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ORIGINAL ARTICLE

Does light cause internal cancers? The problem and challenge of an ubiquitous exposure

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Abstract

Visible light of sufficient intensity and duration inhibits melatonin biosynthesis, and experimental studies suggest that melatonin may protect against cancer. From a public health point of view it is important to verify or falsify the hypothesis that artificial light – or even sunlight itself – suppresses melatonin production sufficiently to increase the risk of developing cancers of internal organs in man. Epidemiology is a discipline that can contribute to *in-vivo* verification of experimental findings. But when attempting to study the effects of light on man, epidemiologists are faced with a major problem: the ubiquitous nature of natural and anthropogenic light, which renders everyone, everywhere exposed. The challenge is to identify populations with demonstrable varying exposures to light.

This paper summarizes how recent epidemiological investigations have sought to tackle the problem by studying shift-workers, blind people and Arctic residents. It is suggested that future studies should test the underlying assumptions regarding endocrine responses to light, i.e., that melatonin levels are reduced among shift-workers, and that they are increased among the blind and those who live in the Arctic. A systematic investigation of exposure-response relationships could be based on "light dosimetry by geography". Such a study is envisaged by European researchers who aim to study melatonin and other hormones in samples from healthy general populations that are differentially exposed to light by virtue of varying ambient photoperiods. Further methodologic options for prospective and retrospective epidemiologic studies are suggested.

It is concluded that the biologically plausible link between ubiquitous light, hormones and the development of very frequent malignancies such as breast cancer and prostate cancer should be investigated rigorously by additional well-designed epidemiological research.

Introduction

Man is exposed to the sun's light everywhere, and anthropogenic light sources constitute further universal exposures to visible electromagnetic radiation. Breast cancer is the leading cause of cancer morbidity and mortality among women in many countries, and prostate cancer is the most common non-cutaneous cancer in men [1]. Large differences in rates of hormone-related cancers internationally suggest that environmental factors play an etiologic role, and since the development of both malignancies involve hormones it seems likely that modulation of endocrine systems is relevant [2, 3]. Light is an ubiquitous environmental factor which does just that. An abundance of experimental and clinical evidence indicates a very robust relationship between visible light, at intensities that we experience regularly, and endocrine systems. Light entering the eyes powerfully controls and modifies circadian and neuroendocrine systems. Melatonin is the key biologic intermediary. Light inhibits [4] and darkness stimulates synthesis of melatonin [5] in the pineal gland in the center of the brain as a product of the tryptophan-serotonin metabolism. A dose-response relationship between light and melatonin suppression has been confirmed in human studies [6–8], and there is some evidence which suggests that the blue-green spectrum (~500 nm) is most effective in reducing melatonin production [6]. It is important to note that considerably more light is needed for melatonin suppression than for vision [9]. Research is under way to clarify how the phototransduction of non-visually mediated phenomena on endocrine systems operates [10].

The experimental, and limited epidemiological evidence available in 1987 was used to formulate the so-called *melatonin hypothesis*. This posited a link between light-at-night (LAN), and extremely low frequency electric and/or magnetic fields (ELF-EMF), to increased breast cancer risks via impaired pineal secretion of melatonin [11]. The idea was that low melatonin levels were expected to result in increased levels of gonadal steroids (e.g., testosterone in males, and estrogens in females, respectively) by specific actions on the pituitary, and would thus eventually promote cancer growth. Empirically, these relations between melatonin secretion and gonadotropins levels have been suggested in men [12], but ELF-EMF have not been shown convincingly to inhibit melatonin secretion [13]. Exposure to light, however, has been linked consistently with impaired melatonin secretion in humans, and experimental evidence suggests that melatonin can suppress mammary tumorigenesis in animals [14] and possibly in humans [15]. Furthermore, a number of clinical studies indicate that low melatonin levels are associated with certain types of hormone-dependent cancers, including breast [3], endometrial [16], and prostate cancer [17]. To date, extensive research over many years has identified some of the mechanisms by which melatonin can reduce cancer incidence and/or growth [3,18].

The melatonin hypothesis is biologically plausible and is testable in principle. It remains then to transform the "biological plausibility" into a convincing mapping of a biological pathway that occurs in real life. Laboratory studies are being pursued intensively in an effort to provide direct evidence that supports or refutes the hypothesized causal link between light, melatonin and cancer. But epidemiological studies of light and hormone-dependent cancers are difficult and still very rare. This paper discusses current strategies and viable additional options for epidemiological studies of the issue. Such research may provide *in vivo* verification of the suggestion that the intriguing experimental and clinical findings summarised above impact importantly on public health.

Problem and challenge

Epidemiology is based primarily on non-experimental or "observational" data, as distinct from controlled experiments in biomedical studies. One consequence, and in contrast to biomedical studies, is that epidemiology is unlikely to unravel mechanisms from an exposure to effects on health. However, epidemiology "has the tremendous advantage that it focuses on the diseases and the deaths that actually occur, and experience has shown that it continues to be second to none as a means of discovering links in the chain of causation that are capable of being broken" [19]. Importantly, epidemiology can identify factors that influence the frequency of disease in humans "without concern about dose-extrapolation or species variability and with built-in accounting for potential modifiers" of human health and disease [20]. In general, epidemiology relies on comparisons of disease rates in different groups of individuals who have been exposed to varying levels of exposure to an hypothesised causal factor. Therefore, epidemiologists seeking to study exposures to light and their effects on health are faced with a major dilemma: the ubiquitous light sources at home and at work may well result in more or less homogenous patterns of exposure across different study populations. If everyone is exposed [21], then risk ratios purporting to reflect the effect of an exposure on human health will tend to be underestimates; the effect may even be undetectable. For example, "if everyone smoked 20 cigarettes a day, then clinical, case-control and cohort studies alike would lead us to conclude that lung cancer was a genetic disease" [22]. The challenge for cancer epidemiology is thus to identify population groups that are differentially exposed to light, i.e., to compare groups for whom levels of the putative risk factor differ appreciably.

Predictions

Current epidemiological efforts to interpret apparently different responses to variations in exposures to natural and artificial light focus on three predictions (P) that either follow directly from the melatonin hypothesis (H), or from a corollary (C) which states that deficits of light enhance melatonin secretion and thus decrease cancer risks. P_1 given H ($P_1|H$) anticipates that female night-shift workers will have elevated breast cancer risks. ($P_2|C$) holds that blind persons have lower hormone-dependent cancer risks than the sighted. ($P_3|C$) asserts that residents in the Arctic have relatively low hormone dependent cancer risks.

– $P_1|H$

Several research groups have studied female shift-workers who experience light during the night, when melatonin levels would normally be at their highest. Results from four epidemiologic studies, in Norway [23], Denmark [24, 25] and the USA [26, 27], are compatible with the prediction that shift-workers do have a higher risk of breast cancer (Table 1).

An editorial accompanying reports of the most recent studies, from the USA, acknowledged that work at night, or exposure to light-at-night, may be acting as a proxy for other, as yet unidentified, risk factors for breast cancer. Moreover, other studies may exist that show no effect, but they may not have been published. It was argued nevertheless that, since studies which used different ways to approximate exposures to light consistently pointed to increased breast cancer risks, further exploration of the possible links between light-at-night, shiftwork, melatonin and cancers were clearly warranted [25]. In addition to further studies of female shift-workers, the possible relationships between light-at-night and another frequent hormone-dependent cancer such as prostate cancer could be investigated in male shift-workers.

– $P_2|C$

Efforts to test a corollary to the melatonin hypothesis, that deficits of light should lead to higher melatonin concentrations and thus to lower human risks of hormone-dependent cancers, have focussed on blind people, because they perceive less or no light visually when compared with the sighted [28]. Results of one study in the USA [29] and four in Scandinavia [30–33] are compatible with the prediction, i.e, blind people may indeed have reduced risks of breast cancer (Table 2).

However, some questions regarding the variable and in part contradictory results from Finland and Sweden were raised subsequently in correspondence [34,35]. A multicentre investigation was suggested to resolve discrepancies [35,33]. But there are other considerations that complicate interpretation of these studies. Czeisler et al. [36] have shown experimentally that application of light can induce nocturnal melatonin suppression in some totally blind persons. It is possible therefore that some individuals in blind study populations, who were assumed to have higher melatonin levels than the sighted, had more nearly "normal" melatonin levels in fact. This would tend to attenuate the hypothesised difference between cancer risks for the sighted and blind. On the other hand, it could be argued that even such

Table 1. Epidemiological studies of women, shift-work and breast cancer

1st author location (year of publication)	Study design	Study population	Exposure; information definition	Exposure category	Number of exposed cases	Covariates considered	Relative Risk estimate (95% CI)
Tynes (1996) Norway [23]	cohort; nested case-control analysis	2619 female radio and telegraph operators of the Norwegian Telecom cohort (1961–1991)	job histories; shift work (category x years)	1) Low > 0–3.1 2) High > 3.1–20.7	1) 6 2) 12	Age	1) OR = 3.2 (0.6, 17.3) 2) OR = 6.1 (1.5, 24.2)
Hansen Denmark (2001a, b) [24, 25]	population-based case-control	7565 women with primary breast cancer, born during 1935–59, 30–54 years of age at time of diagnosis; one control per case at random	employment records; number of years with employment in jobs with predominant non-daytime work	1) Ever > 1.5 y 2) > 6y	1) 434 2) 63	age, parity, age at first and /or last child	1) OR = 1.5 (1.2, 1.7) 2) OR = 1.7 (1.3, 1.7)
Davis (2001) USA [26]	case-control	813 case patients (women aged 20–74 years) from 11/1992 – 3/1995; one control per case patient, frequency matched to 5-year age groups	in-person interview; number of hours with work between 7:00 PM and 9:00 AM	1) Ever 2) Hours/week continuous 3) Years ≥ one shift/ week continuous	1) 37 2) 767 3) 743	age, parity, family history of breast cancer, oral contraceptive use, recent discontinued use of hormone replacement therapy	1) OR = 1.6 (1.0, 2.5) 2) OR = 1.06 (1.01, 1.13) 3) OR = 1.13 (1.01, 1.27)
Schernhammer (2001) USA [27]	prospective cohort	121701 female registered nurses 30–55 years of age in 11 large U.S. states were enrolled in the Nurses' Health Study; 85197 respondents answered the question on night work; 2441 incident breast cancer cases were documented during June 1988 to May 1998	biennial-mailed questionnaire; years on rotating night	1) 1–14 y 2) 15–29 y 3) ≥ 30 y	1) 1324 2) 134 3) 58	age, parity, age at first and/ or last child, family history of breast cancer, oral contraceptive use, recent hormone replacement therapy, age at menarche, age at menopause, weight change between age 18 years and menopause, body mass index at age 18	1) RR = 1.08 (0.99, 1.18) 2) RR = 1.08 (0.90, 1.30) 3) RR = 1.36 (1.04, 1.78)

Table 2. Epidemiological studies of blind people and cancer risks

1st author (year of publication) location	Study design	Study population	Exposure information; definition	Exposure category	Cancer Endpoint	Number of exposed cases	Covariates considered	Relative Risk estimate (95% CI)
Hahn (1991) USA [29]	case-control	all 11769 women with breast cancer from National Hospital Discharge Survey sample 1979-1987 as cases; all 71615 women (without diagnosis of diabetes) in the sample with coronary heart disease and 21664 women with stroke as controls	discharge records; profound binocular blindness	1) < 15 years of age	Breast cancer	1) 19	Age, marital status	1) OR = 0
				2) 15 – 44		2) 1572		2) OR = 0
				3) 45 – 64		3) 5005		3) OR = 0.34
				4) ≥ 65		4) 5155		4) OR = 0.99
Feychting (1998) Sweden [30]	cohort	1567 totally blind and 13292 severely visually impaired subjects identified from the Hospital Discharge Registry and via the Swedish Federation of the Visually Handicapped	medical records, medical certificates, local vison centers; severe visual impairment: better than perception and localization of light	1) totally blind 2) severely visually impaired	All cancers	1) 136	age, sex, calendar year	1) SIR = 0.69 (0.59, 0.82)
						2) 1709		2) SIR = 0.95 (0.91, 1.0)
					Breast cancer	1) 16		1) SIR = 0.82 (0.47, 1.34)
						2) 214		2) SIR = 1.06 (0.92, 1.21)
					Prostate cancer	1) 20		1) SIR = 0.71 (0.43, 1.09)
						2) 220		2) SIR = 0.98 (0.86, 1.12)
Pukkala (1999) Finland [31]	cohort	17557 individuals from the Finnish Register of Visual Impairment (FRVI); follow-up for cancer via the Finnish Cancer Registry from 1983-95	data base of the FRVI; 5 categories of the degree of visual impairment referred to as 'partially sighted', 'almost blind' and 'blind'	1) partially sighted 2) almost blind 3) blind	All cancers in men	1) 401	gender, five-year age group, calendar period of observation	1) SIR = 1.18 (1.07, 1.29)
						2) 122		2) SIR = 1.11 (0.93, 1.32)
						3) 18		3) SIR = 2.20 (1.30, 3.47)
					All cancers in women	1) 544		1) SIR = 1.11 (1.02, 1.20)
						2) 160		2) SIR = 1.17 (0.99, 1.35)
						3) 10		3) SIR = 1.15 (0.55, 2.11)
					Breast cancer in women	1) 91		1) SIR = 1.05 (0.84, 1.28)
						2) 20		2) SIR = 0.80 (0.49, 1.23)
						3) 1		3) SIR = 0.52 (0.01, 2.91)
					Prostate cancer	1) 90		1) SIR = 1.00 (0.80, 1.22)

						2) 27		2) SIR = 0.98 (0.64, 1.41)
						3) –		3) SIR = 0 (0.00, 2.17)
Verkasalo (1999) Finland [32]	"nested" case-control	10935 visually impaired women were identified from the FRVI; follow-up for cancer via the Finnish Cancer Registry from 1983-96	presumably data base of the FRVI; 5 categories of the degree of visual impairment	1) moderate low vision 2) severe low vision 3) profound low vision 4) near-total blindness 5) total blindness	Breast cancer	1) 81	age at cancer diagnosis, calendar period of observation, time since initial registration, latest degree of visual impairment, age at onset of visual impairment	1) SIR = 1.05 (0.84, 1.30)
						2) 21		2) SIR = 0.96 (0.59, 1.46)
						3) 15		3) SIR = 0.79 (0.44, 1.29)
						4) 6		4) SIR = 0.66 (0.24, 1.44)
						5) 1		5) SIR = 0.47 (0.01, 2.63)
					All cancers	1) 385		1) SIR = 1.1 (0.99, 1.21)
						2) 133		2) SIR = 1.34 (1.12, 1.59)
						3) 99		3) SIR = 1.13 (0.92, 1.38)
						4) 49		4) SIR = 1.35 (1.00, 1.79)
						5) 9		5) SIR = 1.23 (0.56, 2.33)
Kliukiene (2001) Norway [33]	cohort	15412 blind or milder visually impaired Norwegian women were followed-up for breast cancer from 1961 to 1997 via the Cancer Registry of Norway	medical registration records; 5 categories (WHO 1980) of the degree of visual impairment	1) moderate low vision 2) severe low vision 3) profound low vision 4) near-total blindness 5) total blindness	Breast cancer	1) 104	marital status, age at first birth (not available for women born before 1935)	1) SIR = 0.92 (0.76, 1.11)
						2) 77		2) SIR = 1.22 (0.96, 1.52)
						3) 63		3) SIR = 1.00 (0.77, 1.29)
						4) 57		4) SIR = 1.21 (0.92, 1.57)
						5) 5		5) SIR = 0.64 (0.21, 1.49)
					All cancers, except breast cancer	1) 534		1) SIR = 1.08 (0.99, 1.17)
						2) 274		2) SIR = 1.00 (0.89, 1.12)
						3) 274		3) SIR = 1.01 (0.90, 1.14)
						4) 197		4) SIR = 1.07 (0.73, 1.51)
						5) 32		5) SIR = 1.07 (0.73, 1.51)

blind individuals, with intact light-melatonin regulation, are likely to have been exposed to less light than the sighted controls ("no sight – why light?"), so that the hypothesised contrast between the cancer risk may not have been compromised.

– **$P_3|C$**

It has been suggested that if the melatonin hypothesis is valid, then winter darkness in the Arctic should increase residents' melatonin levels, *per diem and per annum*. Thus the prediction is that hormone-dependent cancers should occur less frequently in people living north of the Arctic circle than in those who live south of this boundary [37].

Complementary excess light during summer nights should not interfere with this reasoning for two reasons. First, *net* melatonin secretions over any one year should exhibit the hypothesised difference because residents north of the boundary, who experience extensive light during summer months, will be expected to protect themselves from light for bed rest during the summer ("anthropogenic shield"). Moreover, evidence from laboratory studies in humans indicates that closed eyelids shield against light and thus prevent melatonin suppression ("natural shield") [38, 39]. Second, the *patterns* of melatonin secretion (be they nocturnal, diurnal, seasonal and annual) will differ between residents north and south of the border, and this difference in patterns can itself be very relevant to carcinogenesis [3].

Empirical data – although limited in scope and methodological weight – support the validity of $P_3|C$: Nine studies in the peer-reviewed literature have examined melatonin levels among healthy individuals living at or north of 60ºN latitude (Table 3). Findings in all these studies are compatible with the assumption that shorter photoperiods in winter, i.e. decreased ratios between the day's and night's length, significantly increase yearly averages of melatonin levels [40].

Furthermore, large population-group ("ecologic") data from the Arctic (Table 4) are strikingly consistent with the prediction of reduced risks of hormone-dependent cancers [37].

It is well known, however, that ecologic data in general, and cancer data in particular, may invite inappropriate inferences because observed associations between variables on an aggregate level may not represent biologic effects at the individual level. On their own, such "ecologic" observations are not sufficient for secure inferences about causality.

Moreover, none of the nine studies actually measured natural and anthropogenic light exposures, and there were important differences between the studies with regard to the measurements of melatonin (sample media, sampling times and frequency, the number of individuals studied, and the age distribution of participants.) Overall, therefore, the nine studies provide only circumstantial evidence that variations of ambient light significantly affect endocrine systems in man. Explanations other than possibly higher melatonin levels must be considered when trying to explain the low risks of hormone-dependent cancers in the Arctic.

– **$P_4|C$**

The reasoning leading to $P_3|C$, namely that there is a cancer risk gradient for humans from North to South, may suggest yet another set of predictions. As indicated above, ecologic data are compatible with the notion that, at least for Arctic residents, hormone-dependent cancer risks are substantially lower than for reference populations in the USA, Canada and Denmark. Conversely, therefore, if there are diseases other than cancer that are more likely to occur when melatonin levels are relatively high, then the prediction would be that the risk of these diseases (e.g., depression [54]) should be demonstrably higher in the Arctic than in lower latitudes. But such predictions are not likely to be verifiable easily. In the first place, a real effect will not be detectable if the higher exposure being considered (in the north) does not exceed what may be a threshold below which the biologic effect does not occur. A more general difficulty, common to all epidemiological research, is that factors other than that under study, which also influence health and disease, may be distributed in the study populations in a way that obscures the hypothesised relationship.

Table 3. Melatonin in healthy residents living at latitudes at or north of 60°N

1st author (year of publication)	Number of study participants		Sample medium	Melatonin measurements
	Men	Women		
Beck-Friis (1984) [41]	14	19	serum	higher daytime levels during winter
Martikainen (1985) [42]	11	–	serum	daytime levels peaked in December and May
Kauppila (1987) [43]	–	11	serum, urine	daytime serum and urinary excretion higher during winter
Kivelä (1988) [44]	–	12	serum	nighttime levels higher in winter
Levine (1994) [45]	34	–	serum	daytime levels higher in winter
Stokkan (1994) [46]	11	6	saliva	daily elevated in January
Laakso (1994) [47]	2	7	saliva	daytime levels higher in winter
Weydahl (1998) [48]	10	19	saliva	levels higher in winter
Wetterberg (1993; 1999)* [49]	50	53	urine	increased yearly nighttime levels when compared with populations at lower latitudes

* In this data set (explored in three publications), yearly means of nighttime melatonin were calculated and compared between populations at different latitudes in the northern hemisphere.

Table 4. Hormone-dependent cancer risks in the Arctic

1st author location (year of publication)	Period	Cancer endpoint	Number of cases	Relative Risk estimate (95% CI)
Blot (1975) Alaska [50]	1960 – 1969	Breast	92	SMR = 0.4 (0.3, 0.5)†
Miller (1996) Alaska [51]	1969 – 1988		78	SIR = 0.5 (0.4, 0.6)
Greenland	1969 – 1988		98	SIR = 0.5 (0.4, 0.6)
Canada	1969 – 1988		17	SIR = 0.2 (0.1, 0.3)
Circumpolar*	1969 – 1988		193	SIR = 0.4 (0.3, 0.4)
Kjaer (1996) Alaska [52]	1969 – 1988	Ovary	15	SIR = 0.6 (0.3, 0.9)
Greenland	1969 – 1988		39	SIR = 0.9 (0.6, 1,2)
Canada	1969 – 1988		7	SIR = 0.5 (0.2, 1.1)
Circumpolar	1969 – 1988		61	SIR = 0.8 (0.6, 1.0)
Blot (1975) Alaska [50]	1960 – 1969	Prostate	54	SMR = 0.7† (0.5, 0.9)
Prener (1996) Alaska [53]	1969 – 1988		26	SIR = 0.3 (0.2, 0.4)
Greenland	1969 – 1988		4	SIR = 0.1 (0.0, 0.2)
Canada	1969 – 1988		7	SIR = 0.2 (0.1, 0.4)
Circumpolar	1969 – 1988		37	SIR = 0.2 (0.1, 0.2)

*: Alaska, Greenland and Canada combined
†: 95 % CI calculated by Erren and Piekarski [37]
CI: Confidence interval
SMR: Standardized mortality ratio
SIR: Standardized incidence ratio

Study options

Prospective studies

Prospective cohort studies measure the incidence of new cases of disease during a defined period of time. In principle, such a study could determine unequivocally whether there is a significant exposure-response relationship between measured exposures to light and cancer incidence in humans, and the prospective capture of data on relevant covariates could also be arranged by design, *a priori*. For cancer end-points, however, such studies may require decades of research before a sufficient number of cases have accumulated to permit sensible conclusions.

Yet prospective biomarker studies could well be appropriate to examine critical assumptions that underpin the epidemiological arguments outlined above. The assumptions are that excessive exposures to light among shift workers do indeed reduce their melatonin levels, and that deficits of exposures to light among the blind and among residents in the Arctic do indeed result in relatively high melatonin levels. A series of surveys of melatonin levels and of other hormones could be accompanied by rigorous prospective assessments of exposures to light and of endocrine responses. Melatonin, gonadal steroids and cortisol or their metabolites might be analyzed in saliva, serum and urine for such studies. A feasible and cost-effective alternative to invasive serum and sometimes irritating saliva tests might be to use morning urine to assess both total nocturnal plasma melatonin output and peak nocturnal melatonin values [55]. If such studies do not identify significant correlations between measurements of light and the selected biomarkers, then this would effectively negate the hypothesized link between light and hormones in shift-workers, blind people and Arctic residents. If, on the other hand, any one the assumptions underlying the melatonin hypothesis and its corollaries were verified in these study populations, then further epidemiological studies would be required to determine whether the relationships are reflected in the hypothesised effects on cancer risks.

Some European researchers recently outlined a proposal for such a biomarker study of "healthy general populations" that are differentially exposed to light [40]. Residents in Greenland, Finland, Sweden, Germany and Italy are exposed to different light intensities per day, per season and per year by virtue of pronounced geographically determined variations in ambient photoperiods. The idea is to measure levels and rhythms of melatonin, of gonadal steroids, and of cortisol in saliva and urine of healthy people residing at or near 70, 60, 50, and 40ºN latitude, i.e., from the Arctic to the Mediterranean. These measurements would then be compared with estimates of the same individuals' exposures to natural and artificial light during significant seasonal periods. The results should make it possible to identify associations, and to estimate relations between, temporal rhythms of melatonin and other hormones on the one hand and (a) exposure to natural light, (b) exposure to artificial light, and (c) total exposure, i.e., (a) + (b). Successful completion of this study would constitute a prudent prelude to any more extensive (and probably more expensive) direct examination of the hypothesised effect on health risks in humans implied by $P_3|C$ and $P_4|C$.

Retrospective studies

Epidemiological strategies that might be considered for the latter purpose include "historical" cohort studies, requiring a retrospective enumeration of cancer incidence in a well-defined group known to be without the disease at a designated previous point in time. This design, as well as the classical case-control approach, which involves recruitment of cases with the disease and controls without, would only be viable if it is possible to make realistic estimates retrospectively of past exposures to light, and of levels of biomarkers that characterise the suspected continuum between exposure and disease.

Measurement of variables

Reliable determination of cancer incidence in selected study groups is not trivial, but relatively easy, given the sophistication of modern diagnostic tools and the availability of well-established cancer registries in many developed countries. More troublesome are the practical constraints on procuring reproducible and valid (i.e., relevant) measurements of the various quantities thought to influence the cancer end-point.

Light

Records of individuals' durations of exposures to measured intensities of light will not be available normally for retrospective epidemiological studies. Plausible surrogate measures of exposure are required. Tables 1 and 2 indicate the kind of approximations that have been used in the past for shift workers (job histories, employment records, questionnaires and interviews with participants), and for the blind or partially sighted (medical records of the degree of visual impairment). The "ecologic" review of hormone-dependent cancer risks in the Arctic (Table 4) appealed simply to latitude as a likely indicator of differential exposure to light. Perkowitz [56] draws attention at this symposium [57] to a further difficulty that would be relevant even in prospective incidence studies. He notes that there may be important variations in biologic effects of light depending on the varying spectral distributions and intensities of the many *types* of artificial indoor and outdoor lighting common nowadays. Surrogate measures of exposures to light-at-night of the kind used in earlier studies may be oversimplistic, in that real effects associated with particular types of lighting may be underestimated or obscured.

Biomarkers

Direct measurement of biological markers in retrospective studies presents further problems. If stored serum banks are available for the populations of interest then it may be possible to use them for laboratory analyses of various hormones. Stevens et al. [58] have argued that melatonin levels in stored sera would be virtually useless because the blood samples will normally have been taken during the day, when melatonin levels are relatively low. However, any stored serum samples that may be available in the Arctic or in Nordic countries are likely to have been obtained during both 'dark' and 'light' daytime periods. Since empirical data suggest that melatonin is also produced during days that are 'dark' (Table 3), stored serum samples may nevertheless provide a useful basis for estimating varying levels of exposure to melatonin, both for case-control studies and for retrospectively defined cohort studies of predictions 3 and 4. Similarly, stored sera of shift-workers and of blind people could be analyzed to examine the melatonin assumptions of predictions 1 and 2.

An alternative indirect measure of "exposure"

It is clear that there are formidable difficulties in an epidemiological setting in measuring variables that represent both the first and the second elements in the hypothesised causal chain of events ending in hormonal cancers. There may be merit, therefore, in considering a possible alternative index of melatonin levels that does not require measurement of biomarkers. The available clinical and experimental laboratory evidence suggests that this could be individuals' cumulative time at sleep. These quantities could be estimated in all kinds of epidemiological studies by using structured interviews with participants or their relatives. The interviews would seek information on average hours of sleep during relevant periods of time. Cumulative time at sleep would be expected to correlate positively with individuals' cumulative melatonin levels, and given the anthropogenic and natural tendencies to reduce exposure to light during sleep mentioned above, might also reflect individuals' cumulative exposures to all kinds of light. If true, then this would justify consideration of individuals' cumulative time at sleep even in studies which contrast groups with assumed major differences in their average exposures to light (e.g., night shift workers *versus* other workers; the blind and visually impaired *versus* others). Individuals' cumulative time at sleep would then be a covariate which might help to explain *within-group* variations of the selected morbid end-point.

One possible way in which cumulative time spent at sleep might be parameterised for use in both retrospective cohort and case-control studies is suggested by recalling research from the late 1940s. At that time, American and British researchers independently investigated the suspected relationship between smoking and lung cancer [59, 60]. In retrospect, two "favorable facts facilitated" the studies: the association between smoking and lung cancer was strong (i.e., the relative risk of lung cancer among smokers was high), and it was easy to obtain information about exposure [61]. Smokers were simply asked when and how much they had smoked, so that exposure gradients could be based on the number of cigarettes smoked per day and the number of years smoked. In occupational medicine, we recognize indices such as WLM (working level months) to assess exposure to radon progeny, and in Germany fiber years are used to assess cumulative asbestos exposure for compensation purposes. Analogously, cumulative hours at sleep might be expressed in terms of 'sleep-years'. An average number of 6, 9 and 12 hours of sleep per day and year might correspond to 1, 1.5 and 2 sleep-years during any sensible time-window before manifestation of the disease of interest. Appropriate refinements of such dosimetry could be based on neuro-physiologic data (empirically, 6, 9 and 12 hours of sleep may more appropriately correspond to cumulative melatonin factors of 1, 1.25 and 1.5).

Advantages of the proposed index are that it is applicable in practice and that gradients are likely to be observed. Admittedly, the absence of an association between an index of sleep-years or some other measure of cumulative time spent in sleep on the one hand and disease incidence on the other would not constitute convincing falsification of the predictions (because the indices may not be sufficiently sensitive to real variations in melatonin production). But if cumulative time at sleep were to correlate significantly with disease then this

would suggest that there is a real effect with possibly important implications for public health.

Perspectives

Experimental research on relationships between light, hormones and cancer dates back many decades, but targeted epidemiological studies of the validity of the melatonin hypothesis and its corollaries are relatively recent. More such research is needed.

Further studies of the first two predictions ($P_1|H$ and $P_2|C$) will involve shift-workers and blind people. These groups, and the chosen reference populations, may differ not only in their exposures to light but also with respect to other determinants of health and disease. Therefore, even if additional studies continue to point to a link between light, melatonin and cancer, interpretation of those results as indicative of a causal chain of events can remain problematical. Moreover, in view of the rather special life conditions of shift-workers and of blind people, findings in these groups may not be generalisable securely to wider populations. On the other hand, soundly designed studies of healthy individuals at different latitudes, to test $P_3|C$ and $P_4|C$, would have the advantage that findings could be regarded as applicable to the general populations from which the study subjects are sampled.

A widely discussed article in *Science* has stated that "epidemiologists have succeeded in identifying the more conspicuous determinants of noninfectious diseases – smoking, for instance, which can increase the risk of developing cancer by as much as 3000%". Epidemiology, it was said, was now "left to search for subtler links between diseases and environmental causes or lifestyles" [62]. The implicit assumption, that all the important risk factors have now been identified and studied, may be wrong. In principle, difficult-to-study ubiquitous exposures could have major, but as yet unquantified, impacts on health and disease in human populations. Until rigorously proven otherwise, the electromagnetic radiation which humans see may seriously amplify risks of internal cancers such as cancer of the breast and prostate, and this could be true for both natural and anthropogenic light. With regard to man-made electromagnetic radiation alone it was suggested recently that "if physical forces introduced to society by industrialisation have biomedical [effects], ... the consequences would be literally incalculable" [63]. For the time being, however, comments on possible public health implications of the existing experimental and limited epidemiological data must be tempered with caution because of the considerable remaining gaps in knowledge.

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REFERENCES

1 Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J, editors. Cancer in Five Continents Vol. VII. Lyon: IARC Scientific Publication No. 143; 1997.
2 Huff J, Boyd J, Barrett JC, editors. Cellular and molecular mechanisms of hormonal carcinogenesis: environmental influences. New York: Progress in clinical and biological research Vol. 394. Wiley-Liss; 1996.
3 Panzer A, Viljoen M. The validity of melatonin as an oncostatic agent. J Pineal Res 1997; **22**:184–202.
4 Lewy AJ, Wehr TA, Goodwin FK, Newsome DA, Markey SP. Light suppresses melatonin secretion in humans. Science. 1980; **210**:1267–1269.
5 Reiter RJ. Melatonin: the chemical expression of darkness. Mol Cell Endocrinol 1991; **79**:C153–158.
6 Brainard GC, Lewy AJ, Menaker M, Fredrickson RH, Miller LS, Weleber RG, Cassone V, Hudson D. Dose-response relationship between light irradiance and the suppression of plasma melatonin in human volunteers. Brain Res 1988; **454**:212–218.
7 McIntyre IM, Norman TR, Burrows GD, Armstrong SM. Human melatonin suppression by light is intensity dependent. J Pineal Res 1989; **6**:149–156.
8 McIntyre IM, Norman TR, Burrows GD, Armstrong SM. Quantal melatonin suppression by exposure to low intensity light in man. Life Sci 1989; **45**:327–332.
9 Brainard GC. Signal transduction of light for melatonin regulation in humans. In: Stevens RG, Wilson BW, Anderson LE, editors. The melatonin hypothesis: breast cancer and use of electric power. Battelle Press Columbus Richland, 1997: p. 267–296.
10 Brainard GC, Hanifin JP, Rollag MD, Greeson J, Byrne B, Glickman G, Gerner E, Sanford B. Human melatonin regulation is not mediated by the three cone photopic visual system. J Clin Endocrinol Metab 2001; **86**:433–436.
11 Stevens RG. Electric power use and breast cancer: a hypothesis. Am J Epidemiol 1987; **125**:556–561.
12 Lerchl A, Partsch CJ, Nieschlag E. Circadian and ultradian variations of pituitary and pineal hormones in normal men: evidence for a link between melatonin, gonadotropin, and prolactin secretion. J Pineal Res 1995; **18**:41–48.
13 Portier CJ, Wolfe MS, editors. Assessment of Health Effects from Exposure to Power-Line Frequency Electric and Magnetic Fields – Working Group Report. NIH Publication No. 98-3981. EMFRAPID Program/LCBRA, NIEHS, NIH, PO Box 12233, MD A3-06, Research Triangle Park, NC 27709; 1998.
14 Tamarkin L, Cohen M, Roselle D, Reichert C, Lippman M, Chabner B. Melatonin inhibition and pinealectomy enhancement of 7,12-dimethylbenz(a)anthracene-induced mammary tumors in the rat. Cancer Res 1981; **41**:4432–4436.
15 Tamarkin L, Danforth D, Lichter A, DeMoss E, Cohen M, Chabner B, Lippman M. Decreased nocturnal plasma melatonin peak in patients with estrogen receptor positive breast cancer. Science 1983; **216**:1003–1005.
16 Grin W, Grunberger W. A significant correlation between melatonin deficiency and endometrial cancer.Gynecol Obstet Invest 1998; **45**:62–65.
17 Bartsch C, Bartsch H, Schmidt A, Ilg S, Bichler KH, Fluchter SH. Melatonin and 6-sulfatoxymelatonin circadian rhythms in serum and urine of primary prostate cancer patients: evidence for reduced pineal activity and relevance of urinary determinations. Clin Chim Acta 1992; **209**:153–167.
18 Reiter RJ. Historical Account of the Research Related to EMF, Melatonin and Cancer. In: Erren TC, Piekarski C, eds.: Low frequency EMF, Visible Light, Melatonin and Cancer"; International symposium; May 4–5, 2000; University of Cologne. Zbl Arbeitsmed 2000; **50**:298–314.
19 Doll R. Introduction and overview. In: Samet JM, editor. Epidemiology of lung cancer. Lung Biology in Health and disease. Volume 74. New York-Basel-Hong Kong: Marcel Dekker, Inc; 1994. p. 10–11.

20 Trichopoulos D. The discipline of epidemiology. Science 1995; 269:1326.
21 Wynder EL, Stellman SD. The "over-exposed" control group. Am J Epidemiol 1992; **135**:459–461.
22 Rose G. Sick individuals and sick populations. Int J Epidemiol 1985; **14**:32–38.
23 Tynes T, Hannevik M, Andersen A, Vistnes AI, Haldorsen T. Incidence of breast cancer in Norwegian female radio and telegraph operators. Cancer Causes Control 1996; **7**:197–204.
24 Hansen J. Increased breast cancer risk among women who work predominantly at night. Epidemiology 2001a; **12**:74–77.
25 Hansen J. Light at night, shiftwork, and breast cancer risk. J Natl Cancer Inst. 2001b; 17; **93**:1513–1515.
26 Davis S, Mirick DK, Stevens RG. Night shift work, light at night, and risk of breast cancer. J Natl Cancer Inst 2001; **93**:1557–1562.
27 Schernhammer ES, Laden F, Speizer FE, Willett WC, Hunter DJ, Kawachi I, Colditz GA. Rotating night shifts and risk of breast cancer in the Nurses' Health Study. J Natl Cancer Inst 2001; **93**:1563–1568.
28 Coleman MP, Reiter RJ. Breast cancer, blindness and melatonin. Eur J Cancer 1992; **28**:501–503.
29 Hahn RA. Profound bilateral blindness and the incidence of breast cancer. Epidemiology 1991; **2**:208–210.
30 Feychting M, Osterlund B, Ahlbom A. Reduced cancer incidence among the blind. Epidemiology 1998; **9**:490–494.
31 Pukkala E, Verkasalo PK, Ojarno M, Rudanko S-L. Visual impairment and cancer: a population-based cohort study in Finnland. Cancer Causes Control 1999; **10**:13–20.
32 Verkasalo PK, Pukkala E, Stevens RG, Ojamo M, Rudanko S-L. Inverse association between breast cancer incidence and degree of visual impairment in Finland. Br J Cancer 1999; **80**:1459–1460.
33 Kliukiene J, Tynes T, Andersen A. Risk of breast cancer among Norwegian women with visual impairment. Br J Cancer. 2001; **84**:397–399.
34 Feychting M, Ahlbom A. Re: visual impairment and cancer: a population-based cohort study in Finland. Cancer Causes Control 1999; **10**:637.
35 Pukkala E, Verkasalo P, Ojamo M, Rudanko SL. Response to the letter by Maria Feychting and Anders Ahlbom (Cancer Causes and Control 10: 637, 1999.) Why is the cancer pattern so different among visually impaired persons in Finland and Sweden? Cancer Causes Control 2000; **11**:99–100.
36 Czeisler CA, Shanahan TL, Klerman EB, Martens H, Brotman DJ, Emens JS, Klein T, Rizzo JF 3rd. Suppression of melatonin secretion in some blind patients by exposure to bright light. N Engl J Med 1995; **332**:6–11.
37 Erren TC, Piekarski C. Does winter darkness in the Artic protect against cancer? The melatonin hypothesis revisited. Med Hypotheses 1999; **53**:1–5.
38 Hatonen T, Alila-Johansson A, Mustanoja S, Laakso ML. Suppression of melatonin by 2000-lux light in humans with closed eyelids. Biol Psychiatry 1999; **46**:827–831.
39 Jean-Louis G, Kripke DF, Cole RJ, Elliot JA. No melatonin suppression by illumination of popliteal fossae or eyelids. J Biol Rhythms 2000; **15**:265–269.
40 Erren TC, Bjerregaard P, Cocco P, Lerchl A, Verkasalo PK. RE: "Invited commentary: Electromagnetic fields and cancer in railway workers". EMF dosimetry by geography – beyond black box epidemiology. Am. J. Epidemiol 2001; **154**:977–978.
41 Beck-Friis J, von Rosen D, Kjellman BF, Ljunggren JG, Wetterberg L. Melatonin in relation to body measures, sex, age, season and the use of drugs in patients with major affective disorders and healthy subjects. Psychoneuroendocrinology 1984; **9**:261–277.
42 Martikainen H, Tapanainen J, Vakkuri O, Leppaluoto J, Huhtaniemi I. Circannual concentrations of melatonin, gonadotrophins, prolactin and gonadal steroids in males in a geographical area with a large annual variation in daylight. Acta Endocrinol 1985; **109**:446–450.
43 Kauppila A, Kivelä A, Pakarinen A, Vakkuri O. Inverse seasonal relationship between melatonin and ovarian activity in humans in a region with strong seasonal contrast in luminosity. J Clin Endocrinol Metab 1987; **65**:823–828.
44 Kivelä A, Kauppila A, Ylostalo P, Vakkuri O, Leppaluoto J. Seasonal, menstrual and circadian secretions of melatonin, gonadotropins and prolactin in women. Acta Physiol Scand 1988; **132**:321–327.
45 Levine ME, Milliron AN, Duffy LK. Diurnal and seasonal rhythms of melatonin, cortisol and testosterone in interior Alaska. Arctic Med Res 1994; **53**:25–34.
46 Stokkan K-A, Reiter RJ. Melatonin rhythms in Arctic urban residents. J Pineal Res 1994; **16**:33–36.
47 Laakso ML, Porkka-Heiskanen T, Alila A, Stenberg D, Johansson G. Twenty-four-hour rhythms in relation to the natural photoperiod: a field study in humans. J Biol Rhythms 1994; **9**:283–293.
48 Weydahl A, Sothern RB, Wetterberg L. Seasonal variations in melatonin may modulate glycemic response to exercise. Percept Mot Skills. 1998; **86**:1061–1062.
49 Wetterberg L, Eberhard G, von Knorring L, Kohan MA, Ylipää E, Rutz W, Bratlid T, lacoste V, Thompson C, Yoneda H, Rosenthal NE, McGuire M, Polleri A, Freedman M, Morton DJ, Redman J, berigannaki JD, Shapiro C, Driver H, Yuwiler A. The influence of age, sex, height, weight, urine volume and latitude on melatonin concentrations in urine from normal subjects: a multinational study. In: Wetterberg L, editor. Light and biological rhythms in man. Oxford, UK: Pergamon Press; 1993. p. 275–286.
Wetterberg L, Bratlid T, von Knorring L, Eberhard G, Yuwiler A. A multinational study of the relationships between nighttime urinary melatonin production, age, gender, body size, and latitude.Eur Arch Psychiatry Clin Neurosci 1999; **249**(5):256–262.
Wetterberg L, Bergiannaki JD, Paparrigopoulos T, von Knorring L, Eberhard G, Bratlid T, Yuwiler A. Normative melatonin excretion: a multinational study. Psychoneuroendocrinology 1999; **24**: 209–226.
50 Blot WJ, Lanier A, Fraumeni JF, Bender TR. Cancer mortality among Alaskan natives, 1960–69. J Natl Can Inst 1975; **55**:547–554.
51 Miller AB, Gaudette LA. Breast cancer in circumpolar Inuit 1969–1988. Acta-Oncol 1996; **35**:577–580.
52 Kjaer SK, Nielsen NH. Cancer of the female genital tract in circumpolar Inuit. Acta-Oncol 1996; **35**:581–587.
53 Prener A, Storm HH, Nielsen NH. Cancer of the male genital tract in circumpolar Inuit. Acta-Oncol 1996; **35**:589–593.
54 Panzer A. Depression or cancer: the choice between serotonin or melatonin? Med Hypotheses 1998; **50**:385–387.
55 Cook MR, Graham C, Kavet R, Stevens RG, Davis S, Kheifets L. Morning urinary assessment of nocturnal melatonin secretion in older women. J Pineal Res 2000; **28**:41–47.
56 Perkowitz S. The physics of light and sunlight. Neuroendocrinol-Lett 2002; **23**(suppl 2): 14–16.
57 Cologne Symposium 2002. Light, Endocrine Systems and Cancer – Facts and Research Perspectives. Neuroendocrinol Lett 2002; **23**(suppl 2): 1–104.
58 Stevens RG, Wilson BW, Anderson LE. Synthesis and conclusions. In: Stevens RG, Wilson BW, Anderson LE, editors. The melatonin hypothesis: breast cancer and use of electric power. Battelle Press Columbus Richland, 1997: p. 739–747.
59 Wynder EL, Graham EA. Tobacco smoking as a possible etiologic factor in bronchogenic carcinoma. JAMA 1950; **143**:329–336.
60 Doll R, Hill AB. Smoking and carcinoma of the lung. Br Med J 1950; **2**:739–748.
61 Wynder EL. Invited commentary: response to Science article, "Epidemiology faces ist limits". Am J Epidemiol 1996; **143**: 747–749.
62 Taubes G. Epidemiology faces its limits. Science 1995; **269**: 164–169.
63 Horrobin DF. Brief Report of a Conference on Low Frequency Electro-Magnetic Fields, Visible Light, Melatonin and Cancer. In: Erren TC, Piekarski C, editors. Low frequency EMF, Visible Light, Melatonin and Cancer"; International symposium; May 4–5, 2000; University of Cologne. Zbl Arbeitsmed 2000; **50**:298–314.