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LETTER TO THE EDITOR

RE.: Impact of long-term lipid-lowering therapy on clinical outcomes in breast cancer

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In a recent publication in *Breast Cancer Research and Treatment,* Li et al. investigated the association between long-term lipid-lowering therapy on clinical outcomes in patients with breast tumors. The study enrolled 1523 patients with ductal carcinoma in situ (DCIS) or invasive breast tumors. Use of statins for at least 5 years ($n = 207$) was associated with improved disease-free survival compared with nonusers. However, the association was not detected in patients who had been exposed to statins for less than 5 years.

There are several potential shortcomings of the study, which may have influenced the study findings.

The inclusion of patients with DCIS and invasive breast tumors leads to a highly heterogeneous study population. DCIS patients are unlikely to die of their disease, and consequently DCIS patients have a survival advantage over patients with invasive breast cancer. We also note a large proportion of missing data regarding tumor stage, lymphovascular invasion, and tumor grade, which may be attributable to the inclusion of DCIS patients. However, there is no information on how missing data are handled in the analytic approach. Furthermore, a description of how patients with previous cancers were handled is lacking.

The definition and subsequent analytic approach when classifying exposure to lipid-lowering drugs is poorly described. Li et al. followed patients from 1995 to 2015. Accordingly, patients had to survive a certain time period in order to be classified as "long-term users" yet there is no evidence in the paper to suggest that Li et al. used a time-varying analytic approach to correctly categorize drug use. Therefore, we believe the study may be prone to immortal time bias. Immortal time bias refers to a period of time during follow-up in which the study outcome could not occur as the study subject has to stay event free to become classified as exposed [1]. Li et al. fail to provide any information regarding how prevalent statin users were managed in the statistical analysis. The inclusion of prevalent users is likely to introduce selection bias [2]. To be able to interpret and compare the results of the study by Li et al. with results from previous studies, further details regarding the description of the exposure variable—statin use—are needed.

The approach to selecting covariates includes forward and backward selection of covariates in the multivariate model, which is not recommended [3].

Although the study results agree with previous studies [4], the methodological limitations of the analyses are extensive. We encourage the authors to revise their analyses—restricting to patients with invasive breast cancer, and include a thoughtful specification of the multivariable regression model, or perhaps better, analyze the data by cloning, censoring, and weighting the observations as suggested when comparing short versus long-term exposure [2].

Compliance with ethical standards

Conflict of interest There are no conflicts of interest.

Ethical approval Not applicable.

Informed consent Not applicable.

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