

Review Article

Association between ezetimibe in combination with statin therapy and cancer risk: a meta-analysis

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Received April 16, 2017; Accepted September 10, 2017; Epub October 15, 2017; Published October 30, 2017

Abstract: The present meta-analysis comprising 7 studies involving 56051 participants aims to assess the association between ezetimibe in combination with statin therapy and cancer risk by pooling the individual ORs and 95% CIs from the original studies based on a comprehensive search in electronic databases. Overall, no evidence of significant association between ezetimibe in combination with statin therapy and increased cancer risk was revealed (OR=1.03, 95% CI=0.78-1.37, $p=0.82$, $P_h < 0.0001$, $I^2=83\%$, random-effect model). Similarly, stratification analyses by reference group showed no significant relevance of ezetimibe in combination with statin therapy to elevated risk of cancer (Ezetimibe+Statin vs. Placebo: OR=1.23, 95% CI=0.77-1.95, $p=0.39$; Ezetimibe+Statin vs. Statin: OR=1.01, 95% CI=0.57-1.78, $p=0.98$). Also, subgroup analyses based on patients source showed no increased cancer risk for ezetimibe in combination with statin therapy in patients with CKD (OR=1.00, 95% CI=0.87-1.15, $p=1.00$) or (OR=1.08, 95% CI=0.68-1.71, $p=0.76$). The current study implied that ezetimibe in combination with statin therapy may be not associated with an increased risk of cancer, suggesting no necessity to excessively concern the cancer risk of the addition of ezetimibe to statin therapy. Further studies are warranted to confirm and specify the association.

Keywords: Ezetimibe, statin, cancer, risk, meta-analysis

Introduction

Despite of the extensive benefit identified with long-term statin therapy in prevention of common cancers [1, 2], plenty of patients remain susceptible to a cancer particularly in populations with high cholesterol for ages, and in which intensive statin therapy is therefore applied popularly due to the achievement to retain a lower low-density lipoprotein (LDL) and rates of nonfatal cardiovascular events [3-5]. However, a significant risk of recurrent adverse events and safety concerns was raised by the administration of high dose statins, which leads to the quest of additional lipid lowering therapies [6-8].

Ezetimibe was recently served as a lipid-lowering agent in the clinical by inhibiting intestinal absorption of dietary cholesterol via the functional blockage of Niemann-Pick C1-like 1 (NPC1L1) protein, a major mediator of cholesterol absorption in gastrointestinal tract epithelial cells and hepatocytes [9, 10]. Reportedly, ezeti-

mibe in combination with statin therapy was able to lead an extra 23 to 24% reduction of LDL cholesterol levels on average compared to statin alone [11]. Therefore, ezetimibe becomes particularly prevalent among prescribing physicians [12]. Nevertheless, the widespread use of ezetimibe has not been suggested by the American Heart Association/American College of Cardiology as yet in view of the lack of compelling evidence to support a benefit in clinical outcomes and the concerns regarding the possibility of an increased incidence of cancer originated from the findings of the SEAS trial [13, 14]. However, inconsistent with SEAS, several latter trails including IMPROVE-IT and SANDS primarily designed to evaluate the effect of an additional ezetimibe therapy added to statins on cardiovascular outcomes failed to observe an increased cancer risk in relation to ezetimibe, engendering to a strong controversy [15, 16]. With the concerns and controversy in mind, we accordingly sought to demonstrate the consistency of small to moderate sized trials and

Ezetimibe and cancer risk

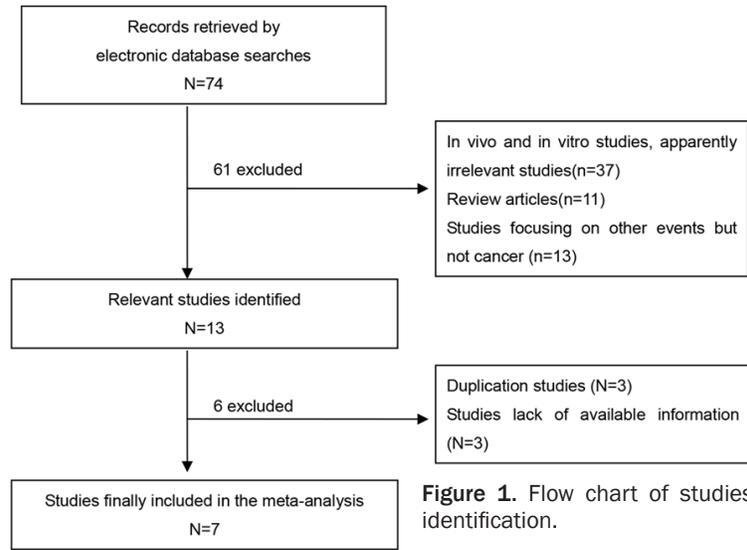


Figure 1. Flow chart of studies identification.

larger scale trials, as well as to systematically evaluate the association between ezetimibe in combination with statin therapy and cancer risk by a meta-analysis.

Materials and methods

Search strategy

Electronic searches of databases including Medline, Embase, Cochrane Database, Web of Science, Scopus, China National Knowledge Internet, Wanfang and Chinese Biomedicine Database were performed from inception until April 2017 for the identification of eligible publications concerning the ezetimibe use in combination with therapy and cancer risk. All identified studies were reported in English and Chinese and retrieved with the following headings: “ezetimibe” and [“cancer” or “carcinoma”]. Bibliographies of the reports of all retrieved studies and reviews relevant to the topic were individually and manually searched for additional eligible articles.

Study selection

All retrieved studies were assessed for eligibility prior to inclusion which was set accordingly as follows: included studies with participants allocated to ezetimibe plus another statin versus the same statin drug or placebo alone were performed to investigate the effect of ezetimibe use added to statin therapy on the clinical outcome involving or concentrating on cancer risk.

Moreover, in case of studies with overlapped presentation, only the most recent publication with the largest sample size was selected for the meta-analysis.

Inclusion and exclusion criteria

Studies were included when meeting the following criteria: i.) reports focusing on the impact of ezetimibe use added to statin therapy on the clinical outcome involving or concentrating on cancer risk. ii.) studies with a randomized or observational design enrolling more

than 100 participants; iii.) studies reporting sufficient information on the clinical outcome. The major exclusion criteria were: i.) studies with insufficient data to evaluate the cancer risk; ii.) studies with inadequate description of method and outcome. iii.) case reports, editorials, review and letter articles.

Data extraction

Data originated from included studies on first author, publication year, country, ethnicity, study design, study contrast, sample size, number of cancer incident in contrasts, source of patients and cancer type were independently extracted employing a uniform predesigned table by two investigators, which was further cross-checked by a third reviewer and any discrepancy was resolved by consensus.

Statistical analysis

Odds ratios (ORs) of the effect of ezetimibe in combination with statin therapy on cancer risk were calculated by RevMan 5.2 software (provided by The Cochrane Collaboration, Oxford, UK; <http://www.cochrane.org/software/revman.htm>) to account for the probability of events occurring in the treatment group versus the control group. The significance of pooled OR was determined by Z test ($P < 0.05$ was considered significant) with a random-effect model when the heterogeneity across studies was significant, otherwise a fixed-effect model was applied [17, 18]. As for the estimation, the het-

Ezetimibe and cancer risk

Table 1. Characteristics of included studies

First author	Year	Country	Ethnicity	Study design	Contrasts	Ezetimibe	Non-ezetimibe	Source of patients	Cancer type
						Events/total	Events/total		
Baigent [22]	2011	UK	Caucasian	Randomized	E+SI vs. P	438/4650	439/4620	CKD	Mixed
Fleg [15]	2008	USA	Caucasian	Randomized	E+SI vs. SI	3/69	2/358	CVD	Mixed
Cannon [16]	2015	USA	Caucasian	Randomized	E+SI vs. SI	748/9067	732/9077	CVD	Mixed
Alsheikh-Ali [23]	2009	USA	Caucasian	Cohort	E+SI vs. SI	73/3842	705/22031	CVD	Mixed
Landray [24]	2006	UK	Caucasian	Randomized	E+SI vs. SI	4/102	0/101	CKD	Mixed
Rossebo [14]	2008	Europe	Caucasian	Randomized	E+SI vs. P	101/943	65/929	CVD	Mixed
Kouvelos [25]	2013	Greece	Caucasian	Randomized	E+RSV vs. RSV	0/126	1/136	CVD	Mixed

E, ezetimibe; SI, simvastatin; RSV, rosuvastatin; P, placebo; CKD, chronic kidney disease; CVD, cardiac vascular disease.

Table 2. Detailed pooled results

Study group	Subgroup	Sample size	OR [95% CI]	P value	Heterogeneity	Effect model
		(Treat/control)			P_h/I^2	
Overall		18799/37252	1.03 [0.78, 1.37]	0.82	<0.0001/83%	R
Patient source	CKD	4752/4721	1.00 [0.87, 1.15]	1.00	0.14/55%	F
	CVD	14047/32531	1.08 [0.68, 1.71]	0.76	<0.0001/88%	R
Reference group	E+S vs. P	5593/5549	1.23 [0.77, 1.95]	0.39	0.008/86%	R
	E+S vs. S	13206/31703	1.01 [0.57, 1.78]	0.98	<0.0001/84%	R

E, ezetimibe; S, statin; CKD, chronic kidney disease; CVD, cardiac vascular disease; P_h , p value of heterogeneity test; R, random-effect model; F, fixed-effect model.

erogeneity was tested with the Cochrane Q and I^2 statistics ($P_h < 0.10$ or $I^2 > 50\%$ was considered indicative of statistically significant heterogeneity) [19]. In addition, potential publication bias was evaluated by Begg's funnel plot, which was further examined by the method of Egger's linear regression test ($P < 0.05$ indicated the presence of publication bias) using Stata 12.0 software (Stata Corp., College Station, USA) [20, 21]. Sensitivity analyses were also performed to assess the stability of the results by sequential omission of each individual study.

Results

Characteristics of included studies

Initially, a total of 74 articles were retrieved based on the established search strategy and seven publications reported in English were ultimately proved eligible [14-16, 22-25]. The flow chart of studies identification is displayed as **Figure 1**. Of which, there were six studies with a randomized design and one study with an observational design. With a total of 560-51 participants, all studies were conducted in Caucasian population comprising patients with a diagnosis of cardiovascular disease (CVD) from 5 studies and chronic kidney disease

(CKD) from 2 studies. Detailed characteristics of the included studies are presented in **Table 1**.

Quantitative data synthesis

As shown in **Table 2** and **Figure 2**, no evidence of significant association between ezetimibe in combination with statin therapy and increased cancer risk was revealed in the overall analysis (OR=1.03, 95% CI=0.78-1.37, $p=0.82$, $P_h < 0.0001$, $I^2=83\%$, random-effect model). Stratification analysis by reference group showed no significant relevance of ezetimibe in combination with statin therapy to elevated risk of cancer (Ezetimibe+Statin vs. Placebo: OR=1.23, 95% CI=0.77-1.95, $p=0.39$; Ezetimibe+Statin vs. Statin: OR=1.01, 95% CI=0.57-1.78, $p=0.98$). Similarly, subgroup analysis based on patients source showed no increased cancer risk for ezetimibe in combination with statin therapy in patients with CKD (OR=1.00, 95% CI=0.87-1.15, $p=1.00$) or CVD (OR=1.08, 95% CI=0.68-1.71, $p=0.76$).

Publication bias and sensitivity analyses

As shown in **Figure 3**, no significant publication bias was suggested by the lack of evidence of

Ezetimibe and cancer risk

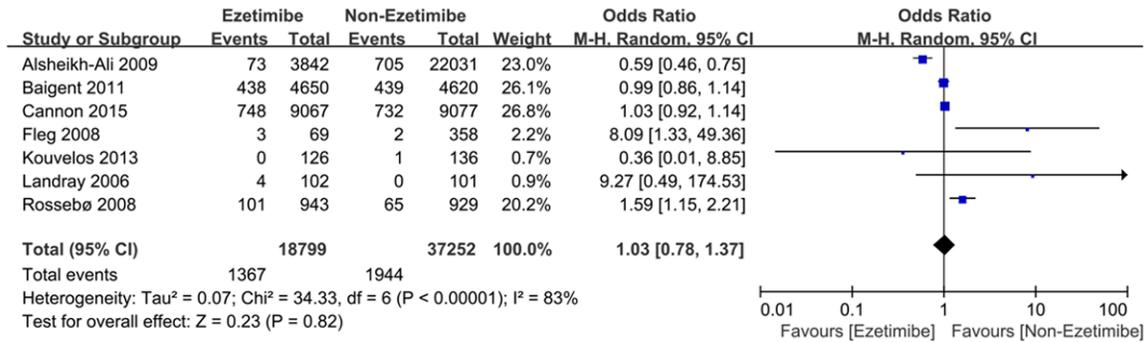


Figure 2. Forest plot of the association between ezetimibe in combination with statin therapy and cancer risk.

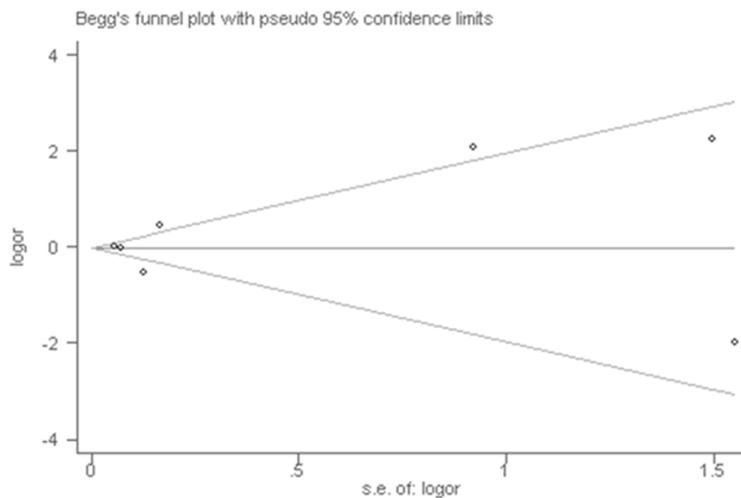


Figure 3. Begg's funnel plot of the association between ezetimibe in combination with statin therapy and cancer risk.

obvious asymmetry observed in the Begg's funnel plot, which was further supported by the Egger's test ($p=0.696$). Meanwhile, no substantial alteration of the pooled results was observed in the sensitivity analyses by omitting any individual studies, indicating the robustness of results.

Discussion

The current study involving 7 individual studies with a total of 56,051 participants for the first time focused on the influence of ezetimibe in combination with statin therapy on cancer risk, demonstrating no increased risk of cancer in patients with ezetimibe use when added to statin therapy.

Similar to other common LDL-C lowering agents, the approval of ezetimibe by the U.S. Food

and Drug Administration gave rise to broad popularity in populations with high-risk CVD since it was reportedly to result in a further approximately 20% reduction of LDL-C by ezetimibe in combination with statins by several trials [26, 27]. Although the favorable clinical outcome with ezetimibe therapy remained controversial due to some inexplicitness of efficacy based on the findings from single studies, ezetimibe was suggestive to be able to acquire clinical benefit of CVD as statins by a recent system review and meta-analysis of Savarese et al. by demonstrating a significant role of

ezetimibe in reducing the risk of MI and stroke [28]. However, another recent meta-analysis by Battaggia et al. failed to draw such conclusions [29]. In contrast to its lipid-lowering function as reported, one major concern to limit the recommendation of ezetimibe use by the current guidelines is the unproven possibility involved in cancer incidence in addition to the undetermined efficacy [30]. A possible excess risk of breast cancer for ezetimibe use was observed by a previous trial [31], however, no significant excess of breast cancer was presented in other statin trials with larger number of participants [32]. Nevertheless, such apparent excess risk of cancer among people over 69 years of age was reported again while there was again no significantly increased risk of cancer among the larger number of such patients in other statin trials [31, 33]. To be noteworthy, such findings

mainly originated from the studies designed for the evaluation of the efficacy and safety of ezetimibe and statins, results may be misleading or unintentionally hidden, which in turn reinforces the value of testing such unexpected byproducts with a more powerful approach.

Considering the lack of compelling evidence specifying the influence of ezetimibe and statins therapy on cancer risk with relative large-scale trials (7 studies), we employed a meta-analysis to systematically evaluate the concern and provide more reliable evidence by pooling small to moderate sized trials and larger scale trials. In line with the findings of the previous meta-analyses (2 studies [29], 2 studies [34] and 5 studies included [28], respectively) mainly designed for evaluation of the cardiovascular benefit and adverse events associated with ezetimibe use, the present meta-analysis involving the largest sample size specified the potential role of ezetimibe in cancer and confirmed no increased cancer risk associated with ezetimibe in combination with statins therapy, suggesting its safety for patients. Similarly, no increased risk of cancer associated with ezetimibe in combination with statins therapy was indicated whatever in CKD patients or in CVD patients. Also, ezetimibe in combination with statins was not found to be associated with an elevated risk of cancer when compared to patients with statins alone or placebo, respectively.

In despite of the advantage in the current meta-analysis, some limitations should be acknowledged. Firstly, data enrolled in the meta-analysis are unadjusted and not on patient-level data, limiting the possibility of performing subgroup analyses based on specific subpopulations and important patient characteristics. Secondly, the included trials are primarily designed to assess the impact of ezetimibe in combination with statins on CVD events and/or mortality, but not on cancer-specific outcomes. Unduly data-dependent emphasis on results may often be extreme in particular studies, leading to misunderstanding. Lastly, the effect may vary across cancer types underlying various uninvestigated mechanisms, however, we have difficulty in clarifying the distinct role in a specific cancer by a combined analysis due to the lack of sufficient information in the original studies.

Conclusion

The current study revealed that the addition of ezetimibe to statins may be not associated with increased specific cancer risk, suggesting the potential unnecessary to undertake excessive concern on cancer with the use of ezetimibe in combination with statins. In light of the limitations, more future studies with large-scale sample size are needed to verify the results and clarify the mechanisms particularly in specific subpopulations and cancer types.

Disclosure of conflict of interest

None.

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Ezetimibe and cancer risk

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