

**The Darkness at the End of the Tunnel: Summary and Evaluation of
an International Symposium on Light, Endocrine Systems and
Cancer**

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Abstract

Research on light at night and cancer is evolving at an accelerating pace, fueled largely by exciting results in rodent toxicology and basic human biology. Epidemiologic research is at a relatively early stage of development in which the exposure surrogates such as shift work and blindness predominate. Causal graphs for shift work, light at night and breast cancer illustrate some of the subtleties that can arise in the use of exposure surrogates of different kinds. Baseline data on circadian rhythms and melatonin cycles among human populations living at different latitudes are needed. Epidemiologic study of this topic is expected to mature soon as studies begin to incorporate quantitative and semiquantitative measurements and personal histories of exposure to light at night. The current emphasis on breast cancer should widen to include other cancers and intermediate outcomes. An advance in epidemiologic studies of blind persons would be to compare cancer rates between the “cortically blind” and the “retinally blind” within levels of visual impairment. Without a proposed intervention to reduce exposure to light at night, attributable fraction and attributable caseload estimates are meaningless. In the near future, both epidemiologic and laboratory research in this area are expected to grow appreciably in scope and scale.

Introduction

It was a pleasure and an honor for an epidemiologist who has conducted no research on light, endocrine systems and cancer, and whose most recent laboratory work was concluded during the Nixon administration, to be asked to summarize and provide evaluative commentary on the International Symposium on Light, Endocrine Systems and Cancer at the University of Cologne, Germany, May 23, 2002. The organizers' desire for a fresh, unbiased perspective unavoidably brought them a perspective of naïveté and ignorance as well. Prudence thus dictates breadth in this closing commentary, with an occasional foray into the author's familiar terrain of general epidemiologic methods.

Consensus and Controversy

Without consensus there is no order. Without controversy there is no progress. In scientific work therefore, as in most other areas of human interaction, a homeostatic balance of discord and agreement is optimal. An optimal balance can be difficult to achieve and even more difficult to maintain. At one extreme, the creative tension created by differences of opinion can escalate all too easily into squabbling, intransigence and boredom. At the other extreme, the bonds of conciliation can tighten all too readily to form a strait jacket of orthodoxy.

In the author's experience, the potential for disrupting an optimal rhythm of consensus and controversy is heightened when a scientific problem is tackled simultaneously by epidemiologists and by toxicologists and other bench scientists. The life spans of laboratory experiments tend to be much shorter, and the costs much lower, than those of epidemiologic studies. This difference gives laboratory science a sizable evolutionary advantage over epidemiology. It is analogous to the advantages insects and microbes have over humans. The process of trial, error, and error reduction

that sometimes seems to occur at a glacial pace in epidemiology is, by contrast, highly accelerated in the laboratory. To cite but one example, Stevens [1] convinced the Nurses Health Study investigators to add information on shift work to their 1988 questionnaire. When the first results on shift work and breast cancer were published 13 years later, the authors had suggestions on better ways of wording questions about shift work in future studies [2]. During that same interval, a sequence of several laboratory studies could have been conducted, the methods and results from each study analogously informing the design of the next.

The many other differences between epidemiology and bench science are too numerous to be listed here. One notable distinction, however is this. Whereas laboratory researchers are almost by definition devoted to elucidating etiologic mechanisms, epidemiologists have a tradition of downplaying the importance of mechanistic understanding. This tradition is by no means uniform or unanimous, but it is strong. It has been captured by the highly evocative expression, “black box epidemiology” [3], which is meant to convey the notion that epidemiologic research is capable of showing convincing associations between health outcomes and exposures, and that these associations can form a crucial part of the basis for effective public health action, in the absence of a well characterized etiologic mechanism. Among the classically cited examples are Snow’s convincing epidemiology on the waterborne transmission of cholera, conducted decades before the *vibrio cholerae* was identified, and the persuasive epidemiologic case made for a causal effect of cigarette smoking on lung cancer incidence before the biologic mechanism for that effect was fully understood.

Laboratory researchers who are committed to the value of discerning etiologic mechanisms understandably rankle, and for good reason, when the virtues of black box epidemiology are extolled. Mechanistic understanding *is* important, and even indispensable. A complete and exquisitely detailed mechanistic understanding may not be essential for every prudent public health action to be taken;

but the more secure the etiologic understanding of mechanism, the greater the confidence will be in any action that is taken.

Sometimes we can prevent disease for the wrong reason, as in the draining of swamps based on miasma theory to reduce malaria rates. But when a better approximation to the right reason becomes known, as in the understanding of a parasite and its swamp-loving insect vector, the preventive opportunities are increased many times over. Thus, when the epidemiology is less than compelling and when actions entail large costs of money, convenience, comfort, pleasure, individual liberty, or other primary goods that are not health, a greater degree of certainty about what might be going on inside the black box of etiologic mechanism may be essential.

Moreover, even the classical examples of black box epidemiology tend to be mythologized. All experts and authorities were not instantly converted by Snow's epidemiology. The *vibrio cholerae* was ultimately identified. When it was, the options for public health action increased dramatically, from moving water intakes upstream and digging deep wells to the disinfection of polluted water. The hypothesis of a carcinogenic effect of cigarette smoke on bronchial epithelium was not devoid of biologic plausibility in the 1950s, and acceptance of the greater effect of smoking and cardiovascular disease was delayed by the lack of an equally plausible mechanistic hypothesis.

Against this backdrop of frequent conflict between black box epidemiologists and bench scientists' intent on discerning mechanism, it is refreshing to observe the current state of harmony among the disciplines in research on light, endocrine systems and cancer. At least as reflected by two days of interchange in Cologne, the balance between consensus and controversy seems close to optimal. There are disagreements, to be sure. But the arguments are not exclusively between epidemiologists in one camp and bench scientists in the other. Toxicologists are arguing with toxicologists. Epidemiologists are arguing with epidemiologists. Epidemiologists are listening to toxicologists.

Toxicologists are listening to epidemiologists. Laboratory researchers and epidemiologists are generating hypotheses for each other to test and attempting to test them.

Fittingly, the symposium's central figures were Russel Reiter, a bench scientist and charismatic leader who has championed research on pineal gland function and melatonin for many years, and Richard Stevens, an epidemiologist of slightly more recent vintage with an inordinately deep and abiding interest in what goes on inside the mechanistic black box. Together, they epitomized the productive mixture of harmony and dissonance that laboratory research and field epidemiology can produce when conditions are right.

The impression a novice to this field receives is that the laboratory science is moving ahead at a relatively rapid pace in comparison with the epidemiology. Results are being obtained, effects are being discerned, mechanisms are being delineated, in studies with rats and other non-human organisms. For the understandable reasons previously outlined, the epidemiology is proceeding at a more measured pace. There is nothing wrong with this. It may even be a desirable state of affairs. One is tempted to draw a contrast with research on hypotheses linking adverse health outcomes to extremely low frequency electric and magnetic fields (ELF-EMF). There the tension between epidemiologists and bench scientists is palpable. Epidemiologic studies, notably on childhood leukemia, provide more or less consistent evidence of an association that is difficult to explain with reference to known sources of error (chance, confounding, selection bias, etc.). But it is still largely an association in search of a mechanism, as over two decades of laboratory research have been frustrating. There, the black-box instincts of the epidemiologist rub abrasively against the bench scientist's inexorable logic that if there is an effect, that effect must have a mechanism. When the laboratory research is leading the way, as it is at the present stage of research on light and cancer, conditions are far more amenable to a healthier blend of controversy and consensus.

Using the Epidemiologic Method to Study Light and Cancer

Outcomes

In contrast with the laboratory science, it is easier to characterize the evolution of the epidemiologic work in this area of research because of its more measured pace. Thus far, attention has focused principally on female breast cancer and its known estrogen modulation. Stevens [1], notably, has postulated an effect by light at night on breast cancer by a pathway by which light affects melatonin, melatonin affects estrogen, and estrogen affects breast cancer. This hypothesis has thus far withstood 15 years of critical scrutiny and empirical research, inside the laboratory and out in the epidemiologic field. No one should be surprised, however, if the story turns out to be more complex than that. The author, for instance, would be highly surprised if it were to turn out that everything that affects breast cancer risk does so by affecting estrogen. Melatonin itself is a hormone and Vollmer et al. [4] provide a glimpse of the exceedingly complex world of endocrine modulation. The exciting work by Blask et al. [5] on chemical carcinogenesis and mechanisms involving tumor uptake of linoleic acid in rat models typifies the expansion of hypothesis and evidence beyond breast cancer and estrogen.

The impact on epidemiologic research should be at least twofold. First, in addition to continued investigation of female breast cancer in connection with light exposure and circadian disruption, other cancers should be placed onto the light at night research agenda. Prostate cancer is an obvious example because of the strong evidence of its hormonal etiology. In time, however, epidemiologic research in this area may well extend to tumors that at present are not typically thought of as “hormonally mediated cancers”. In fact, it may not be too bold to envision a time when the sharp demarcation of cancers into those that are hormonally mediated and those that are not may become blurred, if not ultimately erased altogether.

The second impact on epidemiology of the burgeoning laboratory research in this area should be more emphasis on epidemiologic studies of intermediate outcomes short of overt cancer. Some of the more obvious possibilities might involve prostate cancer, with its vast reservoir of preclinical disease and the widespread availability of test methods for prostate-specific antigen. A question that did not receive as much explicit attention at the symposium as it must in some forum is this: Among the findings in rats and other species that can be studied ethically in humans, which should be given the highest priority for such replication?

This question might have a tendency to fall into a crack in the research agenda. Among laboratory researchers, a view of varying temporal and interindividual strength exists that findings that can be replicated in rodents may not need to be demonstrated in humans. This view, of course, is less a dogma than a usually implicit corollary of the case for studying rodents at all. Among epidemiologists, cancer epidemiologists tend to do different kinds of studies from epidemiologists whose research skills are best suited to studying short term effects on intermediate endpoints. Thus, there may be no strong proponents as of yet in this research area for creating and pursuing a research agenda for the study of outcomes short of cancer in humans. If so, this is a problem that could be solved rather readily by convening laboratory researchers and epidemiologists, more broadly defined than cancer epidemiologists, to address this question specifically.

Populations and exposure sources

Thus far, the epidemiologic study of light and cancer has been largely confined to three approaches: studies of latitude, studies of shift workers, and studies of the blind. Each of these takes advantage of special exposure situations. Each has its own set of advantages and disadvantages. Ultimately, attempts will be made to study general populations with some attempt to assess light exposure from multiple sources.

Parallels with nutritional epidemiology are easy to draw. The study of groups with special light exposures is analogous to studies of populations with special diets, such as vegetarians. Future studies of light exposure from multiple sources in general populations will face challenges analogous to those faced by nutritional epidemiologists who for decades have attempted to measure histories of intake of foods and nutrients with instruments such as the food frequency questionnaire.

Latitude

The use of latitude of residence as a light exposure metric is ably discussed by Erren [6]. Such studies may be ecologic in their design, comparing populations at different latitudes, with all the uncertainties, potential for intractable confounding, and special biases that are peculiar to ecologic designs. Or a study of latitude might be at the individual level in its design, but ecologic in its exposure metric. This is the combination incorporated into the proposed research plan Erren describes for a biomarker study of healthy general populations in a wide range of latitudes. This is essential research that will characterize light exposures, melatonin cycles, and circadian rhythms from the Arctic to the Mediterranean, in a systematic and comprehensive way, to supplement what now exists primarily as a scattered set of small studies and isolated reports. It will not answer any questions about cancer and light, but solid research to answer those questions will not be able to be designed sensibly without the information this crucial baseline study will produce.

Studies of migrants were among the earliest epidemiologic research providing strong evidence that the etiologies of many cancers, including breast cancer, have environmental etiologies, with “environmental” very broadly defined. Classical studies of international migrants have shown with remarkable consistency that rates of many cancers, including breast cancer, begin to approximate those of persons native to the country of adoption within a generation or two [7]. Presumably, one must now add light to the list of possible contributory factors. For instance, although the movement

of Japanese migrants from Japan to Hawaii to California may not have entailed a pronounced change in latitude, it might have been accompanied by an appreciable change in light exposure. One can imagine agrarian lifestyles in Japan early in the 20th Century dominated by bright light outdoors during the day and darkness at night, shifting inexorably for migrants to indoor work with less bright light during the day and bright light indoors at night a generation or two later.

A final note about latitude is that solar radiation exposure is determined by far more than mere latitude. On a map Perkowitz [8] showed of the United States, parts of Texas receive less solar radiation than parts of Northern California. This variability, if it is taken adequately into account, will be an epidemiologic advantage. Confounding factors that vary strongly with latitude may be less intractably correlated with actual solar radiation levels.

Studies of shift workers

As Stevens [1] notes, the literature now contains three studies of shift work in relation to breast cancer. One should expect that in a decade the number of such studies will increase by several fold. Thinking about shift work as a surrogate measure of exposure to light at night caused the author to begin a catalog of the various ways in which a measured variable can serve as a surrogate for an exposure of interest. Four such ways are depicted in Figure 1, using Pearl's formalized system of causal graph notation of Pearl [9, 10], which epidemiologists recognize as a systematization and extension of the traditional "confounding triangle."

A measured variable that serves as a surrogate for an unmeasured exposure can be a causal intermediate between the exposure and the disease (Figure 1A), an extraneous effect of the exposure (Figure 1B), an effect of a cause of the exposure (Figure 1C), or a cause of the exposure (Figure 1D), among other possibilities. Epidemiologists tend to be satisfied with the mere presumption that a surrogate is associated with the exposure of interest, without drawing explicit distinctions among

these, and other, ways in which those associations may come about. The author suspects, however, that these distinctions may have implications for the validity of effect measures that are estimated for the surrogate when the exposure is not measured.

Shift work as a surrogate for light at night is arguably an example of the relation shown in Figure 1D and, more specifically, in Figure 2A, where shift work causes exposure to light at night, which causes breast cancer. It is possible, of course, that shift work might affect breast cancer in ways that do not involve light at night. Thus, one analytic strategy might be to adjust for factors, labeled U_1 in Figure 2B, that lie on these other hypothetical causal pathways. As several authors have noted [10-15], this strategy may be described as an attempt to estimate a “direct” effect of shift work with regard to these other pathways; that is, a portion of the shift work effect that is mediated through pathways involving light at night.

Several cautions are in order in this regard. First, the effect being estimated is an effect of shift work, however partial, and not an effect of light at night. There are sources of exposure to light at night other than shift work. Exposure to light at night varies among shift workers. In plausible scenarios, this imperfect correlation between the surrogate, shift work, and the exposure of interest, light at night, would cause the effect of the former to be lower than the effect of the latter, even if both were estimated perfectly [16].

Second, the estimated effects of factors U_1 could be confounded by common causes of those factors and breast cancer, which would need to be measured. These confounders could be adjusted by standard methods as long as none of them are affected by shift work. Any that are affected by shift work, as depicted by U_2 in Figure 2B, would need to be adjusted by special methods, such as Robins’ g-estimation algorithm [11, 12], direct effect nested structural models [17], or marginal structural models [18].

Third, classical confounders of the estimated shift work effect, shown as U_3 in Figure 2B, would need to be measured and adjusted by standard methods. Finally, factors that would confound the estimated effect of light at night, were it measured (U_4 in Figure 2B), would not confound the estimated shift work effect and should not be adjusted, even though shift work is considered a surrogate for light at night. Arguably illustrative members of the three covariate classes in this context might be parity in U_1 , age at first full-term pregnancy in U_2 , alcohol consumption in U_3 and social class in U_4 .

As a consequence of the foregoing analysis, it appears that the use of a surrogate for exposure is not as simple a matter as we might tend to think. The use of other kinds of surrogates, including but not limited to those depicted in Figures 1B through 1D, would be expected to produce their own peculiar sets of complicating circumstances. See Robins [19] for other subtleties that can arise in examples with the same basic structure as Figure 1D, but with the surrogate and the exposure both measured.

Fortunately, when an attempt is made to measure light at night rather than to use variables such as shift work as surrogates, the methodologic issues become conceptually simpler, as shown in Figure 2C. The factors depicted by U_1 , U_2 , and U_3 in Figure 2B would not confound the estimated effect of light at night and thus are not shown in Figure 2C. Shift work, if it has an effect on breast cancer other than its effect on light at night (as in Figure 2B), would become a classical confounder, along with the factors U_4 .

This conceptual simplification would come at a steep price, however: Light at night is much more difficult to measure than shift work. The challenge would shift from identifying the proper covariates to adjust and using suitable methods to adjust them, without any hope of actually estimating a light at night effect, to measuring and specifying light at night and its confounders accurately, omitting any factors affected by light at night. As previously noted, this light at night measurement challenge

would be analogous to the challenge in nutritional epidemiology of estimating lifetime intake histories of nutrients present in wide varieties of foods. One might expect to see an effort to develop and validate light at night source frequency questionnaires and source-light data bases, analogous to the food frequency questionnaires and food-nutrient data bases that have been developed in nutritional epidemiology over many years, with arguable success.

A final note is in order concerning the evolution from studying shift work as a surrogate for unmeasured light at night exposure to studying shift work as a source (and potential confounder) of measured light at night exposure. That is the presently ill-defined relationship between sleep disruption and exposure to light at night. The two are obviously correlated in free-range human populations. Sometimes the causal arrow goes from sleep disruption to light at night. Other times, the arrow goes in the opposite direction. The author is unaware of the degree of overlap between sleep researchers and light at night researchers, especially in the laboratory. At the symposium, however, sleep disruption was seldom mentioned. And when it was, it tended to be mentioned in ways that were somewhat disquieting. Sometimes sleep disruption was equated with light at night exposure, sometimes one was invoked as a cause of the other, sometimes the other was invoked as a cause of the one, and other times hints were dropped of potential synergism between the two.

The issues differ dramatically between the rodent cage and the human environment. In studying rodents, investigators typically control the light regime and merely observe the sleeping behavior. Among humans, both must be observed in non-experimental research, of course. But both can be controlled, not only in the human laboratory but in real-world applications. Humans can and do attempt to control their sleeping behavior, their exposure to light at night, or both. It would be wise to begin to take steps to disentangle these complex interrelationships now, rather than to allow sleep research and light at night research to go their separate ways.

Studies of the blind

As Stevens [1] has noted, several studies have been conducted of breast cancer among blind women. We might expect to see several more such studies emerge as time goes by. Of note is the report by Verkasalo et al. [20] of a trend of decreasing breast cancer incidence on a scale of increasing visual impairment, with the highest rate among women with moderate low vision to the lowest rate among women with total blindness. Stevens [1] and Brainard [21] describe basic research that might lead to testable hypotheses concerning these and other epidemiologic results. Scales of visual impairment such as the one used by Verkasalo et al. might well vary in their correlation with the degree to which light signals might be received by the retina and transmitted to the pineal gland. It appears, as an oversimplification, at least theoretically possible that epidemiologic researchers might be able to distinguish the “retinally blind,” for whom no signal would reach the pineal gland, from the “cortically blind,” for whom the retinal receptors and pathways to the pineal gland would remain intact despite their visual loss. If so, and if a distinction between the unilaterally and bilaterally blind can be added to the scale, the result might be a considerable improvement in overall exposure assessment in studies of the blind.

Attempts should be made along these lines, not only for new studies, but for existing studies such as the one by Verkasalo et al. It would be possible for the monotonic trend in breast cancer incidence the investigators reported to be strengthened or weakened by improved exposure scaling. If the pineal glands of one-third of profoundly blind persons can respond to bright light, as has been reported [22, 23], we should expect to see an association with pineal light response among the profoundly blind. If it can be accomplished, such an analysis would constitute a crucial test of the light hypothesis as an explanation for the decreased breast cancer incidence reported thus far among blind persons.

Of additional interest with regard to studies of the blind is the decision by Stevens [1] to perform an attributable fraction and attributable caseload computation. As he correctly notes, such computations are usually reserved for situations in which a high degree of certainty in the causal hypothesis has accrued. The reason for this caution is that attributable caseload figures are highly newsworthy and exceedingly liable to sensationalisation. Curiously, Stevens' computation was motivated by an unpublished attributable caseload figure that appeared in news coverage. Stevens estimates the briefly reported figure to correspond to approximately 800 attributable breast cancers per year in the United States. Among its many limitations, this figure is not for light at night, but for rotating shift work in a study whose investigators, as previously noted, had second thoughts about the manner in which they asked study participants about their shift work histories. Nevertheless, Stevens finds the figure of 800 attributable breast cancers per year in the United States so low as to trivialize unfairly the etiologic hypothesis for light at night, which might turn out to have considerably greater public health potential than that figure seems to convey. The question, however, is how much?

As the basis for an alternative computation, Stevens chooses not studies of shift work, but studies of the blind. The change in the definition of the "high risk group" is dramatic. Whereas only about 1% of United States women are estimated to engage in rotating shift work, 98% of all women are sighted. The rationale Stevens offers for using the sighted as the "exposed group" is an argument going back at least to Walter [24], and recapitulated more recently by Wacholder [25]. It is that, under very specific conditions, the population attributable fraction is unbiased by the use of a binary exposure scale that is so sensitive (i.e., so good at identifying true positives) that the number of false negatives is reduced essentially to zero.

Greenland [26], however, has shown that the approach of using such a "broad definition of exposure" [25] is highly sensitive to three presumptions. One is that exposure misclassification does

not differ by disease status. The other is that distributions of degree of exposure within the broadly defined “exposed group” are invariant between populations, in particular the study population and the target population for the computation. The presumption of nondifferential misclassification is reasonably secure in cohort data such as those of Verkasalo et al. [20]. The presumption that the distributions of degree of exposure (e.g., of exposure of the pineal gland to transduced light signals) within the broadly defined exposed group, the sighted, do not differ between women in Finland and in the United States is much more difficult to assess. One might also add that the results of Verkasalo et al. [20] and others suggest that there is variation in breast cancer incidence, and presumably of pineal exposure to transduced light signals as well, within this computation’s “unexposed group,” the blind.

The third presumption that Greenland [26] stressed, however, was one that Wacholder [25] stressed as well, and that is grossly violated by Stevens’ computations. This is the presumption that the interest and intent is in eliminating an exposure entirely, rather than in reducing less completely the proportion of exposed persons in a population or in shifting its exposure distribution in some other way. Technically, Stevens’ attributable caseload computation are for an unimaginably grotesque intervention that would blind the 98% of United States women who currently are sighted. This is clearly ludicrous. Thus, Stevens’ computations that 30,000 to 80,000 breast cancers a year in the United States might be “attributable” to light at night are indefensible.

Few specific recommendations have been made for public health actions to control light at night. Those that have been made have been very general, seldom amounting to little more than, “Try to avoid bright light at night as best you can”. In modern societies, neither shift work nor many other activities requiring or currently entailing bright light at night will be eliminated anytime soon. When experts do try to imagine specific recommendations, they tend to refer to research that is yet to be done. One example is the possibility of identifying specific light frequencies that might be

responsible for, say, a breast cancer effect and redesigning artificial lighting sources to exclude those frequencies. As Perkowitz [8] and Brainard [21] note, there are encouraging leads from the laboratory along these lines, but they are far from forming a sufficient basis for a massive program of light source redesign. And even in the most optimistic future scenario for this research, no one would seriously project that light source redesign might have an effect comparable to the unthinkable intervention of blinding all currently sighted women.

It is devoid of meaning to claim that a fraction of a population's caseload of a disease is attributable to a given exposure without at least alluding to at least a potentially realistic intervention that might reduce a population's exposure enough to achieve a caseload reduction of that magnitude. No intervention based on research as it exists today could achieve caseload reductions anywhere near the 30,000 to 80,000 attributable breast cancers in the United States each year that, according to Stevens' computations, might be achieved if every sighted woman were blinded. These figures are not "useful as an upper limit." They are far higher than any reasonable upper limit that might be tenably defended at the present time.

Conspectus

Scientists in a given field of inquiry seldom feel that their topic receives too much public attention or research funding. Laboratory and epidemiologic investigators in the nascent area of light and night and cancer are no different. But the days of relative neglect are almost certain to change. Not only the disadvantages but the advantages as well of working in a small, low-profile research program will soon be transformed into those of big-time, managed science. Researchers on light at night and cancer will quickly find what they have been seeking: the darkness at the end of the tunnel. One

hopes that they find a way to maintain their healthy balance of controversy and consensus along the way.

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Figure 1. Causal diagrams for four ways in which a measured variable can serve as a surrogate for an unmeasured exposure that affects a disease. A. The surrogate lies on a causal pathway from the exposure to the disease. B. The surrogate is affected by the exposure but does not affect the disease. C. The surrogate is affected by a cause of the exposure but does not affect the disease. D. The exposure lies on a causal pathway from the surrogate to the disease.

Figure 2. Causal diagrams depicting hypotheses that shift work affects light at night, that light at night affects breast cancer and that shift work affects breast cancer through other causal pathways. A. A simplistic diagram assuming no confounding when shift work is measured and light at night is not. B. Some classes of variables that can confound the estimated effect of a portion of the shift work effect that is mediated by light at night, U_1 through U_3 , and one class that does not, U_4 . C. Shift work and U_4 , other variables that can confound the estimated effect of light at night when it is measured, given diagram 2B.