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STATIN DRUGS (B. WIGGINS, SECTION EDITOR)

Protective Effects of Statins in Cancer: Should They Be Prescribed for High-Risk Patients?

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Abstract
Purpose of Review Statins are one of the most widely prescribed drug classes in the USA. This review aims to summarize recent research on the relationship between statin use and cancer outcomes, in the context of clinical guidelines for statin use in patients with cancer or who are at high risk for cancer.
Recent Findings A growing body of research has investigated the relationship between statins and cancer with mixed results. Cancer incidence has been more extensively studied than cancer survival, though results are inconsistent as some large meta-analyses have not found an association, while other studies have reported improved cancer outcomes with the use of statins. Additionally, two large studies reported increased all-cancer survival with statin use. Studies on specific cancer types in relation to cancer use have also been mixed, though the most promising results appear to be found in gastrointestinal cancers. Few studies have reported an increased risk of cancer incidence or decreased survival with statin use, though this type of association has been more commonly reported for cutaneous cancers.
Summary The overall literature on statins in relation to cancer incidence and survival is mixed, and additional research is warranted before any changes in clinical guidelines can be recommended. Future research areas include randomized controlled trials, studies on specific cancer types in relation to statin use, studies on populations without clinical indication for statins, elucidation of underlying biological mechanisms, and investigation of different statin types. However, studies seem to suggest that statins may be protective and are not likely to be harmful in the setting of cancer, suggesting that cancer patients who already take statins should not have this medication discontinued.

Keywords Statins · Cancer · High-risk patients

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Introduction

Statins are one of the most widely prescribed drug classes in the USA. Statins are also known as 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitor medications or HMG-CoA reductase inhibitors. These medications have been shown to decrease cardiovascular morbidity and mortality in high-risk patient groups in numerous studies [43]. Under the 2013 American College of Cardiology/American Heart Association Guidelines [59] based on results from randomized controlled trials, the clinical indications for statins were broadened to include four major patient groups rather than specific low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein

cholesterol (HDL-C) targets. These groups include the following: (1) individuals with clinical atherosclerotic cardiovascular disease (ASCVD), (2) patients with LDL-C cholesterol levels ≥190 mg/dL, (3) diabetic patients without ASCVD aged 40–75 with LDL-C 70–189 mg/dL, and (4) patients without cardiovascular disease (CVD) but with LDL-C 70–189 mg/dL and 10-year atherosclerotic cardiovascular disease risk of ≥7.5 %. Over 50 million people in the USA use statins due to these clinical indications, with this number expected to continue to increase in the future [50].

Cancer is currently the second leading cause of death in the USA [51]. The literature suggests that the use of statins may affect cancer incidence and survival, as some large meta-analyses as well as studies on individual cancers have reported an association between statins and cancer. This review aims to summarize recent relevant research in this field and to further explore whether the available evidence supports clinical practice changes for statin use in cancer patients. Currently, no formal guidelines exist on the use of statins for cancer patients; however, in some cases, statins may be stopped due to concern for adequate nutrition in cancer patients who may experience cachexia and appetite loss as a result of their disease and/or treatment. Given the high prevalence of both cancer and statin use in the USA, it is critical to better understand their linkage as well as implications for clinical practice guidelines.

Literature Review

Statins and All-Cancer Outcomes

In recent years, some studies have reported that statin use may be associated with lower risk of cancer incidence and increased cancer survival; however, not all studies have found this effect. Additionally, results of studies are mixed depending on the type of cancer studied. Two large studies have examined the relationship between statin use and all-cancer survival, with promising findings. A retrospective Danish study of 295,925 cancer patients reported that statin users had 15 % reduction in all-cancer mortality (HR 0.85, 95 % confidence interval (CI) 0.82–0.87) [48••]. The decrease in cancer mortality among statin users was found for 13 specific cancer types, in addition to cancer overall. The Women's Health Initiative similarly reported that compared with never-users, current use of statins was associated with a significantly lower risk of cancer death (HR 0.78, 95 % CI 0.74–0.88). This effect was observed for multiple but not all cancer types studied. This study additionally found that though there was a reduction in all-cancer death, there was no significant reduction in all-cancer incidence [62••]. The strengths of these two studies include their large sample size, detailed information on statin use, and information on potential confounders in relation to cancer outcomes.

Results of Meta-Analyses

Multiple meta-analyses have reported the effect of statin use and cancer, with mixed results. One systematic review and meta-analysis of 42 studies (17 randomized controlled trials (RCTs), 10 cohort studies, and 15 case–control studies) found that statins had no effect on overall cancer incidence. However, within specific cancer types, statins were associated with no effect on lung, breast, and prostate cancer; protective effects on stomach, liver, and lymphoma; and increased incidence of melanoma and non-melanoma skin cancer [40]. A meta-analysis on statins and cancer mortality including 39 cohort studies and 2 case–control studies with 990,649 patients found that statin use after diagnosis was associated with significantly decreased all-cancer mortality (HR 0.77, 95 % CI 0.68–0.88) [72••]. Additionally, a meta-analysis including 25 studies with 523,193 patients found that statin use was associated with significantly reduced all-cause mortality in cancer patients (HR 0.82, 9 % CI 0.76–0.89) [41••].

Multiple RCTs with non-cancer primary endpoints have also reported on cancer outcomes in relation to statin use. The Cholesterol Treatment Trialists' (CTT) Collaboration database meta-analysis of 27 RCTs reported no association between statin use and cancer mortality or incidence [12]. However, it is important to note that the primary outcomes in these studies were cardiovascular events such as major vascular events, major coronary events, stroke, coronary revascularization, and mortality. In addition, a meta-analysis of 26 RCTs focused on cardiac outcomes with 6662 incident cancers, and 2407 cancer deaths also found no association between incidence of cancer (OR, 1.02; 95 % CI, 0.97–1.07) or cancer deaths (OR, 1.01; 95 % CI, 0.93–1.09) with statin use. The study also did not find any effects for individual cancers [16].

Statin Use in Relation to Specific Cancer Types

In addition to the above literature, studies focused on specific types of cancer have also investigated statin use in relation to cancer outcomes. Studies on incidence of specific cancers have been mixed, reporting both no effect [4, 9, 19, 30, 36, 40, 60] and protective effects [21, 26, 54] [55]. One meta-analysis of seven RCTs and nine observational studies did not find a protective effect of statins on breast cancer risk [6]. Another meta-analysis of 5 prospective studies (60,911 patients) on breast cancer mortality and 11 prospective studies, 12 case–control studies, and 9 RCTs (83,919 patients) on breast cancer incidence found that statin use was associated with decreased mortality of breast cancer patients. No significant relationship between breast cancer incidence and statin use was reported in this study [68]. One retrospective database study of 31,114 Finnish women found that statin use (either before or after cancer diagnosis) was associated with up to 66 % lower risk of breast cancer mortality [46].

Additionally, a cohort study of 17,880 breast cancer patients found reduced cancer and all-cause mortality for patients who used statins following diagnosis [11]. Results from biomarker-based studies of statins as possible chemoprevention agents for breast cancer have been inconsistent [3, 33, 61].

Studies on gastrointestinal cancers and statins have reported some promising results. A meta-analysis including 76,851 patients reported that prediagnosis statin use was associated with reduced all-cause (HR 0.73, 95 % CI 0.61–0.88, $P = 0.001$) and cancer-specific mortality (HR 0.80, 95 % CI 0.77–0.84, $P < 0.001$) in colorectal cancer patients [42]. Another meta-analysis involving 26 RCTs and 8 observational studies found that statin use demonstrated a statistically significant 27 % reduction in the risk of gastric cancer (RR 0.73, 95 % CI 0.58–0.93) [69]. Additionally, a meta-analysis of 5581 cases of gastric cancers in both Western and Asian populations found protective effects of statin and cancer [56]. Other meta-analyses have found an association between reduced esophageal and hepatocellular carcinoma incidence in relation to statin use [57, 58]. Despite these meta-analyses, some individual studies including large cohort studies and case control studies have not reported the same protective association of statins in relation to colorectal cancer [14, 35, 53, 70].

Studies on statins in relation to lung, prostate, and gynecologic cancers have shown mixed results. A meta-analysis of 20 studies (five RCTs, eight cohort studies, and seven case–control studies) found a decrease in total lung cancer risk among all statin users that was not statistically significant (RR = 0.89, 95 % CI) [0.78, 1.02] [64]. Several case–control studies did not report an association between lung cancer and statin use [5, 13, 29]. A study on statins and all-cancer survival did find significantly increased cancer survival among statin users, but this association was not found for lung cancer [62••]. However, one case–control study among a veteran population reported that statin users had significantly decreased risk of lung cancer with OR 0.45, 95 % CI 0.42–0.48 [39]. It is also important to consider that some lung cancer studies have not had complete access to cigarette smoking data, which is the largest risk factor for developing lung cancer; therefore, confounding may be an issue [8•].

Most studies on gynecologic cancers have not found any statistically significant association between statin use and cancer, though some studies have been limited by small sample size [5, 25, 26, 71]. However, a retrospective study found that statins were associated with reduced risk of death from uterine malignancies by 45 %, while statins and aspirin together were associated with 84 % decrease in deaths [47]. For prostate cancer, the literature is mixed, as studies have reported both protective associations [23] and no association with statin use [7, 44, 45]. In particular, several meta-analyses have not reported any association between prostate cancer and statin use [1, 16, 34].

Several articles have reported results regarding a potential relationship between cutaneous cancers and statin use. The Women's Health Initiative reported that among 118,357 women, the use of any statin at baseline was associated with significantly increased non-melanoma skin cancer (NMSC) incidence (OR 1.21, 95 % CI 1.07–1.35) [63]. A case–control study in Denmark of 38.484 NMSC cases nationwide, case–control study in Denmark also found significantly increased risk of basal cell carcinoma (with statin use (OR 1.09, 95 % CI 1.06–1.33)). Additionally, the first two simvastatin trials (the Scandinavian Survival Study [4S] and the Heart Protection Study [HPS]) found that NMSC was observed more often in the treatment groups, with a significant effect when both trials were combined [31] ("Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S)" [52]). However, multiple studies have also reported no association between statin user and cutaneous cancers, for both melanoma and NMSC [2, 4, 30, 36].

The literature has also reported promising findings on statin use in relation to other types of cancer, including brain cancers [27, 28] and lymphoma [24, 49], though some studies have had small sample sizes. In addition to the aforementioned studies, some (but not all) prospective cohort studies of cardiovascular disease have found associations between lower cholesterol levels and lower risk of death from several cancers [10, 37, 38].

Overall, the literature on statins and cancer is mixed and inconsistent, particularly when different cancer types are studied. However, while some studies have reported protective associations between statin use and cancer incidence and mortality, several major limitations must be taken into account when interpreting this data. First, study results are inconsistent and conflicting, for both all-cancer studies as well as studies of specific cancers. Studies have not investigated this question among patients who do not have an existing clinical indication for statins, and therefore, caution must be taken in trying to generalize findings to a wider population. Additionally, this question has not yet been investigated by the gold standard of randomized controlled trials with cancer outcomes as a primary endpoint, and retrospective and observational studies are subject to possible bias.

Plausible Biological Mechanisms

Statins and other lipid-lowering medications may lead to higher cancer survival through several biological mechanisms. Decreased cholesterol levels and blocking the mevalonate pathway are hypothesized to interfere with cell proliferation and migration needed for cancer growth and metastasis [8•, 17, 22, 32]. In addition, as a downstream effect of inhibiting HMG-CoA reductase, statins may affect cancer progression by inhibiting the formation of lipid isoprenoid intermediates, which affect the prenylation of small G-proteins believed to be important for carcinogenesis [18, 66].

Expression of certain G-proteins (particularly Rho) have been associated with poor prognosis in certain cancers [18]. Tumor cells also have increased sensitivity to isoprenoid-mediated suppression [66]. Basic science has also linked statins to modifying adhesion, inflammatory mediators, and lymphocyte function [20]. Statins can also lead to apoptosis through regulation of the RAF-mitogen activated protein kinase 1 pathway [67], in addition to arresting the cell cycle [15]. Statins have also been shown to have anti-angiogenic properties, which can affect tumor growth and metastasis [65]. However, despite multiple proposed mechanisms, the exact biological effect of statins on cancer incidence and mortality remains unclear and warrants further investigation. In particular, given differing effects of statins in relation to multiple cancer types reported in the literature, it is important to study not only the underlying mechanisms but also if these mechanisms vary depending on the specific type of cancer.

Conclusions

Though some studies suggest that statin use may be associated with a decreased risk of cancer incidence and increased survival, overall the literature is inconsistent, with many studies reporting no association. The studies for cancer survival appear to be more promising that those for cancer incidence, though the literature is mixed. However, it is somewhat rare for studies to report an increased cancer risk or decreased survival with statin use (though negative associations with cancer outcomes appear to be more common among cutaneous cancers). Additional research is needed in multiple areas before any change in clinical guidelines can be recommended, as detailed below:

1. Randomized controlled trials: To date, no randomized controlled trials have investigated the question of statin use and cancer incidence and/or survival with cancer outcomes as a primary endpoint. RCTs are necessary to move beyond observing associations and to directly study the effect of statins on cancer. Without evidence from RCTs, it is not possible to exclude confounding or bias as major contributors to the findings on statins and cancer thus far. This is particularly important for the issue of statin use and cancer because the use of statins may be related to other healthy behaviors and better access to health services. Though many studies in this review attempted to adjust for confounders, some datasets did not have access to extensive confounder data. This question can be much more cleanly investigated through RCTs using cancer survival and incidence as primary endpoints given these significant potential issues. Additionally, RCTs should carefully define their timescale and study statin both prior to and after diagnosis (which may involve randomizing different populations), as the literature has investigated both of these timescales.
2. Cancer incidence vs. survival: While the body of literature on cancer outcomes in relation to statin use is extensive as detailed in this review, more studies have investigated cancer incidence compared to cancer survival. However, the findings on cancer survival have been somewhat more promising, as two large studies on statins and all-cancer survival have reported favorable results (see Literature Review section). Statins may differentially affect carcinogenesis and progression, and future studies should clearly investigate both of these outcomes (which would involve separate timescales as described above), ideally in the same cohort.
3. Patients without clinical indication for statins: Another important issue (which is also important for designing an RCT on this subject) is that studies thus far have only included patients who take statins due to an existing clinical indication. Therefore, findings cannot be generalized to the entire population of cancer patients, and there is no evidence currently to support prescribing statins for patients with cancer or at high risk for cancer who do not otherwise have a clinical indication for using a statin. Further studies should also investigate the effect of starting statins in cancer patients who do not already take statins due to cardiovascular or other conditions, to compare the findings in this population to existing studies.
4. Specific cancer types: Cancer is a heterogeneous group of diseases, and it is possible that statins may have differing effects depending on the type of cancer. It is important to study the effects of statins on individual cancers, as studies have suggested that certain types of cancer (including cutaneous cancers) may have less favorable associations with statin use.
5. Underlying biological mechanisms: Related to the above, better understanding of the underlying biological mechanisms of how statins may affect cancer is critical in order to elucidate drivers of associations between statin use and cancer. While multiple mechanisms have been hypothesized or demonstrated in the lab, it remains unclear which of these mechanisms are the critical mediators of the statin–cancer relationship, how these mechanisms interact with each other, and how these mechanisms may differ depending on the type of cancer. Further elucidating these biological mechanisms will help clarify clinical indications for statins in cancer patients.
6. Statin type: Statins cannot be assumed to all be equivalent as different statins are associated with different potency, lipophilicity, and other properties. While some studies have investigated the effects of specific statin types in relation to cancer incidence, this area also warrants additional investigation. Additionally, the effect of other lipid-lowering medications (such as fibrates, bile acid binding resins, cholesterol absorption inhibitors, and niacin) should be studied in relation to cancer outcomes.

It is also important to note that given the high morbidity and mortality associated with CVD, the clinical use of statins should be mainly considered in relation to cardiovascular risk factors according to official guidelines, as the evidence for statins and other conditions (including cancer) is not well-established. However, despite the need for additional investigation as detailed above, for cancer patients (or patients with high risk of cancer) who have a clinical indication for using statins, the literature suggests that continuing statin use is unlikely to cause harm and may be beneficial for some cancer types. This is important clinically as statins are sometimes stopped for cancer patients due to concerns about adequate nutrition as these patients may experience appetite loss and cachexia.

In summary, as cancer consists of a very heterogeneous group of diseases, the relationship between statin use and cancer warrants additional investigation in multiple areas before changes in clinical guidelines can be recommended (in terms of prescribing statins for cancer patients or patients with high cancer risk). However, even though the existing research has limitations, some early results suggest that statins could represent another tool against the development and progression of this widespread disease.

Compliance with Ethical Standards

Conflict of Interest Ange Wang, Aaron K. Aragaki, Jean Y. Tang, Allison W. Kurian, JoAnn E. Manson, and Marcia L. Stefanick declare that they have no conflict of interest.

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- • Of importance
- •• Of major importance

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