Statins are associated with reduced risk of gastric cancer: a systematic review and meta-analysis

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Background: Several observational studies have shown that statins may modify the risk of gastric cancer (GC). We carried out a systematic review and meta-analysis of studies evaluating the effect of statins on GC risk.

Patients and methods: We conducted a systematic search of multiple databases up to December 2012. Studies that evaluated exposure to statins, reported GC outcomes and odds ratio (OR) or provided data for their estimation were included in the meta-analysis. Pooled OR estimates with 95% confidence intervals (CIs) were calculated using the random-effects model.

Results: Eleven studies (eight observational, three post-hoc analyses of 26 clinical trials) reporting 5581 cases of GC were included. Meta-analysis showed a significant 32% reduction in GC risk with statin use (adjusted OR, 0.68; 95% CI, 0.51–0.91). After exclusion of one study which was contributing to considerable heterogeneity, a significant 16% reduction in GC risk was a more conservative, consistent estimate (adjusted OR, 0.84; 95% CI, 0.78–0.90). This chemopreventive association was present in both Asian (adjusted OR, 0.68; 95% CI, 0.53–0.87) and Western population (adjusted OR, 0.86; 95% CI, 0.79–0.93).

Conclusions: Meta-analysis of studies supports a protective association between statin use and GC risk, in both Asian and Western population, in a dose-dependent manner.

Key words: cancer risk, chemoprevention, gastric cancer, statins

Introduction

With an annual incidence of nearly 1 million, gastric cancer (GC) is the fourth most common cancer worldwide and the second most frequent cause of cancer death with >0.7 million deaths annually [1]. Over 70% of new cases and deaths occur in developing countries, predominantly in Eastern Asia and Eastern Europe, which has been attributed to chronic Helicobacter pylori infection and dietary habits. Unfortunately, almost half of the patients present with advanced, inoperable disease with a 5-year survival rate of <5% [2]. Even in patients with resectable disease, prognosis is dismal with 5-year survival rates in the order of 25–35% [3, 4]. Early endoscopic detection of GC is feasible and could potentially improve outcomes, but is cost prohibitive [5]. Current strategies for improving outcomes in GC are aimed at reducing chronic H. pylori infection, screening patients at highest risk and identifying chemopreventive agents.

Statins, or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, used for primary and secondary prevention of cardiovascular diseases, decrease the risk of certain cancers [6, 7] and reduce cancer-related mortality [8]. In vitro and animal studies have shown that in addition to cholesterol reduction, statins have anti-proliferative, pro-apoptotic, anti-angiogenic and immunomodulatory effects, which prevent cancer development and growth [9]. This effect has also been shown in human GC-derived cell lines [10]. Some recent observational studies have shown that statins may be associated with a lower risk of GC [11, 12], whereas others have shown no beneficial effect [13, 14].

To better understand this issue, we carried out a systematic review with meta-analysis of existing randomized, controlled trials (RCT) and observational studies that investigated the association between statins and the risk of developing GC.

Methods

This systematic review was conducted following guidance provided by the Cochrane Handbook [15] and is reported according to the Meta-analysis of Observational Studies in Epidemiology guidelines [16]. The process followed an a priori established protocol.

Data sources and search strategy

First, a systematic literature search of PubMed (1966 through 1 December 2012), Embase (1988 through 1 December 2012) and Web of Science (1993 through 1 December 2012)
databases was conducted for all relevant articles on the effect of statins use on the risk of GC. Search terms used included ‘HMG-CoA reductase inhibitor(s)’, ‘statin(s)’, ‘atorvastatin’, ‘fluvastatin’, ‘lovastatin’, ‘pravastatin’, ‘rosuvastatin’, ‘pitavastatin’ or ‘simvastatin’ combined with ‘cancer’ or ‘neoplasm(s)’. The results were exported to a common EndNote (reference manager) file. After this, duplicates were removed, and a total of 2370 unique studies were identified. Then, according to the protocol-defined study inclusion and exclusion criteria (see below) both authors independently reviewed the studies to see whether the inclusion criteria were met. Based on the review of the title and abstract, 2281 studies were excluded since they provided insufficient information on the risk of GC and statins. For the remaining 89 articles which were related to this topic, both authors reviewed the full text of the articles, independently, and reported the studies that each felt should be included or excluded. The coefficient of agreement between the two reviewers ($\kappa = 0.86$, 95% CI, 0.73–1.00) was excellent. Second, we searched the bibliographies of these selected articles as well as relevant narrative and systematic review articles to identify any additional studies. Third, we also searched conference proceedings of major oncology (American Society of Clinical Oncology annual meeting as well as the Gastrointestinal Research Forum; European Society of Medical Oncology annual meeting and meeting as well as the Gastrointestinal Research Forum; American Society of Clinical Oncology annual meeting and meeting as well as the Gastrointestinal Research Forum; World Congress on GI Cancer) and gastroenterology conferences (Digestive Diseases Week, American College of Gastroenterology annual meeting) from 2005 to 2012 for studies that had been published only in the abstract form. Figure 1 summarizes the study identification and selection process.

study selection

Studies considered in this meta-analysis were either RCTs or observational studies that met the following inclusion criteria: (i) evaluated and clearly defined exposure to statins, (ii) reported GC incidence and (iii) reported relative risks (RR) (for cohort studies) or odds ratio (OR) (for case–control studies) or provided data for their calculation. Inclusion was not otherwise restricted by study size, language or publication type. Articles were excluded from the analyses if there were insufficient data for determining an estimate of RR/OR and a 95% confidence interval (CI), though these were included in the systematic review and described qualitatively. When there were multiple publications from the same population, only data from the most recent comprehensive report were included.

data abstraction and quality assessment

Data were independently abstracted onto a standardized form by both the authors. The following data were collected from each study: study design, time period of study/year of publication, country of the population studied, primary outcome reported, type, dose and duration of statin use, information source for exposure measurement, total number of persons in each group (exposed to statins versus not exposed), OR and 95% CIs with and without adjustment for potential confounders and potential confounders used for adjustment. Data on the following confounding risk factors for GC were extracted from each study: age, sex, race, cigarette smoking, body mass index (BMI), history of H. pylori, diet, other medication use [aspirin/non-steroidal anti-inflammatory drugs (NSAID)] and alcohol use. Conflicts in data abstraction were resolved by consensus, referring back to the original article.

The methodological quality of case–control and cohort studies was assessed by both the authors independently using the Newcastle–Ottawa scale, with very good agreement ($\kappa = 0.77$; 95% CI, 0.65–0.90) [17]. In this scale, observational studies were scored across three categories: selection (four questions) and comparability (two questions) of study groups, and ascertainment of the outcome of interest (three questions), with all questions with a score of one, except for comparability of study groups, where separate points were awarded for controlling age and/or sex (maximum two points). A score of ≥7 was suggestive of a high-quality study. The methodological quality of randomized trials was assessed using the Cochrane Collaboration’s tool for assessing the risk of bias in randomized trials [15]. Any discrepancies were addressed by a joint re-evaluation of the original article.

outcomes assessed

The primary analysis focused on assessing the risk of GC among users of statins. A priori hypotheses to explain potential heterogeneity in the direction and magnitude of effect among different studies included location of study (Asian population versus Western population), study design (observational studies versus clinical trials) and study setting (hospital-based versus population-based).

In the three studies which provided data on relationship between dose/duration of statin use and risk reduction in GC [11, 12, 14], long duration of statin use was defined as: more than median cumulative defined daily dose of statins [11] or >2 years of statin use [12] or >4–6 years [14]. Likewise, short duration of statin use was defined as: less than median cumulative defined daily dose of statins [11] or 0.5–1.0 years of statin use [12] or 1–2 years [14].

data synthesis and analysis

We used the random-effects model described by DerSimonian and Laird to calculate summary OR and 95% CI [18]. We assessed heterogeneity between study-specific estimates using two methods [19]. First, the Cochran’s Q statistical test for heterogeneity, which tests the null hypothesis that all studies in a meta-analysis have the same underlying magnitude of effect, was measured. Because this test is underpowered to detect moderate degrees of heterogeneity [20], a $P$ value of < 0.10 was considered suggestive of significant heterogeneity. Second, to estimate what proportion of total variation across studies was due to heterogeneity rather than chance, $I^2$ statistic was calculated. In this, a value of >50% was suggestive of considerable heterogeneity [21]. Once heterogeneity was noted, between-study sources of heterogeneity were investigated using subgroup analyses by stratifying original estimates according to study characteristics (as described above). In this analysis also, a $P$ value for differences between subgroups of < 0.10 was considered statistically significant (i.e. a value of
Table 1. Characteristics of included studies assessing the risk of gastric cancer (GC) with statin use

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Location/setting</th>
<th>Time Period</th>
<th>Exposure ascertainment</th>
<th>Outcome assessment</th>
<th>All subjects</th>
<th>On statins</th>
<th>Not on Statins</th>
<th>Confounding variables adjusted for*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GC Total</td>
<td>GC Total</td>
<td>GC Total</td>
<td></td>
</tr>
<tr>
<td>Chiu et al. [11]</td>
<td>C–C</td>
<td>Taiwan; Population-based</td>
<td>2005–2008</td>
<td>National Pharmacy Database</td>
<td>Medical diagnostic codes</td>
<td>337</td>
<td>1685</td>
<td>56</td>
<td>354</td>
</tr>
<tr>
<td>Huakka et al. [28]</td>
<td>Nested C–C</td>
<td>Finland; Population-based</td>
<td>1996–2005</td>
<td>National Pharmacy Database</td>
<td>Record linkage, with Finnish Cancer Registry</td>
<td>1667</td>
<td>944 962</td>
<td>770</td>
<td>472 481</td>
</tr>
<tr>
<td>Kaye et al. [13]</td>
<td>C–C</td>
<td>UK; Population-based</td>
<td>1990–2002</td>
<td>National Pharmacy Database</td>
<td>Medical diagnostic codes</td>
<td>39</td>
<td>18 088</td>
<td>4</td>
<td>3244</td>
</tr>
<tr>
<td>Graaf et al. [27]</td>
<td>Nested C–C</td>
<td>Netherlands; Population-based</td>
<td>1985–2008</td>
<td>PHARMO Record Linkage</td>
<td>Hospital discharge records</td>
<td>104</td>
<td>20 105</td>
<td>NR</td>
<td>1444</td>
</tr>
<tr>
<td>Vinogradova et al.[14]</td>
<td>Nested C–C</td>
<td>UK; Population-based</td>
<td>1998–2008</td>
<td>National Pharmacy Database</td>
<td>Medical diagnostic codes</td>
<td>1992</td>
<td>10 271</td>
<td>322</td>
<td>1685</td>
</tr>
<tr>
<td>Lee et al. [12]</td>
<td>C–C</td>
<td>South Korea; Hospital-based</td>
<td>1999–2008</td>
<td>Pharmacy dispensing records</td>
<td>Medical diagnostic codes</td>
<td>983</td>
<td>1966</td>
<td>99</td>
<td>466</td>
</tr>
<tr>
<td>Marelli et al. [29]</td>
<td>Nested C–C</td>
<td>USA; Population-based</td>
<td>1991–2009</td>
<td>Pharmacy dispensing records</td>
<td>Electronic Medical Record review</td>
<td>31</td>
<td>91 714</td>
<td>13</td>
<td>45 857</td>
</tr>
<tr>
<td>Cholesterol Treatment Trialists’ (CTT) [25]</td>
<td>22 RCTs (post-hoc)</td>
<td>Europe/USA/Australia; Hospital-based</td>
<td>–</td>
<td>Individual drug dispensation</td>
<td>Adverse event reporting by investigators</td>
<td>192</td>
<td>134 537</td>
<td>92</td>
<td>67 258</td>
</tr>
<tr>
<td>Matsushita et al. [30]</td>
<td>Three clinical trials (individual patient data)</td>
<td>Japan; Hospital-based</td>
<td>–</td>
<td>Individual drug dispensation</td>
<td>Adverse event reporting by investigators</td>
<td>95</td>
<td>13 724</td>
<td>43</td>
<td>7375</td>
</tr>
<tr>
<td>Sato et al. [31]</td>
<td>RCT (post-hoc)</td>
<td>Japan; Hospital-based</td>
<td>1991–1995</td>
<td>Individual drug dispensation</td>
<td>–</td>
<td>4</td>
<td>263</td>
<td>3</td>
<td>179</td>
</tr>
</tbody>
</table>

*1, age, 2, sex, 3, race, 4, BMI, 5, smoking/alcohol, 6, *H. pylori*, 7, peptic ulcers, 8, other medications (aspirin/NSAIDs), 9, other lipid lowering agents, 10, healthcare utilization, 11, socioeconomic status, 12, comorbidities, 13, calendar year, 14=region.

C–C, case–control; CTT, cholesterol treatment trialists’ Collaboration; RCT, randomized, controlled trials; NR, not reported.
Meta-analysis [24]. All needed to remove the significance from the findings of this meta-analysis [24]. All P-values were two-tailed. For all tests (except for heterogeneity and publication bias), a probability level of <0.05 was considered statistically significant.

Since outcomes were relatively rare, ORs were considered approximations of RR. We also calculated the number needed to treat with statins to prevent one case of GC in the general population, based on the current estimates of incidence of GC. All calculations and graphs were carried out using Comprehensive Meta-Analysis version 2 (Biostat, Englewood, NJ).

results

search results

Eleven studies met the defined inclusion criteria for this meta-analysis (seven case–control, one cohort, three post-hoc analysis of 26 clinical trials) [11–14, 25–31]. An abstract search from meeting proceedings did not yield any additional articles. These cumulatively reported 5581 cases of GC in 5,459,975 patients. Of the total, 962,192 patients were classified as statin users (16.7%). There were two Taiwanese studies from the same cohort [11, 32] and hence, only the most comprehensive report from these was included [11].

characteristics of included studies

The characteristics of these studies are shown in Table 1. The earliest study period began in 1985, and the latest ended in 2009. Seven studies were carried out in the Western population (four in Europe, two in United States and one was collaboration of multi-center trials across Europe, North America and Australia); [13, 14, 25–29] four studies were in the Asian population (two in Japan, one in South Korea, one in Taiwan) [11, 12, 30, 31]. The studies used both lipophilic and hydrophilic statins.

Chiu et al. carried out a case–control study on Taiwanese patients >50 years of age with new diagnosis of GC from 2005 to 2008 [11], while Huakka et al. [28], Graaf et al. [27] and Vinogradova et al. [14] carried out nationwide population-based nested case–control studies on statin exposure and the risk of various cancers, in Finland, the Netherlands and UK, respectively, through record linkage between the pharmacy dispensing records and the national cancer registries. Marelli et al. carried out a propensity-matched cohort analysis of the incidence of cancer in older adults who had or had not used statins, using the General Electric Centricity electronic medical records database of >11 million patients [29]. Friedman et al. used the pharmacy information management system and cancer registry of the Kaiser Permanente Medical Care Program of northern California, United States to estimate the risk of cancer in patients exposed to statins [26]. Lee et al. carried out a single-center, matched case–control, hospital-based study in patients with diabetes mellitus to assess the association between GC and statin use [12]. Matsushita et al. carried out an analysis of individual patient data from three large-scale clinical trials in patients with hyperlipidemia in Japan [30]. Emberson et al. carried out an individual patient data analysis of 22 RCTs of statins versus controls conducted by the Cholesterol Treatment Triallists’ (CTTs) collaboration to assess cancer incidence with statin exposure [25].

quality of included studies

Six observational studies were considered high-quality (Newcastle–Ottawa score ≥7) [11, 13, 14, 27–29]. Tables 2 and 3 depict the methodological quality of all studies. Though most studies adjusted or matched for demographic variables, they did not consistently account for other potential confounders: BMI (3 of 11), smoking and/or alcohol use (3 of 11), history of H. pylori (2 of 11) and other medication use (aspirin/NSAIDs) (4 of 11). None of the studies adjusted for dietary risk factors for GC. For outcome ascertainment, most studies relied on medical diagnostic codes for GC, others reported record linkage through the cancer registry; both strategies had been validated to have high accuracy in the respective databases. In order to account for detection bias, three studies adjusted for the frequency of healthcare utilization in statin users and non-users [11, 13, 27]. In all included studies, a temporal relation of development of GC to statins was established by excluding cases of GC developing before exposure to statins, though there was variable duration of minimum statin use before new incident GC cases were included for analysis (0 months–2 years were reported). The overall quality of included RCTs was moderate to high [25, 30, 31]. However, all clinical trial studies were post-hoc analyses of RCTs carried out to assess the safety and efficacy of statins in the management of hyperlipidemia and/or coronary heart diseases.

risk of gastric cancer

On meta-analysis of all studies assessing the risk of GC, the use of statins was associated with a statistically significant 30% reduction in GC incidence (unadjusted OR, 0.70; 95% CI, 0.51–0.97) (Figure 2). There was, however, considerable heterogeneity observed across studies (Cochran’s Q-test, P < 0.01; I² = 93%). This risk reduction with statins persisted even after adjusting for potential confounders (adjusted OR, 0.68; 95% CI, 0.51–0.91) (Figure 2), though the heterogeneity persisted (Cochran’s Q-test, P < 0.01, I² = 89%). For the remainder of the analysis, the maximally adjusted OR reported in each study was used.

On restricting analysis to high-quality observational studies [11, 13, 14, 27–29], statin use continued to be associated with reduced risk of GC (n = 6 studies; adjusted OR, 0.83; 95% CI, 0.76–0.90). Moreover, the results were consistent across studies with minimal heterogeneity (Cochran’s Q-test P = 0.71; I² = 0%).
We carried out pre-planned stratified analyses of studies based on study design, location and setting (Table 4). None of these stratifications could account for the heterogeneity observed in the overall analysis. Statin use was associated with a reduced risk of GC in observational studies, and a
non-significant reduction in risk was in post-hoc analyses of RCTs. Statin use was associated with a reduced risk of GC in a subset of studies carried out in the Western population; there was a similar trend in the Asian studies, though this was not statistically significant and considerably heterogeneous.
A trend toward a dose–duration response was seen on pooled analysis of three studies which provided sufficient data for this analysis [11, 12, 14]. A ‘long’ duration of statin was significantly more likely to have chemopreventive effect (adjusted OR, 0.35; 95% CI, 0.16–0.76) than ‘short’ duration of statin use (adjusted OR, 0.73; 95% CI, 0.51–1.05). Sufficient information was not available to carry out stratified analysis based on the age, gender, location of GC (cardia or non-cardia) or on the type of statins (lipophilic versus hydrophilic).

sensitivity analysis

To assess whether any one study had a dominant effect on the meta-analytic OR, each study was excluded and its effect on the main summary estimate and Cochran’s Q-test P value for heterogeneity was evaluated. While no study significantly affected the summary estimate, exclusion of the study by Lee et al. resulted in resolution of the previously observed marked heterogeneity in the analysis [12]. The favorable and strong effect sizes observed in this single study were causing heterogeneity in the strength, but not the direction, of overall association. On analysis after excluding this study, the summary OR for both unadjusted (OR, 0.88; 95% CI, 0.83–0.95) and adjusted analysis (OR, 0.84; 95% CI, 0.78–0.90) remained significant and no heterogeneity was observed in the analysis (for unadjusted OR, Cochran’s Q-test, \( P = 0.56, I^2 = 0\% \); for adjusted OR, Cochran’s Q-test, \( P = 0.74, I^2 = 0\% \)).

Subgroup analyses were repeated after excluding this study (Table 4). The previously statistically non-significant association between statin use and GC risk in the Asian population became statistically significant.

On replacing one Taiwanese study [11] with another study from Taiwan from the same cohort [32], the overall results (adjusted OR, 0.64; 95% CI, 0.47–0.88), as well as in the subgroup of Asian studies (adjusted OR, 0.38; 95% CI, 0.17–0.85), were unchanged.

publication bias

There was no evidence of significant publication bias, both quantitatively (Egger’s regression test, \( P = 0.54 \)) and on visual inspection of the funnel plot (data not shown). Furthermore, we estimate that 136 unpublished null studies (which fail to show a chemopreventive association between statins and risk of GC) would be needed to remove the significance from the findings of this meta-analysis.

number needed to treat

Due to significant heterogeneity between studies and varying incidence of GC across different regions of the world, a single summary estimate for the number needed to treat with statins to prevent one case of GC could not be inferred. Using an age-adjusted incidence rate of GC in men in East Asia of 42.4 per 100 000 person years and a 32% reduction in GC risk with statin use, 7372 East Asian men would need to be treated with statins to prevent one case of GC per year [1]. Similarly, using an age-adjusted incidence rate of GC of 9.0 per 100,000 person years in Western Europe and a 14% reduction in GC risk with statin use, 79,371 men would need to be treated to prevent one case of GC [1].

discussion

With the high incidence of GC and very poor prognosis associated with the diagnosis, identification of potential chemopreventive agents is highly desirable. While aspirin and NSAIDs [33, 34] and H. pylori eradication therapy may be associated with reduced risk of GC [35], they are not without significant side-effects. In this comprehensive meta-analysis of all existing studies in almost 5.5 million patients with 5581 cases of GC, we found that statin use is associated with a 32% reduction in the risk of GC, after adjusting for multiple confounding factors. Given considerable heterogeneity attributed to one study, a 16% risk reduction with statin use

Table 4. Subgroup analysis of all studies

<table>
<thead>
<tr>
<th>Grouping variable</th>
<th>Subgroups</th>
<th>No. of studies</th>
<th>Unadjusted OR</th>
<th>95% CI</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>Heterogeneity between groups (( P_{interaction} ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>Observational</td>
<td>8</td>
<td>0.66</td>
<td>0.45–0.99</td>
<td>0.65</td>
<td>0.45–0.93</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>RCT (post-hoc analyses)</td>
<td>3</td>
<td>0.85</td>
<td>0.65–1.07</td>
<td>0.83</td>
<td>0.66–1.05</td>
<td></td>
</tr>
<tr>
<td>Study location</td>
<td>Western</td>
<td>7</td>
<td>0.90</td>
<td>0.84–0.97</td>
<td>0.86</td>
<td>0.79–0.93</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>4</td>
<td>0.51</td>
<td>0.21–1.25</td>
<td>0.50</td>
<td>0.23–1.09</td>
<td></td>
</tr>
<tr>
<td>Study setting</td>
<td>Population-based</td>
<td>7</td>
<td>0.89</td>
<td>0.82–0.96</td>
<td>0.84</td>
<td>0.78–0.91</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>Hospital-based</td>
<td>4</td>
<td>0.56</td>
<td>0.20–1.55</td>
<td>0.56</td>
<td>0.22–1.39</td>
<td></td>
</tr>
<tr>
<td>After excluding Lee et al. [12]</td>
<td>Observational</td>
<td>7</td>
<td>0.89</td>
<td>0.82–0.96</td>
<td>0.84</td>
<td>0.78–0.91</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>RCT (post-hoc analyses)</td>
<td>3</td>
<td>0.85</td>
<td>0.65–1.07</td>
<td>0.83</td>
<td>0.66–1.05</td>
<td></td>
</tr>
<tr>
<td>Study location</td>
<td>Western</td>
<td>7</td>
<td>0.90</td>
<td>0.84–0.97</td>
<td>0.86</td>
<td>0.79–0.93</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>3</td>
<td>0.71</td>
<td>0.56–0.91</td>
<td>0.68</td>
<td>0.53–0.87</td>
<td></td>
</tr>
<tr>
<td>Study setting</td>
<td>Population-based</td>
<td>7</td>
<td>0.89</td>
<td>0.82–0.96</td>
<td>0.85</td>
<td>0.79–0.91</td>
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</tr>
<tr>
<td></td>
<td>Hospital-based</td>
<td>3</td>
<td>0.85</td>
<td>0.65–1.07</td>
<td>0.83</td>
<td>0.66–1.05</td>
<td></td>
</tr>
</tbody>
</table>

*for adjusted OR.

No, number; OR, odds ratio; RCTs, randomized, controlled trials.
may be a more conservative and consistent estimate. Such a chemopreventive effect of statins has also been observed for some inflammation-associated cancers (including hepatocellular cancer [6], esophageal cancer [36]), but not for others (such as sporadic colorectal cancer [37], breast cancer [38] and prostate cancer [38]). This is comparable with 22% reduction in the risk of GC seen with aspirin/NSAID use (OR, 0.78; 95% CI, 0.69–0.87) seen in a previous meta-analysis of observational studies [34]. Importantly, the latter may confounded by indication, since patients with gastric ulcers (a group at high risk for GC) may be less likely to be prescribed aspirin/NSAIDs, thereby overestimating the apparent chemopreventive effect of these medications.

The strengths of this analysis include the comprehensive and systematic literature search of both observational studies and RCTs, consistency of association between statins and GC, ability to evaluate the potential influence of measured confounders on the summary estimates and evaluation of duration–response effect. The likelihood of important selection or publication bias in our meta-analysis is small. During the identification and selection process, we did not exclude any article because of methodological characteristics. Our results are consistent with a previous small meta-analysis. Kouppala et al. included only two cohort studies in their analysis and observed a significant chemopreventive effect of statin use (OR, 0.59; 95% CI 0.40–0.88) [38]. In our analysis, we added numerous additional studies, including data from RCTs, to bring the evidence base up to date, and provide a more robust pooled estimate on the effect of statins on GC risk. With the larger number of studies, we were able to carry out multiple subgroup analyses, evaluate heterogeneity and the presence of publication bias.

**anti-neoplastic effect of statins**

GC has two histological subtypes that have distinct carcinogenic pathways [39]. Intestinal or well-differentiated tumors progress through atrophic gastritis followed by intestinal metaplasia, dysplasia and carcinoma, whereas diffuse or poorly differentiated carcinomas are not characterized by preceding steps other than the chronic gastritis associated with *H. pylori* infection. Among the genetic changes implicated in the multi-stage gastric carcinogenesis, amplification of c-myc and mutations of K-ras have been commonly reported [40]. In mice models, atorvastatin has been shown to block MYC phosphorylation and activation, suppressing tumor initiation and growth through a HMG-CoA reductase-dependent pathway [41]. The anti-neoplastic effects of statins have also been demonstrated in human GC cell lines through reduced cell division and increased apoptosis. Using human GC cell line HGT-1, Follet et al. have shown that lovastatin strongly suppresses genes involved in cell division on whole transcriptome microarrays [10]. Lovastatin also induced upregulation of cell-cycle inhibitor p21 and suppression of anti-apoptotic survivin and Mcl-1 proteins in these GC cell lines.

**differences in observational studies and clinical trials**

The chemopreventive effect of statins was seen primarily in observational studies which accounted for a large majority of the included GC cases (5290 cases, 94.8%). RCTs included in the study did not demonstrate any significant chemopreventive effect of statins though there is a trend toward statistical significance (adjusted OR, 0.83; 95% CI, 0.66–1.05). Importantly, the RCTs included in the meta-analysis represented *post-hoc* analyses of 26 clinical trials carried out on the effect of statins on cardiovascular morbidity [25, 30, 31]. By design, the patients enrolled in these RCTs were not at high risk of development of GC. Also, these studies were not adequately powered to detect a significant difference in GC incidence. Moreover, since the occurrence of cancer was not the primary objective of these trials, patients were not routinely screened for development of GC; this might have affected the detection rate of GC. The follow-up duration in these RCTs was short. These factors may explain why current clinical trials of statins do not demonstrate a statistically significant chemopreventive effect of statins against GC.

On the other hand, the chemopreventive effect of statins seen in observational studies may also over-estimate its true effect. Observational studies lack the experimental random allocation of the intervention necessary to test exposure-outcome hypotheses optimally. Despite adjusting for numerous covariates, it is not possible to eliminate the potential of residual confounding. It is possible that the observed decreased risk of GC seen in statin users may relate to a ‘healthy user’ bias [42]. Patients taking statins may be more likely to be prescribed preventive medications and/or be more compliant with preventive health measures, when compared with patients not taking statins. The latter poorly compliant patients may have other unhealthy lifestyle practices predisposing them to GC. In our analysis, on restricting analysis to studies which adjusted for frequency of healthcare utilization, statins continued to show a stable and consistent chemopreventive effect against GC (adjusted OR, 0.68; 95% CI, 0.52–0.90) [11, 13, 27]. Hence, given the strength and consistency of association along with *in vitro* data that suggest biological plausibility of preventive effects of statins on GC, ‘healthy user’ effect is unlikely to be the primary driver of results. Observational studies are inherently not able to definitely establish when the intervention may exert its influence, the minimum effective dose–duration and frequency of medication intake that is required to achieve a benefit. Although we found a potential duration benefit, differing exposure definitions between studies make recommendations regarding dosing regimens difficult.

**limitations**

First, the included studies did not provide data based on the location or histological subset of GC, which are associated with different pathogenesis and prognosis. Second, all studies did not adjust for the same confounders. Importantly, studies failed to adjust for *H. pylori* infection which is strongly associated with GC risk. However, though biologically plausible, multiple RCTs and meta-analyses have failed to show a clinically significant reduction in GC risk with *H. pylori* eradication [35, 43–45]. Moreover, in our analysis, there was no significant difference in the pooled analysis of unadjusted and maximally adjusted data from each study, suggesting that any difference attributable to using different...
confounders for adjustment is likely small. Another potential limitation that particularly applies to case–control studies evaluating GC is recall bias. However, in most studies pharmacy drug prescriptions information was used, and hence, the effects of this are likely minimal. The significant heterogeneity observed in the meta-analysis could be explained by excluding a single study. In their single-center study of a diabetic cohort in high-risk South Korean population, Lee et al. observed a marked 70%–80% reduction in GC risk [12]. This marked decrease in risk may be related to detection bias in this referral center study as well as potential confounding by concomitant use of other putative chemopreventive effect of aspirin and metformin [46]. Finally, we did not contact authors of RCTs to solicit unpublished data, and this may have resulted in reporting bias. However, we estimated that 136 unpublished null studies (which fail to show a chemopreventive association between statins and risk of GC) would be needed to remove the significance from the findings of this meta-analysis.

conclusion

Based on this comprehensive meta-analysis, statins appear to have chemopreventive effects against GC in both Asian and Western population. However, since the observed magnitude of GC risk reduction associated with statins is relatively modest, especially in the Western population, the number needed to treat to prevent one case of GC would be large. A definitive, randomized chemoprevention trial is needed to more rigorously assess the effects of statins on incident GC, but would be lengthy, logistically challenging and resource intensive. To facilitate further clarification of statins’ GC chemopreventive potential, clinical evaluation in an enriched patient population (i.e. East Asian men with history of gastric atrophy or ulcers) may be the first best step. Meanwhile, in patients with borderline eligibility for statin therapy, other risk factors for GC may be informative with respect to balancing risks versus benefits for clinical decision-making.

disclosure

The authors have declared no conflicts of interest.

references

Targeted therapies and the treatment of non-clear cell renal cell carcinoma

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Background: Targeted therapies have shown profound effects on the outcome of patients with advanced renal cell carcinoma (RCC). However, the optimal treatment for RCC of non-clear cell histology (nccRCC)—typically excluded from trials of targeted agents—remains uncertain.

Materials and methods: By carrying out extensive searches of PubMed and ASCO databases, we identified and summarised research into the biological characteristics, clinical behaviour and treatment of different histological subtypes of nccRCC, focusing on targeted therapy.

Results: The available data suggest that treatments currently approved for RCC are active in ncc subtypes, although the overall clinical benefit may be less than for clear cell RCC. Temsirolimus has proven benefit over interferon-alpha (IFN-α) in patients with nccRCC, based on phase III data, while everolimus, sunitinib and sorafenib have all demonstrated some degree of activity in nccRCC in expanded-access trials. No clear picture has emerged of whether individual histological subtypes are particularly responsive to any individual treatment.

Conclusions: Further molecular studies into the pathogenesis of RCC histological subtypes will help direct the development of novel, appropriate targeted agents. Clinical trials specifically designed to evaluate the role of targeted agents in nccRCC are ongoing, and data from trials with sunitinib and everolimus will be reported soon.

Key words: chromophobe renal cell carcinoma, non-clear cell RCC, papillary RCC, sarcomatoid features, targeted therapies, Xp11 translocated RCC

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