



Letter to the Editor

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Response to Ijaz S, et al. "Night-shift work and breast cancer - a systematic review and meta-analysis"

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There continues to be strong interest in the possibility that working non-day hours is associated with an increased risk of cancer, most notably breast and prostate cancer. There is now a substantial body of scientific evidence regarding this question. The findings to date from numerous epidemiologic studies, employing both case–control and cohort designs, support such an association although there are some inconsistencies, particularly in the definition of “shift work”. Most studies find an association but a few do not.

One alternative to the comparison of individual studies is a formal meta-analysis that combines data from several studies and treats those data as one large study. Although meta-analyses can be informative, they are subject to a number of important limitations that must be considered in interpreting the results and drawing conclusions. Perhaps the most difficult aspect of conducting a meta-analysis is the degree of similarity among studies, both in design and execution. Especially important in this regard is the assessment of exposure.

Ijaz et al (1) recently published the results of a new meta-analysis designed to evaluate the epidemiological studies of night shift work and breast cancer risk. Although this appears to be a carefully done study, it is also a good example of the inherent limitations of meta-analyses and the effects of such shortcomings on the final disease risk estimates. Of primary concern is that the studies included in Ijaz et al’s meta-analysis employed very different methods to define the exposure, such that no two studies defined their primary exposure variable(s) in exactly the same way. Each study is different regarding the definition and use of factors that can characterize non-day work. These include: (i) shift system (eg, rotating or permanent, start, and end times, etc.); (ii) years on shift; and (iii) shift intensity (time-off between shifts) (2). These more detailed aspects of non-day shiftwork will influence circadian rhythms, melatonin suppression, and sleep deprivation; all of which are hypothesized to be etiologic factors for breast and perhaps other types of cancer as well.

Thus, it is vitally important that indicators of exposure to factors associated with non-day work be as accurate and reproducible as possible. This would greatly improve the ability to compare results across studies, and future studies would be much more uniform in

exposure assessment. Current approaches can result in substantial degrees of exposure misclassification. This occurs in two different ways. One is general misclassification, often referred to as non-differential. This tends to reduce the risk estimates towards the null, therefore reducing the magnitude of the exposure–disease association. If the misclassification is strong enough, it can even mask true associations. The other is differential exposure misclassification, which can bias results in either direction. For example, it is not difficult to imagine that the probability of whether an identified subject would or would not participate in a given study could depend on their work schedule; day workers are more difficult to reach by, for example, telephone and therefore controls over-represent night workers compared to the general population.

“Shift work” as assessed in some of the case–control studies that used personal interviews was not subject to any significant recall bias because it was derived from detailed occupational histories, which are accurately remembered by most people. It should also be kept in mind that several of the case–control studies used existing occupational records for workers and so no interview was conducted at all; and, in almost all of the case–control studies that did use interviews, those interviews were conducted before the International Agency for Research on Cancer (IARC) evaluation of October 2007 and thereby before the light-at-night hypothesis was widely publicized.

The original reason for examining the non-day shift was as a surrogate for melatonin suppression and “circadian disruption” from electric light at night. Non-day workers were presumed to have more of this exposure than day workers. However, all women in the modern world are exposed to electric light to some extent during the period from dusk to dawn. So in all the epidemiological studies of shift work, the comparison group of day-working women also have a history of exposure to light-at-night. Therefore, if light-at-night does increase the risk of breast cancer, then the shift work studies only capture a small portion of the societal impact.

A major limitation of meta-analyses is that internal validity largely depends on the quality of the primary contributing studies; in other words, a meta-analysis cannot overcome the methodological limitations inherent

to the design of each individual study. The conclusions of Ijaz et al (1) depend crucially upon their subjective assessments of “quality”, and those assessments are not compelling for many of the studies. Their methods for defining “long-term” are also problematic. Other investigators who have recently published meta-analyses on the same topic (3, 4) came to different conclusions regarding the quality of several of the individual studies and the overall result. Finally, a recent case–control study not included in these meta-analyses also gives support to the association between long-term, non-day work and breast cancer risk (5).

Given the vastly different exposure metrics used in each study, heterogeneity in results should be expected. Despite the dissimilarity of study design and an unknown but possibly substantial degree of non-differential exposure misclassification, Ijaz et al (1) do observe a 5% significantly increased risk of breast cancer per each five years of non-day work [risk ratio (RR) 1.05, 95% confidence interval (95% CI) 1.01–1.10] based on 12 studies. The authors assert that the cohort studies in their meta-analysis found little or no association, yet the case–control studies did; this, they suggest, is due to recall bias in the case–control studies, although as noted above recall bias almost certainly did not occur in those case–control studies. In addition, two of the three cohort studies included in the meta-analysis clearly report significantly elevated risks for long-term exposure, which is at odds with the authors’ assertion of a meaningful difference between the case–control (N=9) and cohort (N=3) results.

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