multivariable model replicates the question confronting the clinician: what does knowledge of *BRAF* V600E status add to existing clinical staging? As we discussed in our Editorial, the analyses by Xing et al suggest that *BRAF* V600E testing does not contribute to the predictive value for PTC-related mortality beyond the information gleaned about aggressive tumor characteristics reported by a pathologist or radiological evaluation.

In contrast, the interaction analyses investigate one tumor feature at a time, under the assumption that the examined tumor feature is independent of the other tumor features. Review of Table 3 in the article shows this is not the case. In the example we cited in our Editorial, of the 45 patients with PTC who died and whose tumors harbored *BRAF* V600E mutations, 34 had distant metastases and 39 had lymph node metastases. At a minimum, 62% of the patients positive for *BRAF* V600E who died had both distant metastases and lymph node metastases, rendering questionable the validity of examining these clinicopathological features independently.

In response to Xing's second point, it would be irresponsible to present a mortality analysis without adjusting for age. It is only through age adjustment that one can discern if patients of similar age have a higher or lower risk of mortality depending on their *BRAF* V600E status.

In response to the third point, there were only 3 deaths in the 1311 patients who had stage I or II disease. Two deaths occurred in patients who had a positive *BRAF* V600E test and one occurred in a patient with a negative *BRAF* V600E test. It is a testament to the overall low mortality of stage I and II disease that a test does not exist to discriminate PTC-related mortality in these patients.

The ability of *BRAF* V600E testing to predict PTC recurrence is an important issue but it is outside the scope of the analyses presented in the study by Xing et al. We fully agree with the conclusion of the article: "These findings support further investigation of the prognostic and therapeutic implications of *BRAF* V600E status in PTC."

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Melatonin Level and Risk for Type 2 Diabetes

To the Editor The finding of an inverse relationship between melatonin level and risk for developing type 2 diabetes in the Nurses' Health Study (NHS) cohort[1] potentially provides additional evidence for the emerging recognition that disruption of circadian timing increases the risk for metabolic and cardiovascular disease.[2]

One of the unique factors of the NHS cohort is exposure to a significant amount of shift work. Previous analyses of the parent cohort found that women working rotating night shifts had an increased risk of developing type 2 diabetes that was cumulative, with the highest risk seen in individuals working rotating shifts for more than 20 years.[3] Additional analysis of this same cohort has shown that cumulative exposure to shift work also increases the risk for stroke.[4] These findings suggest that chronic circadian misalignment may be more detrimental to health than current exposure to shift work.

The question then is whether the lower urinary melatonin levels observed in this study served as a marker for underlying circadian misalignment related to cumulative (though, as the authors pointed out, not necessarily current) shift work. It has previously been demonstrated that working 8 or more night shifts per month results in significantly lower urinary melatonin levels compared with workers exposed only to day shifts[5]; however, it is not known how long the decreased melatonin levels persist after stopping shift work.

As the authors proposed, even though there certainly is evidence for a direct effect of melatonin on metabolism, the question is to what degree the changes in melatonin levels are directly responsible for the magnitude of risk observed. In addition, it is biologically plausible that lower melatonin secretion is a surrogate marker for underlying circadian misalignment of multiple behavioral, biological, and rhythmic processes that are known to regulate energy balance.

Circadian dysregulation due to unconventional work schedules or social media is common in modern society, but its effect on health remains underrecognized. The universal practice of exposure to light at night can adversely affect circadian alignment and suppress melatonin, resulting in increased risk for cardiometabolic disorders. Therefore, circadian and sleep-based approaches have the potential to open new avenues for improving cardiometabolic health.

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In Reply Drs Abbott and Zee comment on the possibility of lower urinary melatonin levels serving as a marker for underlying circadian misalignment related to cumulative shift work. We have also contemplated the possibility that melatonin levels are simply a reporter of circadian alignment rather than a marker for abnormal glucose metabolism.

Melatonin levels among individuals in the NHS have been shown to be inversely associated with the number of night shifts performed in the 2 weeks preceding the measurement,[1] whereas no association was found between melatonin levels and the total number of years of previous shift work for individuals in the NHS.[2] This suggests that shift work likely does not have a sustained effect on melatonin secretion.

Additionally, the association of increased shift work with increased risk of incident type 2 diabetes shown in the NHS cohort appeared to be largely mediated by increased body mass index,[3] whereas the association of melatonin with incident type 2 diabetes in our study was independent of body mass index. Nevertheless, we think that Abbott and Zee raise an important issue about the relationship between other forms of chronic circadian misalignment and melatonin secretion.

If the low levels of nocturnal melatonin secretion within our cohort were indeed attributable to circadian misalignment due to factors other than prior or current shift work, then the association between low melatonin secretion and incident type 2 diabetes could simply represent an association of circadian misalignment and incident type 2 diabetes. Careful studies are needed to delineate which circadian intervention may be suited to beneficially affect glucose metabolism and whether melatonin levels are a modifiable risk factor.

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Therapy for Chemotherapy-Induced Peripheral Neuropathy

To the Editor Dr Smith and colleagues[1] concluded that "among patients with painful chemotherapy-induced peripheral neuropathy, the use of duloxetine compared with placebo for 5 weeks resulted in a greater reduction in pain."

The overall strength of effect underpinning this conclusion, however, is relatively small, despite reaching statistical significance. The authors most clearly demonstrated this in Figure 2 in the article, which shows closely approximated or overlapping confidence intervals in both the initial and crossover treatment periods.

Small effects, which are difficult to interpret clinically, are a common problem in pain studies.[2] One of the reasons for this is the use of placebo in the inactive group of randomized controlled pain trials, without appropriate adjustment for the dynamic nature involved in the placebo phenomenon.

Rather than being an inactive effect, the endogenous opioid system has been shown to underlie the placebo response.[3] In the context of pain trials, the importance of this is obvious: if the primary outcome measure is a decrease in mean pain score, stimulation of the naturally occurring analgesic system in the control group of the study could be influential and needs to be accounted for. In parallel design neuropathic pain trials, the response to placebo has been shown to range between 4% and 44% of the mean change in pain score from baseline.[4]

Failure to consider this possible confounding physiological phenomenon can result in underestimation of effect size. This may have influenced Smith et al's findings. Not accounting for the influence of placebo in pain trials can even lead to oversight of clinically important effects.

One possible way to overcome this problem is to include functional magnetic resonance imaging (fMRI) in pilot studies and trial methods. Functional MRI has yielded important insight into both the placebo and pain responses of individuals.[5] Robust use of this research tool allows for a priori stratification based on characteristics of likely responders. This optimizes trial design and interpretation of the results and allows for confident implementation of research findings into clinical practice.

An argument against use of fMRI is that it remains expensive. However, in the context of large pain trials, which are financially and organizationally taxing, the main aim both scientifically and ethically is to produce conclusive results. Because appropriate implementation of fMRI can help achieve this purpose, its use in large pain trials is arguably a worthwhile investment.

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