In their cohort study of cancer and statin therapy, Farwell et al. (1) may have introduced a serious bias by excluding nonmelanoma skin cancer. In 4S, the Scandinavian Simvastatin Survival Study (2), and in HPS, the Heart Protection Study (3), the two first simvastatin trials, this cancer type was observed more often in the treatment groups. The difference was statistically significant if the results from both studies are combined (in simvastatin groups, 256 of the 12,490 participants; and in control groups, 208 of the 12,490 participants; \( P = .028 \)). For unknown reasons, nonmelanoma skin cancers have been excluded in all reports from subsequent statin trials, but I hope that the relevant data can be made available on request.

The lag time between carcinogenic exposure and the clinical appearance of a cancer depends on its location. Lung cancer, for instance, is not diagnosed until after decades of smoking, whereas superficial nonmelanoma cancers may be observed much earlier. An increased number of patients with skin cancer in a trial is therefore alarming because this is the first cancer type that we should expect to find under conditions of general carcinogenicity.

A statistically significant number of other easily detectable cancer types associated with statin treatment compared with nontreatment have been reported. Iwata
et al. (4) found that 29 (13.3%) of 221 patients with lymphoid cancers had been treated with statins (mean treatment time = 48 months) but that only 64 (7.3%) of the 879 orthopedic and otorhinolaryngological control individuals without cancer had used statins (multivariable odds ratio = 2.24; 95% confidence interval [CI] = 1.37 to 3.66; P = .001). Furthermore, in CARE, the Cholesterol and Recurrent Events Trial (5), 12 of the 286 women in the pravastatin group had breast cancer at follow-up (P = .002).

Several of these breast cancers were recurrences, again a disquieting finding because recurrences may appear earlier than primary cancers. The hypothesis that statin treatment may provoke recurrences is not possible to test, however, because after the publication of the CARE report, previous cancer has become an exclusion criterion in all trials.

Farwell et al. (1) also excluded patients who were diagnosed with cancer within 2 years after entry. Dormant cancer is a common finding in elderly people, and a carcinogenic effect should therefore appear earlier in that patient group. Indeed, in the PROSPER trial (6), which included elderly people only, 245 of the 2891 participants in the pravastatin group but only 199 of the 2913 in the placebo group had new cancer (the number of recurrences was not given). The difference was already obvious after 1 year, and it increased steadily during the trial period to become statistically significant (P = .02) after 4 years.

Another bias may have been introduced by comparing patients on statin treatment with untreated individuals. The first group is a selection of people with high cholesterol and the second is dominated by people with normal and low cholesterol, and numerous cohort studies have found an inverse association between cholesterol and cancer.

A further warning comes from a cohort study by Matsuzaki et al. (7). In a cohort study of 47294 Japanese patients treated with low-dose simvastatin and followed for 6 years, the authors found that the number of cancer deaths was statistically significantly higher in patients whose total cholesterol at follow-up was less than 160 mg/dL than in those whose cholesterol was 200–219 mg/dL (relative risk = 3.16; 95% CI = 1.72 to 5.81; P = .001).

Statin treatment is prescribed to millions of people for the rest of their life. More information in this area is therefore urgently required. For this reason, meta-analyses of the statin trials should include subgroup analyses of obvious risk groups (for instance, older people and smokers) and of early detectable cancers and recurrences.

UFFE RAVNSKOV

References


Notes

Correspondence to: Uffe Ravnskov, MD, PhD, Magle Stora Kyrkogata 9, 22350 Lund, Sweden (e-mail: ravnskov@tele2.se).

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Response

We thank Drs Platz and Ravnskov for their interest in our paper. Dr Platz raises the issue of detection bias with respect to prostate cancer. We agree with Dr Platz that detection bias is a potential limitation of many observational studies that use administrative and electronic clinical datasets. We attempted to reduce detection bias in our study by restricting our study population to patients who made visits to a health-care provider on a routine basis and by restricting our comparison to patients taking statin vs patients taking antihypertensive medications. These restrictions resulted in analyses among patients with similar access to health care. Unfortunately, we do not have data at the present time that will allow us to describe the stage at diagnosis of prostate or other forms of cancer in our dataset.

Dr Ravnskov raises concern that statins may increase general carcinogenicity. He appears to combine results from the Scandinavian Simvastatin Survival Study (1) and the Heart Protection Study (HPS) (2) to infer that a statistically significant relationship may exist between statin use and increased risk for nonmelanoma skin cancer. We used the traditional definition of total cancer as all cancer excluding nonmelanoma because of historical precedent and the imprecision that is inherent in identifying noninvasive cancer through administrative codes alone. We agree that further investigation should examine the relationship between statins and nonmelanoma skin cancer. However, one should take care when combining unverified outcomes from different studies. In several of the studies (3,4,5) that Dr Ravnskov refers to as indicating a potential increased risk of cancer among statin users, pravastatin is either the study medication examined in the trial or the primary statin observed among the case and control subjects. Studies (6) have suggested a difference in the potential anticarcinogenic effect of statins on the basis of their lipophilic nature, with less lipophilic statins such as pravastatin having less potential anticarcinogenic effect. It is important to remember that all-cause mortality in the HPS was statistically significantly reduced among patients taking simvastatin compared with placebo, and other studies have established the general safety of statins, including pravastatin (7).

Dr Ravnskov also expressed concern that we may have failed to account for the relationship between serum cholesterol and cancer. We agree with Dr Ravnskov that previous
observational studies have found a relationship between levels of serum cholesterol and future risk of cancer incidence. This is one reason why we included serum cholesterol in our multivariable-adjusted model of statins and cancer incidence. As we stated in our paper, adjustment for serum cholesterol did not statistically significantly impact the relationship between statins and cancer incidence in our multivariable-adjusted model. We are currently performing analyses to examine the relationship between cholesterol and cancer in our dataset and how this relationship may be affected by statins.

References

Notes
Affiliations of authors: Massachusetts Veterans Epidemiology Research and Information Center, VA Boston Healthcare System, Boston, MA (WRF, EVL, RAL, MTB, LDF, JMG); Division of Aging (WRF, RES, EVL, JMG) and Cardiovascular Division and Division of Preventive Medicine (JMG), Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA; Department of Epidemiology (EVL) and Department of Biostatistics (RAL), Boston University School of Public Health, Boston, MA; Department of Medicine, Boston University School of Medicine, Boston, MA (MTB, LDF).

Correspondence to: Wildon R. Farwell, MD MPH, Massachusetts Veterans Epidemiology Research and Information Center, VA Boston Healthcare System, Boston Division (151 MAV), 150 S Huntington Ave, Boston, MA 02130 (e-mail: wildon.farwell@va.gov).

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