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Time scale in follow-up studies: considering disease prognosis

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To the Editor:

Colonge et al.'s manuscript on the choice of primary time scale for epidemiologic follow-up studies makes an important contribution to methods for longitudinal data analysis.¹ We agree with their assessment that the choice of time scale should be based on "the goals of the study and the need for confounder adjustment." As the authors say, in most studies of disease *incidence*, age will be the appropriate time scale (especially when compared to time on study), but there may be other relevant time scales for different applications. For example, in studies of disease *prognosis*, time since onset or diagnosis is commonly used.^{2, 3} In a study examining the association between the use of a particular medication and breast cancer recurrence, time since initial breast cancer diagnosis may be an important confounder and one that should be accounted for flexibly. Risk of breast cancer recurrence depends on time since diagnosis in a complex way (Figure 1, unpublished data). And, time since diagnosis might also be associated with the exposure of interest, making it a confounder. If time since diagnosis is chosen as the time scale, age should be adjusted for as a covariate in multivariable regression models as it, too, is related to the recurrence risk. The choice of age as a timescale (with adjustment for time since diagnosis) is not incorrect for this application as age is also associated with recurrence risk and, in some cases, exposure; however, we think using time since diagnosis may adjust more completely for confounding in some studies of disease prognosis. If both elements of time are potential confounders, both should be accounted for – one as the timescale and one as a covariate in the model. The interpretation of the hazard ratios is essentially the same regardless of which is selected as time scale and which is modeled; however, the choice may affect the ability to control for confounding. Whether it is better to use age or time since diagnosis as the time scale in studies of prognosis may depend on the specific application; in some cases, it may not affect the results.⁴ With the growing interest in follow-up studies of disease outcomes, additional research on how to select among multiple biologically relevant time scales is necessary.

References

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Figure 1. Kernel-smoothed estimate of hazard of second breast cancer event over years since diagnosis by age at diagnosis, in a cohort of early stage breast cancer patients diagnosed in 1990–2008.