Published OnlineFirst November 8, 2009; DOI: 10.1158/1055-9965.EPI-09-1027

Editorial

Cholesterol and Cancer: Answers and New Questions

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Many epidemiologic studies published in the 1980s documented an association between low circulating cholesterol and higher overall cancer incidence and mortality (1). This association has been attributed to reverse causation, that is, undiagnosed cancer causing a reduction in cholesterol levels. Reverse causation is strongly supported by observations that cholesterol levels decline before cancer diagnosis (2, 3) and that associations between low cholesterol and cancer incidence and mortality weaken when the first few years of study follow-up are excluded (4). In addition, a meta-analysis of randomized trials of cholesterol-lowering statins found no effect on risk of cancer, although only short-term effects could be addressed due to the short duration of most trials (5). Despite strong evidence for reverse causation, it has been difficult to entirely rule out the possibility that low cholesterol levels might be associated with a modest long-term increase in risk of cancer. One very large study (6) found an association between low cholesterol and modestly increased cancer mortality even after excluding the first 5 years of follow-up, and a second study found an association between low cholesterol and elevated cancer incidence among men even after excluding the first 6 years of follow-up (7).

The association between cholesterol and risk of cancer is revisited in this issue of *Cancer Epidemiology Biomarkers & Prevention* (1, 8). In a comprehensive and well-conducted analysis of a large cohort of Finnish male smokers followed for 18 years [the α-Tocopherol, β-Carotene Cancer Prevention Study (ATBC); ref. 1], low total cholesterol measured at baseline was associated with increased risk of cancer. However, this association was completely eliminated by exclusion of the first 9 years of follow-up, a longer period of follow-up than had been excluded in previous studies. These results provide additional evidence that the association between low total cholesterol and risk of cancer is due to reverse causation and is not causal.

In addition to examining total cholesterol, the ATBC analysis examined associations between cancer incidence and high-density lipoprotein (HDL) cholesterol (sometimes called "good" cholesterol). Few previous studies have examined HDL cholesterol in relation to individual cancers, and no large studies have examined overall cancer incidence. High HDL cholesterol was associated with slightly lower overall cancer incidence [highest versus lowest quintile relative risk, 0.89; 95% confidence interval (CI), 0.83-0.97]. This association was not attenuated by exclusion of the first 9 years of follow-up and is therefore unlikely to be explained by reverse causation. Most of the apparent reduction in overall cancer incidence seems to have been driven by relatively small and statistically nonsignificant reductions in incidence of the two most common cancers, lung cancer (highest versus lowest quintile relative risk, 0.89; $P_{trend} = 0.19$) and prostate cancer (highest versus lowest quintile relative risk, 0.89; $P_{trend} = 0.12$). Together, these two cancers accounted for more than half of all cancers in the ATBC cohort. Although the strongest reduction in risk was observed for hematopoietic cancers, no association with hematopoietic cancers was apparent after exclusion of the first 9 years of follow-up.

Is the association between higher HDL cholesterol and lower overall cancer incidence observed in the ATBC cohort likely to be causal? A causal association is biologically plausible, as HDL cholesterol has anti-inflammatory properties (9). However, it is also plausible that this association reflects the effect of factors that are associated with both HDL cholesterol and risk of cancer, such as insulin levels and inflammation. High insulin levels are associated with both low HDL cholesterol (10) and substantially increased risk of prostate cancer in the ATBC cohort (11). Inflammation reduces HDL cholesterol (12) and likely increases risk of lung cancer (13). It is also important to note that all of the participants in the ATBC cohort were smokers, and that associations between HDL cholesterol and risk of cancer may differ in nonsmokers, particularly given that smoking is associated with higher levels of markers of systemic inflammation (14).

A second report in this issue of *Cancer Epidemiology Biomarkers & Prevention* carefully examines the association between total cholesterol and prostate cancer incidence in the placebo arm of a randomized trial of finasteride [the Prostate Cancer Prevention Trial (PCPT); ref. 8]. A unique and important strength of this analysis is that all men who had not been previously diagnosed with prostate cancer underwent a prostate biopsy at the end of the trial, greatly reducing the possibility of detection bias. Consistent with results from the ATBC analysis and from previous studies, no association was observed between total cholesterol and overall risk of prostate cancer. However, low total cholesterol (<200 mg/dl) was associated with a striking reduction in risk of high-grade prostate cancer (odds ratio, 0.41; 95% CI 0.22-0.77 for cancer with a Gleason score of 8-10). In other words, higher cholesterol was associated with an elevated risk of high-grade prostate cancer. This result is potentially important because although high-grade prostate cancers account for a relatively small proportion of all prostate cancers, they have a far worse prognosis.

Considerable evidence supports the plausibility of an association between low cholesterol and reduced risk of high-grade prostate cancer. Several studies have reported

Cancer Epidemiol Biomarkers Prev 2009;18(11):2805–6

Received 9/30/09; accepted 9/30/09; published OnlineFirst 11/3/09.

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doi:10.1158/1055-9965.EPI-09-1027

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an association between statin use and reduced risk of advanced or high-grade prostate cancer (15, 16). In addition, an inhibitory effect of low cholesterol on prostate cancer progression is biologically plausible. Laboratory evidence suggests that lowering cholesterol levels could inhibit cell-signaling pathways that are important for prostate cancer progression (17). This hypothesis is supported by experiments in mice in which lowering serum cholesterol with dietary modification or a cholesterol-lowering drug reduced the cholesterol content, size, and vascularity of human xenograft prostate tumors (18).

Direct epidemiologic evidence for an association between low total cholesterol and reduced risk of high-grade prostate cancer, however, remains limited. Some support comes from the only previous analysis of circulating cholesterol and high-grade prostate cancer, a nested case-control analysis from the Health Professionals Follow-Up Study (19). In the Health Professionals Follow-Up Study analysis of high-grade cancer (defined as Gleason score of 7-10), a test for trend with increasing cholesterol level was not statistically significant, but there was evidence of reduced risk when comparing the lowest quartile to the three highest quartiles combined (odds ratio, 0.61; 95% CI, 0.39-0.98). As described above, a clear association between low cholesterol and reduced risk of high-grade prostate cancer was observed in the placebo arm of the PCPT. However, there were only 60 cases of high-grade prostate cancer in the placebo arm.

As a result, the size of the potential reduction in risk is uncertain. In addition, the PCPT analysis was not able to examine whether the reduced risk associated with low cholesterol could be explained by statin use, although this did not seem to be true in the Health Professionals Follow-Up Study analysis (19). Finally, low cholesterol was not associated with reduced risk of high-grade prostate cancer in the finasteride arm of the PCPT (odds ratio, 1.03; 95% CI, 0.68-1.57 for cholesterol of <200 mg/dl). It should be noted that the investigators had decided *a priori* to focus on the placebo arm and there may be biologically plausible reasons why finasteride treatment would alter results. The absence of an association in the finasteride arm raises the possibility that cholesterol levels might influence androgen-signaling pathways inhibited by finasteride. Nonetheless, the null results from the finasteride arm suggest that the striking reduction in risk of high-grade prostate cancer in the placebo arm could have been at least partly due to chance.

Results from the two analyses of cholesterol and risk of cancer published in this issue of *Cancer Epidemiology Biomarkers & Prevention* provide one answer and raise two new questions. Results from the ATBC analysis clearly show that low total cholesterol is unlikely to increase risk of cancer. At the same time, the ATBC results raise a new question about the potential role of high HDL cholesterol and its correlates in reducing risk of cancer. Future analyses should clarify if specific cancers are meaningfully associated with HDL cholesterol, and if so, whether these associations are independent of other metabolic and inflammation-related factors. Results from the PCPT analysis raise a second, more specific, question. Does low total cholesterol reduce risk of high-grade prostate cancer? Analyses to replicate the association between low total cholesterol and reduced risk of high-grade prostate cancer are well justified. Analyses of associations of cholesterol levels and use of cholesterol-lowering drugs with prostate cancer progression among men with localized low-grade prostate cancer could also clarify the role of cholesterol in prostate carcinogenesis. If results of such observational studies support the hypothesis that low cholesterol inhibits prostate cancer progression, then it would raise the question of whether prostate cancer patients choosing active surveillance (20), rather than immediate treatment, could reduce their risk of disease progression by using statins or other cholesterol lowering drugs. This question, however, would need to be answered by a randomized trial.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Cancer Epidemiology, Biomarkers & Prevention

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Cancer Epidemiol Biomarkers Prev 2009;18:2805-2806. Published OnlineFirst November 8, 2009.