

Statins: emerging role in chemoprevention for hepatocellular carcinoma?

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Statins have well established efficacy in reducing morbidity and mortality from coronary artery disease in both the primary and secondary setting (1,2). This is almost certainly achieved by reduction in plasma LDL levels and other purported circulatory/anti-atherosclerotic effects (3). Beyond its therapeutic value in cardiovascular disorders, there is now emerging interest in developing statins as an anti-cancer agent. Inhibition of 3-hydroxy-3-methylglutaryl CoA reductase by statins impede the rate-limiting step of mevalonate pathway leading to reduced levels of mevalonate and its downstream products which are important in cellular homeostasis, cell signalling, protein synthesis and cell cycle progression. Growth inhibitory signals exerted by statins in cancer cell lines and tumor-bearing animal models further support potential pro-apoptotic, anti-proliferative and anti-invasive properties (4). Aberrant regulation of cholesterol homeostasis has also been associated with cancer pathogenesis. Interestingly there has been recent genetic link identified between cholesterol and cancer risk further providing rationale for cholesterol targeting as a therapeutic or preventive strategy. Smith *et al.* (5) demonstrated anti-cancer function of cholesterol exporter ABCA1 (ATP-binding cassette transporter AI) in cell lines. Defective cholesterol efflux following suppression of ABCA1 gene expression in response to oncogenic mutations or loss of function mutation has been implicated in malignant cell transformation. ABCA1 deficiency allows for elevated mitochondrial cholesterol which supports cancer cell survival.

A number of epidemiologic studies have investigated the effects of statins on reducing site-specific cancer incidence and overall cancer incidence with contrasting conclusions. A nested case-control study including 6,721 beneficiaries

of health care plan in Quebec selected between 1988 and 1994 found a 28% reduction in risk of any cancers among users of statins compared to bile acid binding resins (rate ratio 0.72; 95% CI, 0.57-0.92). There was however no association between specific cancer sites and statin usage (6). The use of statins was associated with a 47% relative reduction in the risk of colorectal cancer in a case control study in Israel. In this study the use of statins for at least five years was associated with a significantly reduced relative risk of colorectal cancer which remained significant after adjustment for other confounders (7).

In contrast to the above mentioned study by Poyner *et al.* (7), a case-control study based on Cancer Prevention Study II Nutrition Cohort found no association between use of cholesterol-lowering drugs and colorectal cancer incidence among 132,136 men and women. Use of cholesterol-lowering drugs was not associated with colorectal cancer incidence (multivariable adjusted rate ratio =1.03, 95% CI, 0.85 to 1.26). Use of cholesterol-lowering drugs for 5 years or more was also not associated with colorectal cancer incidence (rate ratio=1.09, 95% CI, 0.83 to 1.43) (8). The associations of statins and other-lipid lowering drugs with breast cancer risk were assessed in the Nurses' Health Study. A total of 79,994 women were followed prospectively for up to 12 years. Compared with nonusers, lipid-lowering drug users experienced similar breast cancer risk (multivariate relative risk, 0.99; 95% CI, 0.86-1.13). Current use of statins also was not significantly associated with breast cancer risk (relative risk, 0.91; 95% CI, 0.76-1.08). There was also no association between cancer risk and duration of drug use in this cohort study (9).

The epidemiologic studies all had some limitations regardless of their conclusions. Differences in study

methods and study populations are likely to account for some of the variations in the results observed. Moreover, interpretation of these studies needs to be done with caution due to residual confounding and unaccounted effect modifications.

At least 2 randomized controlled trials investigating the effect of statins on cardiovascular outcomes reported an increased risk of cancer incidence. Lowering the cholesterol levels in patients with prior myocardial infarction with average levels of LDL with pravastatin has been shown to reduce risk of coronary events. The frequency of fatal coronary events was 10.2% in the pravastatin group versus 13.2% in the placebo group, an absolute difference of 3% and a 24% reduction in risk (95% CI, 9-36%, $P=0.003$). This study however showed a higher incidence of breast cancer among patients who received pravastatin compared to the patients who received placebo, 12 versus 1 ($P=0.002$) (10). In another randomized controlled trial, pravastatin lowered LDL cholesterol concentrations by 34% and reduced the incidence of coronary death, non-fatal myocardial infarction, and fatal or non-fatal stroke to 408 events compared with 473 on placebo (HR 0.85, 95% CI, 0.74-0.97, $P=0.014$) in the elderly. New cancer diagnoses were however more frequent on pravastatin than on placebo (HR 1.25, 95% CI, 1.04-1.51, $P=0.020$) (11).

A number of meta-analyses have also contributed insights into the association between statins and cancer incidence. In contrast to observational studies, the meta-analyses consistently reported a lack of association between statins and cancer risk. Herbert *et al.* (12) reported a meta-analysis of 16 trials that included approximately 29,000 patients with average follow up of 3.3 years, and found no reduction in risk of cancer with statins with a relative risk ratio of 1.03 (95% CI, 0.90-1.17). Dale *et al.* (13) reported a meta-analysis of 26 randomized controlled trials including 86,936 patients, each with a minimum follow up of 1 year and a minimum of 100 patients and found an odds ratio of 1.02 (95% CI, 0.97-1.07) for cancer incidence based on 20 studies and an odds ratio of 1.01 (95% CI, 0.93-1.09) for cancer mortality based on 22 studies. Bonovas *et al.* (14) reported a literature based meta-analysis of 35 randomized control trials including 109,143 individuals with an average follow up of 4.5 years and showed no evidence for association between statin therapy and overall cancer risk (relative risk 0.99; 95% CI, 0.94-1.04). Within the same publication, a separate meta-analysis restricted to trials with a minimum duration of 3 years and which enrolled at least 3,000 patients was performed. A total of 78,000 individuals

were included with an average follow up of 5.3 years. Once again there was no association between statins therapy and overall cancer risk (relative risk 1.01; 95% CI, 0.96-1.06). More recently, the Cholesterol Treatment Trialist (CTT) Collaboration (15) reported an individual patient data meta-analysis involving 169,618 individuals. No increased risk of cancer incidence or death was detected after median follow up of 4.9 years.

These randomized controlled trials and meta-analysis do suffer from limitations in assessing the relationship between statins and cancer risk. The trials were not powered to assess secondary outcomes such as cancer and follow up periods were relatively short compared to the long latency period of cancer. Although meta-analysis of randomized trials attempt a more objective appraisal of the evidence and serve as a tool for studying rare and unintended effects of treatment, the results ought to be interpreted with caution. The limitations include short follow up period, inconsistent duration of statins use, failure to evaluate the dose/duration association and perhaps failure to account for different types of statins used.

In summary the findings from numerous observational studies and meta-analysis indicate a lack of association between statins therapy and cancer incidence.

The effect of statins on incidence of hepatocellular carcinoma (HCC) has not been as extensively studied. Tsan *et al.* (16) recently reported that statins exposure may reduce the risk of HCC in patients with hepatitis B virus (HBV) infection in a population based cohort study in Taiwan. 33,413 patients with HBV infection were followed up from 1997 to 2008, of which 8.3% had documented statins usage. The incidence of HCC in patients on statins was 210.9 per 100,000 person-years compared with incidence rate of 319.5 among non-users. After adjusting for potential confounders like age, sex, cirrhosis, diabetes and medications, the hazard ratio for HCC in statins users compared to non-users was 0.47 (0.36-0.61). The authors also managed to show a dose-response relationship between statins use and HCC. The adjusted hazard ratios were 0.66 (95% CI, 0.44-0.99), 0.41 (95% CI, 0.27-0.61) and 0.34 (95% CI, 0.18-0.67) for patients with statins use of 28-90, 91-365 and more than 365 cumulative defined daily dose.

This study has some distinct strengths. The investigators tested the association of statins exposure with HCC in a high risk group of patients who had HBV infection. The study population was taken from a computerized database in Taiwan with a long follow up period of 328,946 person-years. Credit should also go to the authors for

their meticulous analysis of possible confounders. The demonstrated clear dose-response relationship is indeed intriguing.

Nevertheless, this study needs to be interpreted with caution due to unaccounted confounders. The authors acknowledged unmeasured confounders such as alcohol intake, smoking status and body mass index. They however, failed to account for differences in risk of HCC even among patients with HBV infection. HBeAg, in addition to HBsAg, may be a useful marker of the risk of HCC. The incidence rate was 324.3 among those who were positive only for HBsAg and 1,169.4 among those who were positive for both HBsAg and HBeAg. The prevalence of HepBeAg among those who were positive for HepBsAg is highest among patients between 30 and 39 (23%). The study also showed a lower prevalence of HepBeAg with age (17). Of note, there was a difference between statin users and non-statin users in terms of age distribution in the study by Tsan *et al.* 37.7% of the patients with documented statin use was more than 50 years of age compared to only 15.9% among the non-statin users.

The finding from this study is consistent with that of 2 other epidemiological studies (18,19). Beyond the purported mechanistic action of statins as described above, it is perhaps more relevant as chemoprevention in HCC. Statins are selectively localized to the liver and less than 5% of the administered dose appears in the systemic circulation. Such selective hepatic uptake does provide a compelling reason to further investigate its role in HCC.

The long standing debate concerning the association between statins and cancer cannot be resolved with more large scale observational studies or meta-analyses of studies. The numerous epidemiological studies including by Tsan *et al.* (16) are informative but not conclusive. Truly, we need well designed randomized controlled trials to instruct us on the real value of statins in reducing cancer risk.

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