies (152–154) have reported an increased risk for breast cancer among nurses, no mention or investigation were made of other concomitant work-related risk factors that might have had some connection with the disease among healthcare workers (eg, radiation, lab reagents, sterilizers, and antineoplastic drugs). It is important to note, however, that for an unknown factor to confound an association in an occupational study of cancer, that fact must be strongly associated with both the exposure under study (ie, shift work) and the disease (ie, breast cancer) (155).

In case of studies on flight attendants (156–165), some of whom tested positive for breast cancer (table 2), many authors claimed the possible concomitant exposure was associated with other risk factors, such as cosmic radiation and jetlag, although no study could report any quantification. This was also the case for the radio and telegraph operators investigated by Tynes et al (8), for whom "shift work highly reflects frequent presence in the radio room both at night and during the day, with possible exposure to light at night, and RF [radio frequency] and ELF [extremely low frequency] fields."

The studies are also quite dissimilar with respect to control for possible confounding and intermediate and associated risk factors. For breast cancer, for example, all nine studies (8–16) controlled for age, smoking and body mass index, but other relevant risk factors were adjusted for in different terms, for example: age at menarche (2 studies), menopause, (5 studies), number of children (3 studies), age at birth of first child (6 studies), parity (7 studies), family history of breast cancer (5 studies), oral contraceptive use (5 studies), hormonal replacement therapy (3 studies), benign breast diseases (3 studies), and socioeconomic status (4 studies).

An issue not sufficiently examined is the interaction between circadian and infradian (ie, menstrual cycle, lifetime endogenous estrogen) rhythms, which has some importance for breast cancer (166–167).

Last but not least, we have to account for the significant "healthy worker effect" present in many cohorts of shift workers, as emphasized in various studies, particularly those concerning long-term chronic effect. This may have had a significant impact on the results of the epidemiological studies (mainly the retrospective and cross-sectional ones but also the prospective ones) if the examiners were not able to follow the whole population.

This can be speculated also in the case of studies on prostate cancer in air crews (164, 168–177), which were almost all negative (see table 3); air crew staff, pilots in particular, are highly select people, who are submitted to rigid medical checks before starting their job and then twice a year in order to keep their license. This obviously induces them to adopt healthier life styles (ie, drinking and smoking habits and physical fitness), and only those in good health are allowed to continue flying.

Concluding remarks

Despite the weaknesses of the methodological aspects related to the assessment of exposure quality and quantity, we have to consider that most studies dealt with very large cohorts, covered a long lifespan, and controlled for several confounders. Therefore, we must take the outcomes published so far into close consideration.

The mechanisms by which circadian disruption may favor the induction and/or promotion of malignant tumors are complex and multifactorial. With or without genetic predisposition, repeated phase shifting with internal desynchronization may lead to defects in circadian cell-cycle regulation, which in some instances may favor uncontrolled growth. The suppression of melatonin acts at multiple levels from hypothalamic centers to local estrogen receptor activity and peripheral estrogen formation leading to an up-regulation of estrogen effects upon the estrogen-sensitive breast epithelial cell. Melatonin suppression favors the linoleic acid uptake and mitogen formation in the epithelial cells and a defect in the function of the immune system. Sleep deprivation leads to a suppression of immune surveillance that may permit the establishment and/or growth of malignant clones. None of these multiple factors is solely responsible for the moderately increased cancer rate among shift workers. The multilevel endocrine changes caused by circadian disruption, with melatonin suppression through LAN, lead to the oncogenic targeting of the endocrine-responsive breast among women and possibly the prostate among men.

The increased cancer incidence among shift workers may be related both to initiation of the tumor and events occurring during the period of promotion of the malignancy until it becomes clinically manifest. Initiation of breast cancer may occur many years before the clinical manifestation of the tumor. During the reproductive lifespan, the epithelium in a breast proliferates and is vulnerable to carcinogenic agents (178–179). The decade between 20–30 years of age, during which exposure to shift work is frequent, may be an important time for carcinogenesis and must be considered in the study of mechanisms and the search for protective and preventative measures.

Taking into account the plausibility of these mechanisms and the amount of significant experimental data, we can say that the hypothesis-generating phase appears to be almost complete; now we have to focus on a precise risk assessment. Perhaps the multifaceted aspect of shift work as a risk factor makes this process more complex than that of chemical or physical factors, but it has to be tackled with the same attention and care.

The rather low odds ratios and relative risks reported in the epidemiological studies on shift workers, and their significant levels only after long-term exposure, may reflect the interaction with many other concurrent non-occupational risk factors, which in some cases might even mask the association when one takes into consideration also the high prevalence of these cancers in the general population.

Considering the health and social relevance and impact on work and life organization, it is necessary and urgent to define a proper protocol for recording more precisely and systematically all the most important information about shift work schedules and the amount of years actually spent in shift/night work, in order to define the "external dose". Hence, it is necessary to collect detailed data on the characteristics of the shift schedule, particularly as concerns: (i) rotating or fixed/permanent shifts, (ii) amount of night shifts (per month and year and number of years), (iii) start and finish time of the shift periods, (iv) speed [fast (1–3 days), intermediate (4–6 days), slow (>7 days)] and direction (clockwise versus counterclockwise) of shift rotation, and (v) interruption on weekends (continuous versus semi-continuous shift systems). It is also important to have detailed information on exposure to LAN (eg, natural/artificial, levels, timing, and duration) and sleeping times, as well as some personal characteristics, such as having a preference for mornings versus evenings (ie, morningness/eveningness), neuroticism, and extraversion, all of which can influence circadian phase and adjustment (180–184). Hopefully in the near future, the recording of some of these biomarkers will enable a better definition of circadian disruption in terms of "internal dose", which, like for the chemical model, may indicate the effective/actual risk, as well as identify some possible susceptibility markers (genomics). Moreover, it is necessary to control for possible associated risk factors, as well as confounders and mediators of the effects, according to the specific work sectors and population under control.

The more carefully and extensively researchers take these factors into account, the more reliable and valid their findings and outcomes will be; social actors (legislators, occupational health physicians, working time planners, managers and workers) will have to consider the results carefully in their assessments and development of preventive and protective actions.

These issues need to be urgently taken into consideration as cancers of the breast and prostate are two of the three most prevalent cancers in the general worldwide population and the number of people involved in shift and night work are on the increase; rapid economic and productive growth in developing countries also adds urgency to the issue.

In the perspective of preventive actions, the alert posed by the IARC working group concerning "shift work which involves circadian disruption" should have a positive effect on risk assessment and shift work management. Work hygienists, ergonomists, occupational health physicians, and employers will be now obliged to evaluate this occupational risk properly, in particular when assessing whether proposed shift schedules are more or less disruptive of the circadian system and when taking into consideration the ergonomic criteria concerning the organization of the shift system for the consequent actions aimed at modifying/improving the shift schedule accordingly (185). Apart from any consideration about cancer risk, this will certainly improve the health and wellbeing of shift workers, diminishing the stress associated with inappropriately planned shift systems.

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