Stats on Statins: Anything but Static

John McLaughlin

The short report on a large cohort study by Jacobs et al. (1) in this issue of the Journal contributes substantially to the growing body of evidence on whether statins have chemopreventive effects and lead to reduced colorectal cancer risk. The search for effective chemoprophylaxis is an important quest that is motivated in part by the potential benefits that could be achieved by preventing colorectal cancer and by the early promise of agents, such as aspirin, other nonsteroidal anti-inflammatory agents, and cyclooxygenase 2 (Cox-2) inhibitors, and the subsequent concerns about their potential adverse effects. Furthermore, should benefits indeed exist, with the high prevalence of cholesterol-lowering drug use in the United States and with statins accounting for more than 80% of the market (2) during the period studied by Jacobs et al., the benefit attributable to statin use may be substantial if statins did indeed prevent colon cancer.

Statins such as pravastatin and simvastatin are agents that are now used widely in the effective management of hypercholesterolemia (2,3). By inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase, statins not only block the synthesis of cholesterol but also have been shown in vitro and in vivo to have effects on cell growth, proliferation, and apoptosis (4,5). With this biological basis, several studies over the past decade explored whether statin use is associated with reduced cancer risk.

Jacobs et al. provide a summary of previous studies on statins and colorectal cancer incidence that is instructive because among other things it demonstrates that, across all completed studies, one of the most consistent findings is that of uncertainty. Early reports arose from randomized trials that focused on cardiovascular outcomes and had little statistical power to examine effects on cancer risk (6–9). Subsequently, observational surveillance studies that involved linkages to pharmacy databases were imprecise (10–13). A large case–control study by Poynter et al. (14) was the first study with reasonable power and was also the only study to detect a statistically significant association. The findings of Poynter et al. heightened interest in this area and began discussion of whether statins should next be evaluated within the context of a chemoprevention trial (15). Although such a trial would clearly serve as the ultimate proof, its justification was weak because it was based primarily on a single informative study (14).

Thus, the report by Jacobs et al. is timely, because it refers to analyses of a large cohort, involving more than 132,000 men and women who were monitored for many years as part of the Nutrition Cohort within the American Cancer Society’s Cancer

Correspondence to: John McLaughlin, PhD, Preventive Oncology, Cancer Care Ontario and Prosserman Centre for Health Research, 620 University Ave., Toronto, Ontario M5G 2L7, Canada (e-mail: john.mclaughlin@cancercare.on.ca).

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 Prevention Study II (CPS-II). Strengths of the study include its large size because the cohort included more than 23,000 users of cholesterol-lowering medications and a relatively large number of incident colorectal cancer diagnoses. The cohort design ensured that bias from selective recall was unlikely, and the scale and comprehensiveness of the study enabled control of several potential confounders in multivariable analyses. The authors acknowledged several limitations of their data, including that some misclassification of both primary exposures and outcomes was inevitable because of the nature of the data. Even so, the study provides a prompt and timely contribution to the literature, because it capitalized on the existence of a large and well-characterized cohort.

Jacobs et al. demonstrated that, within the CPS-II cohort, there was no evidence of a strong association between colorectal cancer risk and use of cholesterol-lowering medications. Thus, although there are still many questions that warrant investigation, it remains premature to conclude that a large chemoprevention trial with statins that is aimed at reducing colorectal cancer risk is warranted.

Complementing the main results, this study also demonstrates what can be achieved efficiently by monitoring disease patterns and testing hypotheses in the context of large and well-characterized cohorts. The CPS-II cohort study began in 1982, many years before statins were developed, and yet Jacobs et al. estimated that 17.6% of the participants used statins during the last decade—a finding that shows how dramatically exposure profiles can change in the population. Fundamental strengths of the cohort approach are demonstrated because it supports exploration of novel hypotheses and can be responsive to changes in the determinants and distributions of both risk factor and outcomes, which are seldom static in real populations. Although the value of updating information within cohorts is apparent, even more can be gained by improving the quality of exposure and outcome information. For example, although the general measures of drug use that can be obtained by self-report have some merit, large-scale studies would benefit from linkages to population-based cancer registries and to pharmacy databases that would permit more detailed assessment of duration, timing, and dose of specific agents. Thus, the report by Jacobs et al. is instructive not only regarding the specific association explored but also as it relates to the detection of risks and benefits that may follow changes that are sometimes dramatic and that occur constantly across populations.

REFERENCES


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