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Review Article

Statin use and risk of gastrointestinal cancer: a meta-analysis of cohort studies

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Abstract: Objective: To evaluate the effect of statins on esophageal cancer, pancreatic cancer, gastric cancer, colon cancer and rectal cancer risk. Methods: Relevant studies were identified by searching MEDLINE, EMBASE, and PUBMED up to Feb 2017. We estimated RR (relative risk) with 95% confidence interval (CI) and subgroup analysis also be conducted. In addition, we estimated RR ratios (RRRs) between men and women. Results: Seventeen cohort studies were included for the meta-analysis. The pooled results showed that statin use could decrease the risk of esophageal cancer, especially for the long-term user (All: RR = 0.72, 95% CI = 0.49-0.96; Long-term use: RR = 0.65, 95% CI = 0.36-0.93). Women had a borderline significant 16% increased risk for esophageal cancer conferred by statin use compared with men (RRR = 0.84, 95% CI = 0.60-1.08). Statin user yielded a decreased risk of gastric cancer (RR = 0.74, 95% CI = 0.56-0.92). The subgroup analyses based on race showed that statin use conferred a significant protective effect on the gastric cancer in Asian population, but not in Western population. Our results did detect significant association of statin use with pancreatic cancer in Asian population, but not in all populations (Asian population: RR = 0.55, 95% CI = 0.48-0.63; All populations: RR = 0.79, 95% CI = 0.51-1.07). Compared with non-users, statin users had a borderline significant 12% decreased risk for rectal cancer (RR = 0.87, 95% CI = 0.74-1.01). The pooled analysis did not detect the significant association of satin use with colon cancer risk (RR = 0.98, 95% CI = 0.92-1.03). Conclusion: Statin use may decrease the risk of esophageal cancer, gastric cancer, pancreatic and rectal cancer. Further well-designed large studies with prospective cohort design are necessary to draw definitive conclusions.

Keywords: Statin use, gastrointestinal, cancer, meta-analysis

Introduction

Esophageal cancer, pancreatic cancer, gastric cancer, colon cancer and rectal cancer are the major malignancies in the gastrointestinal tract, which is still a deadly threat in human health due to tumor metastasis and relapse [1, 2]. Although gastrointestinal cancer is a heterogeneous disease involving multiple genetic and environment factors, the modifiable risk factors such as physical activity and aspirin use have also been identified to decrease the development of gastrointestinal cancer [3].

Statins are widely used to lower cholesterol levels and can decrease incidence of cardiovascular disease [4]. Additionally, the previous studies demonstrated that statins could inhibit the growth of carcinoma cell, induce apoptosis in intestinal epithelial cells and retard invasive behavior, which suggested that statins might suppress tumor growth and metastasis, and had the anticancer effect [5, 6]. However, some recent epidemiological studies that investigated the relationship between statins and risk of gastrointestinal cancer had inconsistent results, while some studies showed that statins might reduce the risk of gastrointestinal cancer, some found the inverse risk and others did not found any associations. Moreover, statin use conferred conflicting effect on the incidence of gastrointestinal cancer the in Asian and Western populations. Compared with men used statins, whether women who used statins were at lower risk of gastrointestinal cancer remained unclear.

Therefore, we carried out a meta-analysis to investigate the association between statins and the risk of developing esophageal cancer, pancreatic cancer, gastric cancer, colon cancer and rectal cancer. Moreover, subgroup analysis

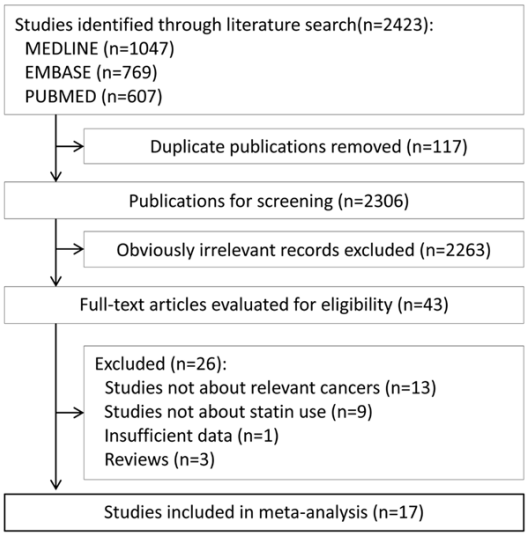

Figure 1. Flowchart for the selection of eligible studies.

was performed to analyze factors causing inconsistent results, and women-to-men ratio (RRR) was evaluated to explore the sex difference.

Materials and methods

Search strategy

The comprehensive literature searches of MEDLINE, EMBASE, and PUBMED databases were conducted to identify relevant studies through Feb 2017 using the following terms: (hydroxymethylglutaryl-CoA reductase inhibitor or statin use) and (gastrointestinal cancer or esophageal cancer or pancreatic cancer or gastric cancer or colon cancer or rectal cancer or neoplasm or malignancy). We did not impose language restriction. Subsequently, all reference lists of eligible articles were searched and evaluated to identify additional relevant publications. If necessary, supplementary data would be checked for insufficient for required data. When overlapping studies were included, we only used the study with the largest sample size.

Study selection

The following screening criteria was applied to determine qualitative eligibility: (1) the study evaluated the association of statin use with the risk of esophageal cancer or pancreatic cancer or gastric cancer or colon cancer or rectal cancer; (2) study design was limited to prospective or retrospective cohort study; and (3) the study provided the relative risks (RRs) or odds ratios (ORs) or hazard ratios (HRs) with their 95% confidence interval (CI) or sufficient data to estimate them. The studies were independently identified and scrutinized by two investigators (S.X.Y. and G.L.S). Any disagreements were resolved by consensus.

Data extraction and qualitative assessment

From each study, the following information was independently extracted: author, year of publication, study design, ethnicity, sex, age, cancer type, numbers of participants, study period, mean follow-up time, confounders for adjustment and RR or OR or HR with 95% CI. The modified Newcastle-Ottawa Scale (NOS) scores was used to assess the quality of each study based on their selection of participants, comparability of groups, and exposure/outcome ascertainment. The score ranged from 0 to 9. A total score of 6 or greater (maximum score, 9) was regarded as high quality [7].

Definition of the outcome and exposures

Esophageal cancer or pancreatic cancer or gastric cancer or colon cancer or rectal cancer was the outcome variable for the analysis, and statin use was the exposure variable. The long-term statin use was defined as ≥ 3 years of statin use and the short-term statin use was defined as < 3 years of statin use.

Statistical analysis

Because the incidence of esophageal cancer or pancreatic cancer or gastric cancer or colon cancer or rectal cancer was relatively rare, the distinction among various measures of RR were ignored and the OR, HR and RR was approximated to RR. Meta-analyses were conducted to obtain summary RR estimates for the association between statin use and these gastrointestinal cancers. When the study provided sex-specific RR and 95% CI separately, female-to-male ratio of RRs (RRR) and 95% Cis were estimated. These RRR were computed for the comparison of statin users with non-users [8]. The Q-statistic as well as the I^2 statistic was used to assess the possible heterogeneity between the results of the individual studies. If $P < 0.1$ in Q statistic or $I^2 > 50\%$, it was consid-

Table 1. Characteristics of studies included in this meta-analysis of statin use and the risk of gastrointestinal cancer

Author	Country	Cancer type	All participants	Study period	Mean Follow-up time (years)	Mean age	Study quality	Cohort type	Confounders for adjustment
Marelli et al, 2011	US	Esophageal, gastric, pancreatic, colon, rectal cancer	91714	1990-2009	4.6	69.8	7	Retrospective	Age, sex, smoking status, duration of observation window, propensity score, LDL levels,
Friedman et al, 2008	US	Esophageal, gastric, pancreatic, colon, rectal cancer	4243067	1994-2003	4.91	NR	8	Retrospective	Calendar year
Chen et al, 2015	China	Esophageal, gastric, pancreatic cancer	61898	2000-2008	NR	40.3	6	Retrospective	Age, sex, comorbidity condition, non- statin lipid-lowering drugs, aspirin, acetylcholinesterase (ACE) inhibitors, area, index year, and anti-HBV drug
Kastelstein et al, 2011	Netherlands	Esophageal cancer	570	2003-2010	NR	NR	7	Prospective	Age, sex, BE length, baseline histology, and use of other medications.
Kantor et al, 2012	US	Esophageal cancer	411	1983-2009	4	62.1	7	Prospective	Age, sex, pack-years smoked (continuous linear), and use of NSAIDs (yes/no) over follow-up
Altawil et al, 2011	US	Esophageal cancer	77	2004-2010	NR	NR	6	Retrospective	NR
Hippisley-Cox J et al, 2010	UK	Gastric, esophageal, colon, rectal cancer	2004692	2002-2008	1.5	44.4	7	Prospective	Age, sex, comorbidity score, BMI, use of NSAID, smoking, hypertension, use of hormones
Leung et al, 2013	China	Gastric, pancreatic, colon, rectal cancer	34205	NR	NR	61.5	6	Prospective	Age, sex, Charlson score and whether using other lipid-lowering agents
Haukka et al, 2010	Finland	Gastric, pancreatic, colon, rectal cancer	944962	1996-2005	3.1	60	8	Retrospective	Age, sex, follow-up period
Sato et al, 2006	Japan	Gastric, pancreatic cancer	263	1991-1995	NR	NR	6	Retrospective	Age, sex, total serum cholesterol level, smoking
Matsushita et al, 2010	Japan	Gastric cancer	13724	NR	4.7	57.9	7	Prospective	Age, sex, smoking habit
Jacobs et al, 2011	US	Prostate, bladder, kidney cancer	133255	1997-2007	NR	> 60	7	Prospective	Age, sex, race, education, smoking, use of NSAIDs, BMI, physical activity, history of elevated cholesterol, diabetes, heart disease, hypertension
Chen et al, 2016	China	Pancreatic cancer	1140617	1997-2010	NR	56.8	8	Retrospective	Age, sex, urban- ization, monthly insured amount with unit of New Taiwan Dollars, and history of pancreatitis, metformin, thiazolidinedione, sulfonylurea, insu- lin, aspirin, nonsteroidal anti-inflammatory drugs.
Karp et al, 2008	Canada	Prostate, bladder, kidney cancer	30076	1998-2004	NR	69.6	6	Retrospective	Age, sex, marital status, comorbidities, use of non-statin cardiac medications, in-hospital procedure performed, length of hospital stay, calendar year, specialty of the treating physician, hospital's teaching status, area of location, and annual volume of admissions
Flick et al, 2009	US	Colon, rectal cancer	69115	2002-2005	NR	60.2	7	Prospective	Age, BMI, physical activity, alcohol use and multivitamin use.
Lee et al, 2011	US	Colon, rectal cancer	91155	1990-2006	NR	68.1	8	Prospective	Age, calendar year, study, pack-years of smoking before age 30, aspirin dose, height, BMI, family history of colorectal cancer in parents and siblings (yes and no), history of endoscopy, red meat intake, alcohol intake, and total energy intake.
Simon et al, 2012	US	Rectal cancer	159219	1993-2010	10.7	65.6	8	Prospective	Age, ethnicity, education, smoking, alcohol use, physical activity, body mass index, percent energy from fat, fruit and vegetable intake, dietary calcium, calcium supplement use, selenium supplement use, current healthcare provider, last medical visit within one year, colon screening, current HT use, family history of colorectal cancer, history of colon polyp removal, NSAID use, hypertension, history of stroke and history of coronary artery disease and stratified by WHI trial randomization and extension study participation.

NR; not reported.

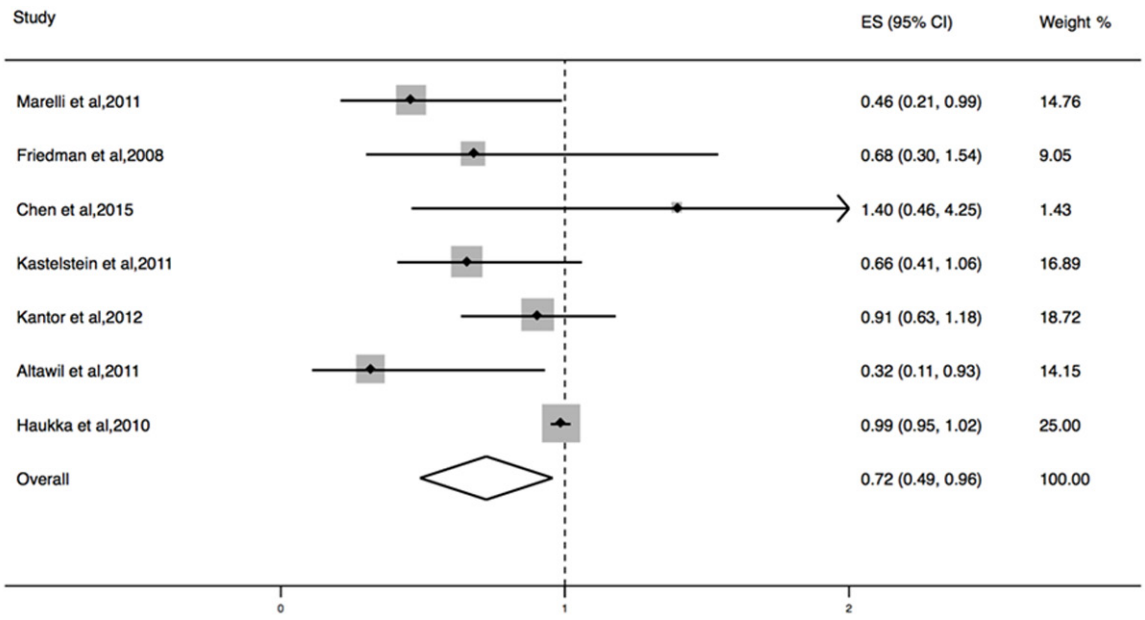

Figure 2. Forest plot on the associations between the statin use and the risk of esophageal cancer.

ered to be substantial heterogeneity and the random-effects model would be chosen; otherwise, the fixed-effects model would be used. In addition, subgroup analyses were performed to explore potential heterogeneity based on the possible factors [Race: Caucasians vs. Asians; Study design: Prospective cohort study vs. Retrospective cohort study; Duration of statin use: Long-term vs. Short-term; Types of statins (Simvastatin vs. Pravastatin vs. Fluvastatin vs. Atorvastatin vs. Rosuvastatin)]. Subsequently, we conducted sensitivity analyses to evaluate whether a single study could markedly affect the robustness of results. Begg's funnel plot and Egger's test was used to assess publication bias. All statistical analyses were carried out using STATA software (version 11; Stata Corporation, College Station, Texas). A p values < 0.05 was considered to be statistically significant.

Results

A total of 2423 articles were identified from MEDLINE, EMBASE, and PUBMED (**Figure 1**). After removal of 117 duplicates, 2306 titles or abstracts were screened, with 43 retrieved for full-text review. In total, 17 studies including 9019020 participants met our inclusion criteria [9-25].

The main characteristics of the studies were listed in **Table 1**. From the 17 included articles, nine studies were prospective cohort design and eight studies were retrospective cohort design. Among these studies, fourteen were conducted in Caucasian population, and five in Asian population. The followed-up ranged from 1.5 to 10.7 years. Assessment of quality scores from NOS scale demonstrated that all studies were high quality, with a range from 6 to 8. Concerning the outcome, 7 studies evaluated incident cases of esophageal cancer, 8 studies for gastric cancer, 8 studies for pancreatic cancer, 7 studies for colon cancer and 7 studies for rectal cancer. Regarding confounding control, 15 studies provided results adjusted for age, and 12 for gender.

Statin use and esophageal cancer

Two studies showed a significantly decreased risk of esophageal cancer, and five studies did not report significant associations. The results of meta-analysis found that statin use could decrease the risk of esophageal cancer, especially for the long-term user (All: RR = 0.72, 95% CI = 0.49-0.96; I^2 = 72.9%; **Figure 2**; Long-term use: RR = 0.65, 95% CI = 0.36-0.93). A subgroup analysis based on study design did not explain the observed heterogeneity (Prospective cohort: RR = 0.63, 95% CI = 0.06-1.21; I^2 = 81.7%; Retrospective cohort: RR = 0.76, 95% CI = 0.47-1.04; I^2 = 66.5%; **Table 2**). The significant association was also observed in Western population (RR = 0.71, 95% CI = 0.47-0.95). In

Table 2. Subgroup analyses of the association between statin use and gastrointestinal cancer risk

Subgroup	N	RR	Lower	Upper	Q	I^2	P
Esophageal cancer							
All	7	0.72	0.49	0.96	22.12	0.729	0.001
Long-term use[1]	3	0.65	0.36	0.93	0.58	0	0.747
Study design							
Prospective	2	0.63	0.06	1.21	5.46	0.817	0.019
Retrospective	5	0.76	0.47	1.04	11.95	0.665	0.018
Ethnicity							
Western population[2]	6	0.71	0.47	0.95	21.93	0.772	0.001
Asian population	1	1.40	0.46	4.25	NA		
Women-to-men RRR	2	0.84	0.60	1.08	0.57	0	0.232
Gastric cancer							
All	8	0.74	0.56	0.92	52.57	0.867	0
Study design							
Prospective	3	0.59	0.25	0.93	15.58	0.872	0
Retrospective	5	0.86	0.68	1.03	12.43	0.678	0.014
Ethnicity							
Western population	4	0.91	0.80	1.01	7.65	0.608	0.054
Asian population	4	0.47	0.23	0.71	5.76	0.48	0.124
Women-to-men RRR	3	1.16	0.90	1.08	6.43	0.257	0.19
Statin type							
Simvastatin	2	0.92	0.76	1.07	5.24	0.618	0.073
Pravastatin	4	0.95	0.87	1.03	6.18	0.353	0.186
Fluvastatin	2	0.99	0.93	1.05	0.09	0	0.955
Atorvastatin	2	0.96	0.91	1.01	2.59	0.227	0.274
Pancreatic cancer							
All	8	0.79	0.51	1.07	60.87	0.885	0
Study design							
Prospective	2	0.87	0.08	1.66	7.01	0.857	0.008
Retrospective	6	0.74	0.45	1.04	35.33	0.858	0
Ethnicity							
Western population	4	0.95	0.68	1.22	1.06	0	0.787
Asian population	4	0.55	0.48	0.63	12.23	0.755	0.007
Statin type							
Pravastatin	2	1.04	0.97	1.11	0.23	0	0.629
Colon cancer							
All	7	0.98	0.92	1.03	11.01	0.364	0.138
Long-term use	2	0.99	0.80	1.19	0.33	0	0.849
Study design							
Prospective	4	0.98	0.82	1.13	5.15	0.418	0.161
Retrospective	3	0.98	0.93	1.04	4.04	0.505	0.133
Ethnicity							
Western population	6	0.97	0.92	1.03	9.37	0.466	0.095
Asian population	1	1.11	0.70	1.52			
Rectum cancer							
All	7	0.87	0.74	1.01	15.3	0.608	0.018
Study design							
Prospective	4	0.67	0.48	0.86	0.46	0	0.794
Retrospective	3	0.96	0.93	0.99	3.29	0.089	0.349
Ethnicity							
Western population	6	0.90	0.78	1.03	11.73	0.574	0.039
Asian population	1	0.54	0.27	1.12	NA		

NA, not available. [1]The long-term statin use was defined as ≥ 3 years of statin use; [2]Western population included participants who lived in western.

addition, the sex-specific association between statin use and the risk of esophageal cancer was in two studies which provided RRs in men and women, respectively. The results showed that women had a borderline significant 16% increased risk for esophageal cancer conferred by statin use compared with men (RRR = 0.84, 95% CI = 0.60-1.08; **Table 2**). Single study sensitivity analysis did not alter the significance level of any results. There was no evidence of publication bias in the analyses (Begg's test: P = 0.85; Egger test: P = 0.91).

Statin use and gastric cancer

Four studies showed a significantly reduced risk of gastric cancer and four studies showed no association between statin use and this disease. The pooled results revealed that statin user yielded a decreased risk of gastric cancer (RR = 0.74, 95% CI = 0.56-0.92; I^2 = 86.7%; **Figure 3**). When we conducted subgroup analyses according to study design, a significant association between statin use and gastric cancer was found in prospective cohort studies, but not in retrospective cohort studies (Prospective cohort: RR = 0.58, 95% CI = 0.25-0.93; Retrospective cohort: RR = 0.86, 95% CI = 0.68-1.03; **Table 2**). The subgroup analyses based on race showed that statin use conferred a significant protective effect on the gastric cancer in Asian population, but not in Western population (Asian population: RR = 0.47, 95% CI = 0.23-0.71; Western population: RR = 0.91, 95% CI = 0.80-1.01; **Table 2**). Regarding statin types, no significant difference was observed (Pravastatin: RR = 0.95, 95% CI = 0.87-1.03; Simvastatin

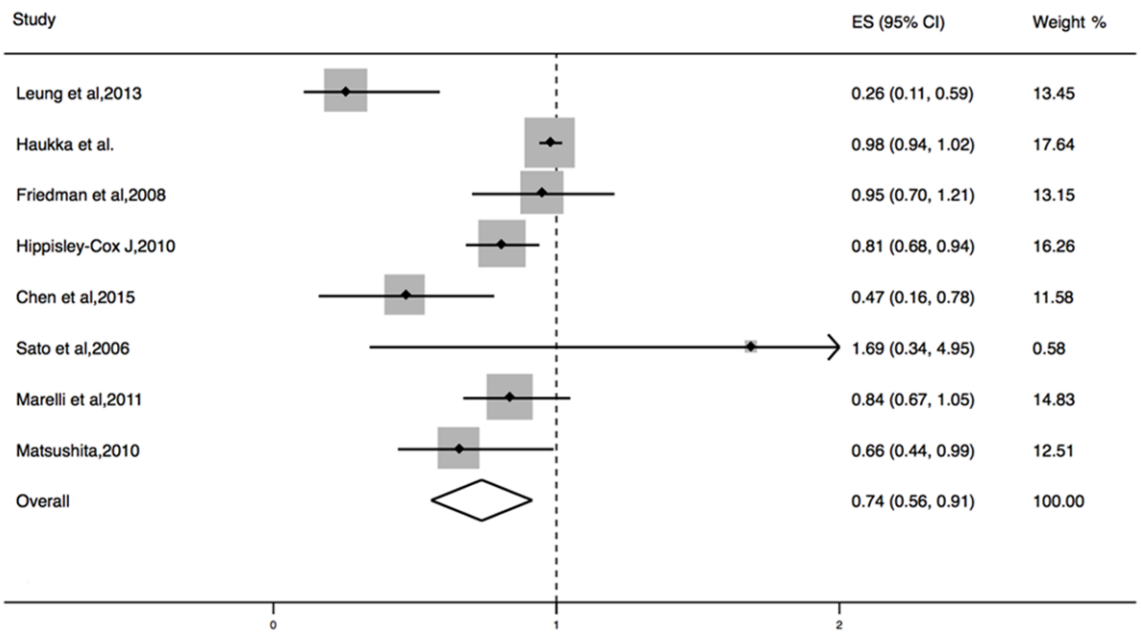

Figure 3. Forest plot on the associations between the statin use and the risk of gastric cancer.

(RR = 0.92, 95% CI = 0.76-1.07; Fluvastatin: RR = 0.99, 95% CI = 0.93-1.05; Atorvastatin: RR = 0.96, 95% CI = 0.91-1.01). In addition, three studies provided RRs in men and women, respectively, and the pooled multiple-adjusted women-to-men RRR for incident gastric cancer was 1.16 (95% CI 0.90, 1.43; **Table 2**). Besides, sensitivity analyses showed that our results were robust, and there was no significant publication bias detected by Begg's test and Egger's test (P > 0.1).

Statin use and pancreatic cancer

One study revealed a significantly lower risk of pancreatic cancer, six studies did not find significant association of statin use with pancreatic cancer, while one study revealed a significantly inverse risk of this disease. The pooled results did not show the significant association between statin use with pancreatic cancer (RR = 0.79, 95% CI = 0.51-1.07; I^2 = 88.5%; **Figure 4**). The subgroup analysis by study design did not find significant difference (Prospective cohort: RR = 0.87, 95% CI = 0.08-1.66; Retrospective cohort: RR = 0.74, 95% CI = 0.45-1.04; **Table 2**). Pravastatin use did not confer a significant effect on the pancreatic cancer (RR = 1.04, 95% CI = 0.97-1.11). However, the significant association of statin use with pancreatic cancer risk was observed in Asian population, but not in Western population (Asian population: RR = 0.55, 95% CI = 0.48-0.63; Western population: RR = 0.95, 95% CI = 0.68-1.22). The sensitivity analyses showed robustness of the results. No significant publication bias detected was detected (P > 0.1).

Statin use and colon cancer

One studies showed a significantly decreased risk of colon cancer, and six studies did not show significant associations. The pooled analysis did not detect the significant association of satin use with colon cancer risk, and the long-term statin use did not show the association (All: RR = 0.98, 95% CI = 0.92-1.03; I^2 = 36.4%; **Figure 5**; Long-term use: RR = 0.99, 95% CI = 0.80-1.19). A subgroup analysis based on study design did not explain the observed heterogeneity (Prospective cohort: RR = 0.98, 95% CI = 0.82-1.13; I^2 = 41.8%; Retrospective cohort: RR = 0.98, 95% CI = 0.93-1.04; I^2 = 50.5%; **Table 2**). The subgroup analysis found that the ethnicity did alter the association (Asian population: RR = 1.11, 95% CI = 0.70-1.52; Western population: RR = 0.97, 95% CI = 0.92-1.03). The sensitivity analyses showed that our results remained stable, and no significant publication bias detected (P > 0.1).

Statin use and rectal cancer

Two studies showed a significantly reduced risk of rectal cancer, and five studies did not show

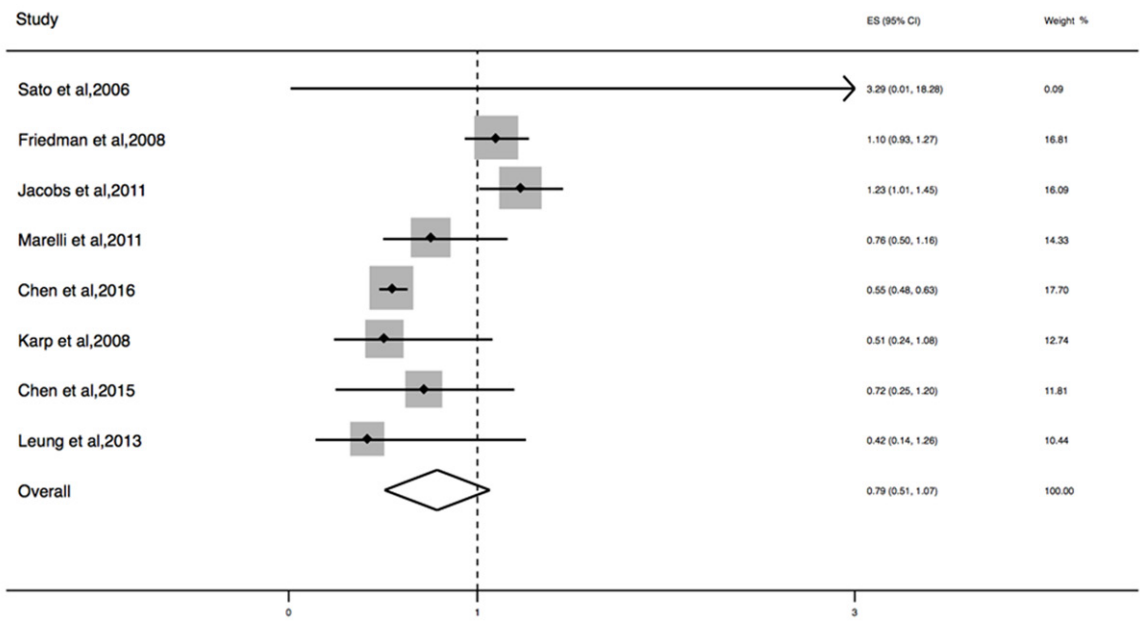

Figure 4. Forest plot on the associations between the statin use and the risk of pancreatic cancer.

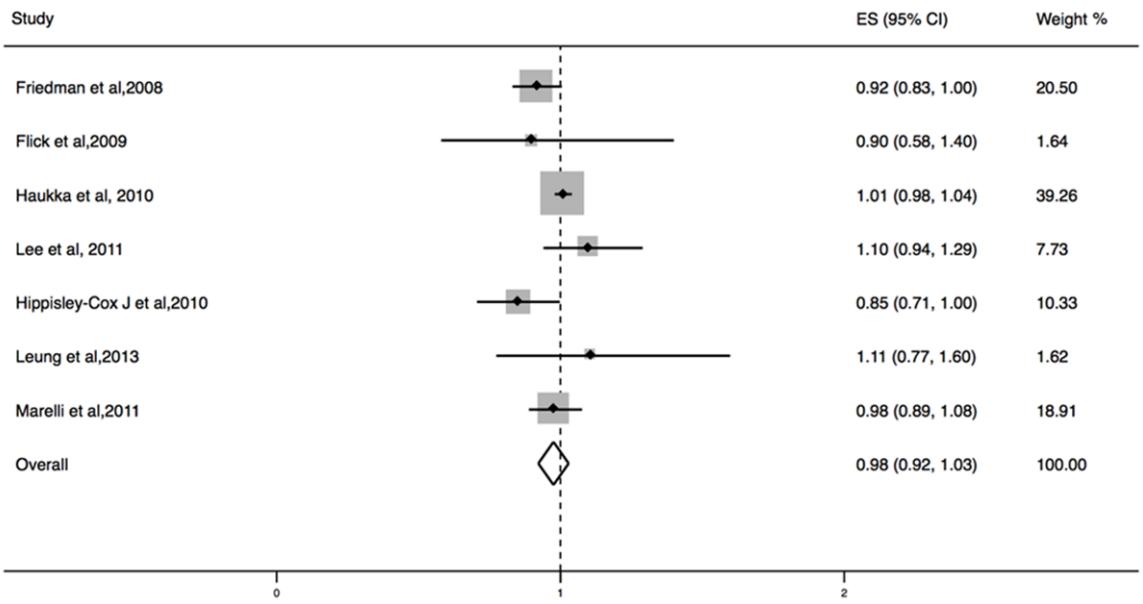

Figure 5. Forest plot on the associations between the statin use and the risk of colon cancer.

significant associations. The pooled results showed that statin users had a borderline significant 12% decreased risk for rectal cancer compared with non-users (RR = 0.87, 95% CI = 0.74-1.01; I^2 = 36.4%; **Figure 6**). Subgroup analysis based on study design could decrease the heterogeneity, and significant associations of statin use with rectal cancer risk were observed (Prospective cohort: RR = 0.67, 95% CI = 0.48-0.86; I^2 = 0%; Retrospective cohort: RR = 0.96, 95% CI = 0.93-0.99; I^2 = 8.9%; **Table 2**). The subgroup analysis found that the ethnicity did alter the association (Asian population: RR = 0.54, 95% CI = 0.27-1.12; Western population: RR = 0.90, 95% CI = 0.78-1.03). The sensitivity analyses showed robustness of the results. There was no significant publication bias (P > 0.1).

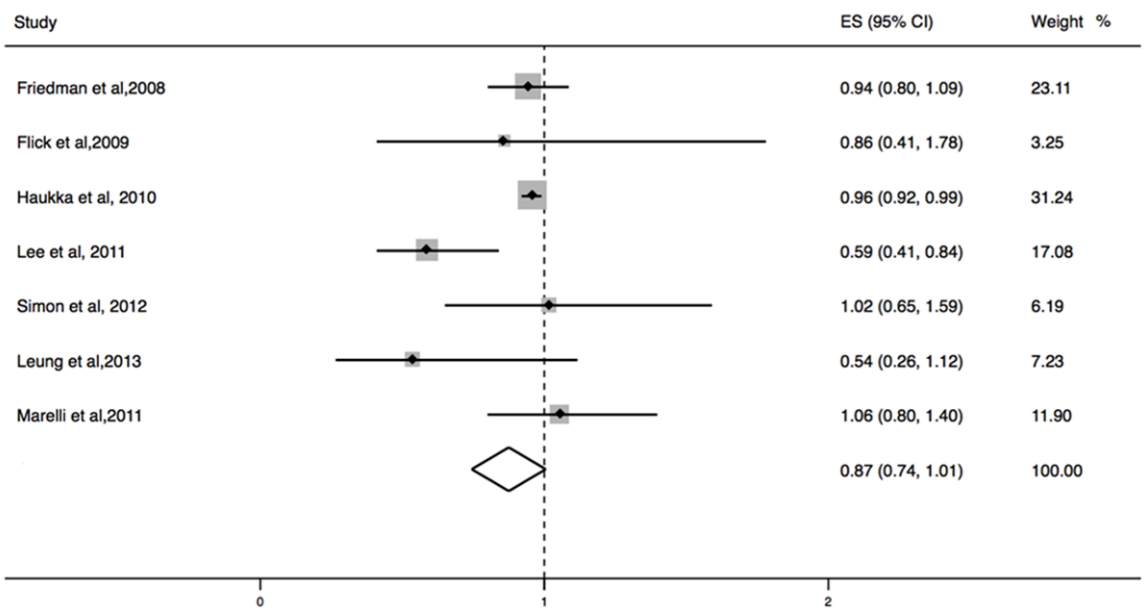

Figure 6. Forest plot on the associations between the statin use and the risk of rectal cancer.

Discussion

The prevent meta-analysis showed that statin use could significantly reduce the risk of esophageal and gastric cancer by approximately 28% and 26%, respectively. Statin use conferred a borderline 13% decrease in the risk of rectal cancer. However, we did not detect a significant association of statin use with pancreatic cancer and colon cancer.

Esophageal cancer

Some recent studies have shown that statins might be associated with a lower risk of esophageal cancer. The previous meta-analysis by Singh et al statins protected against esophageal cancer [26]. In consistent with this study, the prevent study demonstrated that statin use would reduce 23% risk of esophageal cancer. The results based on Western population showed the similar protective effect. Because only one study in Asian population was included, we did not conduct a meta-analysis based on this population. Moreover, a stronger protective influence on development of esophageal cancer was detected in the long term statin use. The previous study by Beales et al reported that statin prescription for > 5 years had a reduced risk of esophageal cancer, compared to 0.5-5 years of use (RR = 0.41, 95% CI = 0.15-0.85) [27]. However, Friedman et al demonstrated that prolonged statin use did not exert a protective effect of statins in the progression of this disease when used for less than 2 years. Using time-varying analysis, Hippisley-Cox et al reported that statins appeared to the reduction in risk of esophageal cancer from one to three years after starting use and the reduction continued during the first five years of statin use [18]. Therefore, statin use was dose-dependent and the long duration could confer a larger cumulative dose of statins, which might explain that more significant effects was exerted in longer-term statin therapy. The previous cohort studies observed that statin use among the men conferred an increased risk of esophageal cancer (RR = 1.70, 95% CI = 1.05-2.75), but statin use among the women exerted a trend toward a lower risk of esophageal cancer [14]. In our analysis, the pooled multiple-adjusted women-to-men RRR showed a tendency of significant sex difference in the influence of statin use on risk of esophageal cancer. However, the mechanisms underlying the sex difference in risk of esophageal cancer was unclear.

Gastric cancer

As for gastric cancer, the previous study of individual patient data observed that statins yielded a preventive effect (HR = 0.66, 95% CI = 0.44-0.99). The another meta-analysis by

Singh et al reporting 5581 cases of gastric cancer showed that statin user experienced a 32% reduction in the risk of this disease (Adjusted RR = 0.68, 95% CI = 0.51-0.91) [28]. In agreement with these studies, we also found a significant association between statin use and the decreased risk of this disease. Subgroup analysis by ethnicity would decrease the heterogeneity. In addition, the stronger chemo-preventive association of statin use with gastric cancer was evident in Asian population, but statin use only conferred a preventive tendency in Western population. Due to the genetic and environmental difference between Asian population and Western population, gastric cancer had a higher incidence in Asian population, especially in China [29]. Statin use might have a potential interaction with genetic and environmental risks for gastric cancer in different populations, which might contribute to reason that statin use appeared to more profitable to reduce the risk of gastric cancer. A population-based cohort study by Chen et al show that statin use reduced the incidence of stomach cancer in men (RR = 0.41, 95% CI = 0.20-0.84) but not in women (RR = 1.19, 95% CI = 0.52-2.70). Although, the pooled multiple-adjusted women-to-men RRR in our study, did not show the significantly potential evidence of sex difference in the influence of statin use on risk of gastric cancer, but men had a significant lower risk tendency for gastric cancer exerted by statin use compared with women. However, sex difference analysis only included three studies, the relatively small sample could result in the wider confidence interval.

Pancreatic, colon and rectal cancer

The pooled results indicated a non-significant decrease of pancreatic, colon and rectal cancer risk among all statin users in agreement with the previous meta-analysis [30, 31]. As for colon cancer, similar results were found in subgroup analyses. However, subgroup analyses showed that statin users conferred a significantly decreased risk of pancreatic cancer in Asian population. Although we did not observe a significant association between statin use and the risk of developing rectal cancer, with a significant heterogeneity (I^2 = 60.8%), subgroup analysis showed that a significant decrease of pancreatic cancer risk was found in the prospective and retrospective cohort studies, respectively. Moreover, the I^2 statistics for the RRs decreased significantly (Prospective cohort: I^2 = 0%; Retrospective cohort: I^2 = 8.9%), which might explain the potential sources of heterogeneity. Therefore, our analyses of the effect of statins on rectal cancer should be interpreted with caution.

Limitations

First, although a significant heterogeneity was observed in meta-analysis, we performed subgroup analyses to explore the potential heterogeneity. Moreover, the case-control studies were excluded, the included studies were cohort studies, and the sample size was relatively large which potentially increasing the strength of this analysis. Second, we did not obtain for original data; although the analysis was based on the completely adjusted data, adjusted confounders varied among studies, which might induce bias of results. In addition, there was a relationship between the adherence to statin therapy and environmental factors, which might affect the cancer outcome. The possible interaction between statin use and risk factors might partly affect the results. Moreover, we did not perform the analysis of sex difference for pancreatic, colon and rectal cancer due to limited included studies. Therefore, the future research taking into account sex difference and environmental factors was necessary to be conducted. Finally, although apparent publication bias was not observed through statistical tests in our analysis, the number of included studies was not abundant to adequately detect biases.

Conclusions

The prevent results showed that statins appeared to have preventive effects against esophageal cancer, especially for the long-term use. Statins could reduce the risk of gastric cancer, especially in Asian population. Statin user in Asian population exert a lower risk of developing pancreatic cancer. The protective tendency for decreased rectal cancer conferred by statin use should be interpreted with caution. Our results suggested there was no significant preventive effect of statin use on colon cancer risk. Future large-scale, prospective and well-designed studies should be conducted to reach a more definitive conclusion.

Disclosure of conflict of interest

None.

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