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CURRENT OPINION

Statins: Do They Have a Potential Role in Cancer Prevention and Modifying Cancer-Related Outcomes?

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Abstract 3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) are currently among the most commonly prescribed pharmaceutical agents worldwide. Apart from their well-established therapeutic value in cardiovascular disease, there is a long-standing debate on their potential association with cancer. To obtain and discuss the existing clinical evidence, an overview of meta-analysis articles addressing this issue was carried out. As of today, the accumulated evidence does not support the hypothesis that statins affect the risk of developing cancer, when they are taken at low doses for managing hypercholesterolaemia. However, current data cannot exclude an increased cancer risk in elderly patients associated with hydrophilic statin use, or decreases in the risks of certain cancers, such as gastric, oesophageal, liver, colorectal and advanced/aggressive prostate cancer. On the other hand, some recent observational studies have provided evidence that statins might be useful in modifying the prognosis of patients diagnosed with malignancy. Until a definitive benefit is demonstrated in randomized controlled trials, statins cannot be recommended either for cancer prevention or for modifying cancer-related outcomes. Further research is warranted to clarify the potential role(s) of statins in the prevention and treatment of cancer.

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Key Points

The accumulated clinical evidence shows that statins are not a 'magic bullet' for cancer. However, it is still possible that statins may have a role to play in cancer prevention or treatment.

Statins cannot be recommended for primary cancer prevention or for modification of cancer-related outcomes, until and unless a definitive benefit is demonstrated in prospective randomized trials.

1 Introduction

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are currently among the most commonly prescribed pharmaceutical agents worldwide [1, 2] as a result of their well-established efficacy in primary and secondary prevention of cardiovascular disease in a variety of populations [3–8]. The release of the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines on the assessment of cardiovascular risk [9] and on the treatment of blood cholesterol, which included recommendations for primary prevention with statins [10], are expected to lead to a further increase in their use [11].

There are currently seven statins on the market: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin. Their main mechanism of action is the reduction of serum cholesterol levels by means of competitive inhibition of hepatic HMG-CoA reductase, which is the rate-limiting enzyme in the mevalonate synthesis pathway [12]. This leads to reduced endogenous

cholesterol biosynthesis and, thus, to decreased levels of low-density lipoprotein, which is a major risk factor for atherosclerosis [13]. In addition, statins have been shown to improve endothelial function, stabilize plaques, reduce free radical formation and inhibit endothelial inflammatory reactions, thereby yielding other potential benefits for patients, regardless of cholesterol level reduction [14–16].

Apart from their well-documented therapeutic value in cardiovascular disease, there is a long-standing debate on the potential association between statins and cancer. In recent years, a growing body of studies has suggested that statins may have a potential role in the field of cancer chemoprevention [17–20] (also termed 'cancer-preventive therapy'). A number of mechanisms have been proposed regarding the potential antitumour effects of statins, through inhibition of proliferation, migration and invasion, and through induction of apoptosis [21]. On the other hand, concerns have also been raised regarding their safety [22]. An early review of rodent carcinogenicity data reported that lipid-lowering drugs, including statins, initiate or promote cancer (liver, forestomach, lung and thyroid tumours, and lymphoma) in rats and mice [23]. However, in most of the reviewed studies, the doses used were substantially higher than the doses recommended for humans, and the employed bioassays were criticized for being inadequate to predict carcinogenicity in humans [24].

There is already a large number of randomized trials and observational studies examining the association between statins and cancer, and even several meta-analyses thereof. Given that meta-analysis is high up in the proposed hierarchies of evidence [25–27], an overview of meta-analysis articles addressing this association was performed in order to obtain and discuss the existing clinical data on the subject.

2 Literature Review

2.1 Methods

Articles of interest for this overview were meta-analyses that examined the association between statins and cancer, having incorporated the evidence from randomized controlled trials of statins against placebo (or no treatment) and/or data from observational studies. The Medline database was searched from inception to 15 April 2014. Search terms included {HMG-CoA reductase inhibitor(s) or statin(s)} combined with {cancer(s), carcinoma(s), malignancy(ies), neoplasm(s) or tumor(s)}. The database search was limited to meta-analysis articles (publication type) and was also limited to the English language, human subjects and having an abstract available.

The titles and abstracts of identified published articles were scanned to exclude irrelevant publications. The full text of the selected articles was carefully read. Meta-analyses were considered regardless of whether they had included randomized trials, observational studies or both study designs; however, the meta-analyses of randomized trials was the preferred source of evidence for this overview, because the randomized controlled trial is the study design that is least likely to be biased. Cancer was the outcome of interest—either all malignancies combined or site- and type-specific cancers. The following information was collected from each meta-analysis article: the first author's last name, journal, year of publication, type of meta-analysis (i.e. individual participant data-based or literature-based), statin medications, cancer sites/types, number and design of included studies, and main and secondary results.

2.2 Search Results

Forty meta-analyses examining the association between statin use and cancer were identified (Table 1) [28–67]. Thirteen of those (32.5 %) included only large-scale randomized controlled trials of statins for cardiovascular outcomes, which reported cancer outcomes as secondary/safety endpoints [29, 30, 45, 49, 50, 52, 59, 61–64, 66, 67]. Eight of the meta-analyses (20 %) included only observational studies [34, 36, 38, 40, 44, 46, 48, 56], while the remaining 19 (47.5 %) included both study designs [28, 31–33, 35, 37, 39, 41–43, 47, 51, 53–55, 57, 58, 60, 65].

The majority of the meta-analyses were literature based [28–44, 46–48, 52–62, 64–67], while five analyzed individual participant data [45, 49–51, 63]. Their publication dates ranged between 2001 and 2014. Of note, these meta-analyses are chronologically built on an ever-expanding array of studies, and so there are inherent correlations from an earlier meta-analysis to a later one.

2.3 Limitations

This overview of meta-analysis articles suffers some limitations; only one database was searched, a single author selected studies for inclusion and quality assessment of the meta-analyses was not performed. Further limitations reflect the nature of the primary data included in the 40 meta-analyses identified. By design, the participants enrolled in the randomized controlled trials of statins for cardiovascular outcomes were at low risk of developing cancer. Given the small numbers of cancer cases, these studies may have not been adequately powered to detect potentially small differences in cancer risk. Moreover, because cancer occurrence was not the primary outcome of these trials, patients were not routinely screened for

Table 1 Meta-analysis articles examining the association between statin use and cancer

First author	Year	Design	Studies	Data	Tumour type studied, findings and comments
Zhang [28]	2014	Both	$n = 12$	AD	Kidney cancer risk (↔)
Bonovas [29]	2014	RCTs	$n = 9$	AD	Breast cancer risk (↔)
Lv [30]	2014	RCTs	$n = 6$	AD	Long-term cancer risk (↔)
Lytras [31]	2014	Both	$n = 40$	AD	Colorectal cancer risk (↓)
Li [32]	2014	Both	$n = 29$	AD	Melanoma risk (↔), non-melanoma skin cancer risk (↔)
Wu [33]	2013	Both	$n = 11$	AD	Gastric cancer risk (↓)
Beales [34]	2013	Obs	$n = 11$	AD	Oesophageal cancer risk (↓)
Singh [35]	2013	Both	$n = 11$	AD	Gastric cancer risk (↓)
Park [36]	2013	Obs	$n = 13$	AD	Recurrence following treatment of localized prostate cancer: overall risk (↔), but among patients treated with radiotherapy (↓)
Singh [37]	2013	Both	$n = 13$	AD	Oesophageal cancer risk (↓)
Pradelli [38]	2013	Obs	$n = 5$	AD	Hepatocellular cancer risk (↓)
Zhang [39]	2013	Both	$n = 13$	AD	Bladder cancer risk (↔)
Scosyrev [40]	2013	Obs	$n = 8$	AD	Biochemical recurrence of prostate cancer after definitive local therapy (↔)
Singh [41]	2013	Both	$n = 10$	AD	Hepatocellular cancer risk (↓)
Wang [42]	2013	Both	$n = 20$	AD	Lung cancer risk (↔)
Tan [43]	2013	Both	$n = 19$	AD	Lung cancer risk (↔)
Mass [44]	2012	Obs	$n = 6$	AD	Biochemical recurrence of prostate cancer after radical prostatectomy (↔)
CCT [45]	2012	RCTs	$n = 27$	IPD	Overall cancer incidence (↔) and mortality (↔)
Undela [46]	2012	Obs	$n = 24$	AD	Breast cancer risk (↔)
Cui [47]	2012	Both	$n = 16$	AD	Pancreatic cancer risk (↔)
Bansal [48]	2012	Obs	$n = 27$	AD	Total prostate cancer risk (↓), advanced prostate cancer risk (↓)
CCT [49]	2012	RCTs	$n = 27$	IPD	Overall and site-specific cancer incidence (↔) and mortality (↔)
CCT [50]	2010	RCTs	$n = 26$	IPD	Overall cancer incidence (↔), and mortality (↔)
Matsushita [51]	2010	Both	$n = 3$	IPD	Overall cancer incidence (↔), and mortality (↔)
Bonovas [52]	2010	RCTs	$n = 16$	AD	Melanoma risk (↔)
Bonovas [53]	2008	Both	$n = 12$	AD	Pancreatic cancer risk (↔)
Kuoppala [54]	2008	Both	$n = 42$	AD	Overall and site-specific cancer incidence (↔)
Bonovas [55]	2008	Both	$n = 19$	AD	Total prostate cancer risk (↔), advanced prostate cancer risk (↓)
Taylor [56]	2008	Obs	$n = 20$	AD	Overall cancer (↓), breast (↔), colon (↓), lung (↔), prostate cancer risk (↔)
Bonovas [57]	2007	Both	$n = 14$	AD	Risk of haematological malignancies (↔)
Bonovas [58]	2007	Both	$n = 18$	AD	Colorectal cancer risk (↓)
Bonovas [59]	2007	RCTs	$n = 12$	AD	Findings suggest an association between pravastatin therapy and cancer risk in elderly patients (↑)
Browning [60]	2007	Both	$n = 38$	AD	Overall cancer (↔), breast (↔), colorectal (↔), prostate (↔), gastric (↔), genitourinary (↔), melanoma (↔), lung cancer risk (↔)
Freeman [61]	2006	RCTs	$n = 12$	AD	Melanoma risk (↔)
Bonovas [62]	2006	RCTs	$n = 35$	AD	Overall cancer risk (↔), respiratory cancer risk (↔)
Stein [63]	2006	RCTs	$n = 8$	IPD	Fluvastatin therapy: overall cancer risk (↓), site-specific cancer risks (↔)
Dale [64]	2006	RCTs	$n = 26$	AD	Overall and site-specific cancer incidence (↔) and mortality (↔)
Bonovas [65]	2005	Both	$n = 16$	AD	Breast cancer risk (↔)
Dellavalle [66]	2005	RCTs	$n = 7$	AD	Melanoma risk (↔)
Bjerre [67]	2001	RCTs	$n = 5$	AD	Cancer incidence (↔) and mortality (↔)

AD aggregate data, *Both* both study designs (i.e. randomized controlled trials and observational studies) were included in the meta-analysis, *CCT* Cholesterol Treatment Trialists, *IPD* individual participant data, *Obs* observational studies, *RCTs* randomized controlled trials

↑, statistically significantly increased risk; ↓, statistically significantly decreased risk; ↔, non-significant association

cancer—a fact that may have affected the cancer detection rate. On the other hand, the observational data may have suffered some common limitations of pharmacoepidemiological studies, such as lack of control for drug dose and duration, short follow-up periods, recall bias from self-reported data, detection bias and confounding by indication, as well as selective reporting and other biases.

3 Do Statins Have a Potential Role in Cancer Prevention?

The evidence from meta-analyses of randomized and observational studies does not support the hypothesis that statin treatment affects cancer risk when taken at low doses for managing hypercholesterolaemia. The null findings are consistent for total cancer (i.e. the aggregate of all malignancies) and for most of the site-specific cancers (e.g. respiratory, breast, pancreatic, haematological, kidney or bladder cancer, or melanoma) [28, 29, 32, 39, 42, 43, 45–47, 49–54, 57, 60–67]. Moreover, a recent meta-analysis of large randomized trials with extended follow-up confirmed that statin treatment did not affect cancer incidence or mortality in the long term (up to 10 years and beyond), having included data for 47,296 individuals with total follow-up ranging from 6.7 to 14.7 years [30].

On the other hand, current evidence cannot exclude a modest decrease in the risk of developing colorectal cancer [31, 56, 58], a lower risk of advanced/aggressive prostate cancer [48, 55] or even larger risk reductions for certain cancer types (i.e. gastric, oesophageal or hepatocellular) [33–35, 37, 38, 41] associated with statin use. These hypotheses are mainly driven by observational studies, while the randomized evidence is scarce. However, observational studies lack the experimental random allocation of the intervention, which is necessary to optimally test exposure–outcome hypotheses. In any event, these findings should be regarded with caution because the possibility of residual confounding cannot be excluded, either from unknown or unmeasured factors, or from imperfectly adjusted real confounders [68, 69].

A yet uncertain issue refers to the hypothesis that the different chemical structures and pharmacokinetic properties of statins may imply different effects on cancer risk [70]. Statins are subclassified as either hydrophilic (such as pravastatin and rosuvastatin) or lipophilic (such as atorvastatin, fluvastatin, lovastatin and simvastatin). It has been suggested that lipophilic statins may be more effective for cancer chemoprevention [71, 72]. Most meta-analyses have pooled hydrophilic and lipophilic statins, ignoring any potential differential effect on cancer risk. However, even those meta-analyses that analyzed by statin class failed to show any difference in cancer risk with hydrophilic versus lipophilic statins [60, 64].

The potential relationship between pravastatin use and the risk of cancer in elderly patients is another issue that remains unclear [59]. The PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) trial [73] showed a higher cancer risk in elderly patients treated with pravastatin, compared with those on placebo ($p = 0.02$). The authors suggested that the increased cancer rate was most likely due to chance [73, 74]. However, a significant increase in cancer rates among elderly patients assigned to pravastatin therapy was also reported in a subgroup analysis of the LIPID (Long-Term Intervention with Pravastatin in Ischaemic Disease) trial [75]. Moreover, in the CARE (Cholesterol and Recurrent Events) trial [6], breast cancer occurred in a greater number of women treated with pravastatin ($p = 0.002$). Similarly, WOSCOPS (the West of Scotland Coronary Prevention Study) [76] showed an increase in prostate cancer risk in the pravastatin group ($p = 0.03$). A meta-regression analysis of all available pravastatin trials [59] suggested the hypothesis that pravastatin therapy may be associated with an increasing risk of cancer as age increases.

Though a causal relationship cannot be established, it has been hypothesized [22] that hydrophilic pravastatin may promote cancer by causing an induction of HMG-CoA reductase and, hence, mevalonate synthesis in extrahepatic tissues. Mevalonate can promote the growth of occult neoplastic or preneoplastic cells [77]. Because of the absence of uptake of pravastatin by most extrahepatic cells, this statin will be unable to mitigate the increase in mevalonate synthesis in extrahepatic tissues that accompanies the decrease in circulating cholesterol caused by its inhibition of hepatic HMG-CoA reductase. Thus, increased mevalonate synthesis in extrahepatic tissues might explain an increased cancer risk in elderly patients, who are expected to harbour a large number of preneoplastic and occult neoplastic lesions [22]. Conversely, the uptake of the lipophilic statins in extrahepatic tissues mitigates the increase in mevalonate synthesis that accompanies the decrease in serum cholesterol that they induce [78]. Thus, lipophilic statins should be expected not to promote cancer [22]. However, the epidemiological evidence on those issues remains unclear. Further research and detailed individual patient data-based meta-analyses, following appropriate methods of analysis, are warranted [79, 80].

4 Do Statins Have a Potential Role in Modifying Cancer-Related Outcomes?

Unlike the plethora of randomized controlled trials and observational studies providing data for the evaluation of

statins for the primary prevention of cancer (and adequate meta-analytic evidence thereof), data are lacking for any effects of statin treatment on cancer prognosis and secondary/tertiary prevention, with the exception of weak evidence from a limited number of large observational studies. Recently, a population-based registry study [81] assessed mortality among over 295,000 Danish patients who had received a diagnosis of cancer between 1995 and 2007. The study reported that statin use (begun before the cancer diagnosis) was associated with a 15 % reduction in cancer-related mortality across a broad range of malignancies. Though this study suffered from some inherent limitations [82] stemming from its observational nature, the results have captured much attention, and further prospective randomized research is urgently warranted to confirm or refute the hypothesis that statin administration prolongs the survival of patients with cancer. Given that numerous experimental studies have also demonstrated that statins, especially the lipophilic ones, exert strong antiproliferative and proapoptotic effects on various tumour cell lines of differing origins [83–86], a role of statins in modifying cancer-related outcomes is still quite possible.

At the level of site-specific cancers, there is also some weak evidence suggesting that statins might be effective to prevent recurrence and/or improve survival in patients suffering from colorectal, breast, prostate or hepatocellular malignancies. In a large population-based cohort study of newly diagnosed colorectal cancer patients [87], statin use after the diagnosis was associated with reduced colorectal cancer-specific mortality. A number of cohort studies have also reported a reduced risk of recurrence in breast cancer patients using statins [88–93], but others have not [94]. Similarly, a recent cohort study [95] demonstrated that statin administration was associated with a decreased risk of prostate cancer mortality. An earlier well-conducted meta-analysis of 13 cohort studies [36] examined the association between statin use and recurrence-free survival following treatment of localized prostate cancer, and suggested a potentially beneficial effect of statins in prostate cancer patients treated with radiotherapy, but not among those patients treated with radical prostatectomy. Nevertheless, this meta-analysis was limited by the observational nature of the primary studies that were included, and the statistically significant between-studies heterogeneity that was identified [36]. On the other hand, a small randomized clinical trial performed in a population of patients with hepatocellular cancer [96] has demonstrated that pravastatin use significantly increased their survival. In contrast, other recently published observational studies have failed to show any beneficial effect of statins on the recurrence and progression of renal [97] and gastric [98] malignancies.

5 Conclusions

A large number of clinical studies have analyzed the cancer risk in statin users. As of today, the accumulated data do not support the hypothesis that statins affect the risk of developing cancer when taken at low doses for managing hypercholesterolaemia. However, current evidence cannot exclude an increased cancer risk in elderly patients associated with hydrophilic statin use, or important decreases in the risk of certain cancers, such as gastric, oesophageal, liver, colorectal and advanced/aggressive prostate cancer. On the other hand, some recently published observational studies provide weak evidence that statins might be useful in modifying cancer-related outcomes in patients who are already suffering from malignancies.

Statins cannot be recommended either for primary cancer prevention or for modification of cancer-related outcomes, until and unless a definitive benefit is demonstrated in prospective randomized trials. However, large-scale clinical trials of statins for cancer prevention are difficult to conduct [99]. Because of statins' widespread use, it would be very difficult to recruit suitable patient populations, and the long duration of such trials would pose many challenges in terms of probable contamination [100]. It is encouraging, however, that several relatively small clinical trials are ongoing. There are currently over 100 studies on the ClinicalTrials.gov website [101], in various stages of recruitment and data collection, which are investigating different aspects of the relationship between statins and cancer. This effort should continue to help clinicians determine the potential role of statin therapy in the prevention and treatment of cancer.

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