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Statins and the risk of colorectal cancer; a systematic review and meta-analysis of cohort and case-control studies

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Abstract

Introduction: Colorectal malignancy is the third furthermost frequent malignancy in the world, and approximately 80% of the cases are related to nongenetic causes, including high cholesterol levels. Accordingly, the present systematic review and meta-analysis aimed to investigate the relationship between statin treatment and the risk of colorectal cancer.

Materials and Methods: The current study was a systematic review and meta-analysis designed based on PRISMA. International databases, including PubMed, Scopus, Web of Science, Cochrane, and Google Scholar search engine, were used to search for studies published until July 7, 2023. Data analysis was directed by STATA software version 14, and *P* values below than 0.05 ($P<0.05$) indicated the significance of statistical tests.

Results: The results obtained from a combination of 30 studies with 2436650 samples indicated that statin use increased the risk of colorectal malignancy by 11% (OR: 0.89; 95% CI: 0.84, 0.95) and reduced the risk of rectal cancer by 16% (R: 0.84; 95% CI: 0.74, 0.94). Instead, statin administration reduced the hazard of colorectal cancer in individuals aged 50 to 59 by 22% (R: 0.78; 95% CI: 0.63, 0.95), 60 to 69 by 14% (OR: 0.86; 95% CI: 0.75, 0.98), and 70 to 79 by 8% (OR: 0.92; 95% CI: 0.87, 0.98). Utilization of statin in male (OR: 0.71; 95% CI: 0.58, 0.87) and female (OR: 0.84; 95% CI: 0.77, 0.92) patients reduced the risk of colorectal cancer by 29% and 16%, respectively. Furthermore, statin use in men (OR: 0.41; 95% CI: 0.26, 0.67) and women (OR: 0.64; 95% CI: 0.42, 0.97) reduced the risk of colon cancer by 59% and 36%, respectively.

Conclusion: Statin administration reduced the risk of colorectal cancer, and the possibility of reduction in risk of colorectal cancer at lower ages was higher than in older adults and also higher in males compared with females.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (CRD42023450984) and Research Registry (UIN: reviewregistry1779) website.

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Introduction

Colorectal cancer is the third most frequent form of malignancy and the second most common cause of mortality by cancer globally (1). Colorectal cancer has a significant global health burden, and with more than 140 000 newly diagnosed cases in the United States in 2019, it is the second most common cancer among women and the third most frequent cancer among men in 2019 (2,3). However, the incidence rate of colorectal malignancy in many low-income and middle-income populations is still increasing (2).

Colorectal cancer risk factors include age, sex, genetics, high-calorie and high-animal-fat diets, alcohol consumption, and obesity (4). Recent studies claimed that high cholesterol levels were related to several cancers, including prostate, breast, and colorectal cancer (5). On the other side, approximately 80% of the diagnosed colorectal cancer cases had no identifiable genetic basis (6,7) and were rooted in pre-existing polyps, which pro-inflammatory factors (8,9), including high cholesterol levels (10,11) play critical roles in their formation. Accordingly, primary prevention and screening are necessary to reduce cancer incidence and mortality rates.

Statins can reduce serum cholesterol levels and are confirmed first-line medications for atherosclerotic coronary artery disease and high cholesterol levels (12). On the other hand, statins are known as new anticancer agents, which are cost-effective and safe to administer (13,14). Statins showed antiproliferative effects in various types of cancer (5) by inhibiting the synthesis of cholesterol and its metabolites (15). Nevertheless, several

Key point

Statins are the mainstay and most common agents in the treatment of hyperlipidemia. Hyperlipidemia is one of the main risk factors in heart disease; therefore, statins play an important role in preventing cardiovascular diseases. In addition to these benefits, some studies point to an increased risk of colorectal cancer in patients treated with statins. On the other hand, this finding is not certain, and most studies indicated no increase or a slight rise in the risk of colorectal cancer in individuals treated with statins. Our findings indicate that statins reduced the risk of colorectal cancer, and the possibility of reduction in risk of colorectal cancer at lower ages was higher than in older adults, and higher in men compared with women.

uncertainties exist regarding the possible relationship between statin administration and increased cancer risk (16). Considering the inconsistent findings of the previous investigations (17-20) on the relationship between statin use and colorectal cancer risk, we utilized systematic review and meta-analysis to investigate this relationship.

Materials and Methods

Study design

The current study is a systematic review and meta-analysis investigating the relationship between statin administration and the risk of colorectal cancer. The study was written according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA), and the protocol was registered at International Prospective Register for Systematic Reviews (PROSPERO) website (CRD42023450984).

Search strategy

Electronic databases, including PubMed, Scopus, Web of Science, Cochrane, and Google Scholar search engine, were used to search for articles published until July 7, 2023, without time limit using standard and MeSH keywords "Hydroxymethylglutaryl-CoA Reductase Inhibitors, Colon Cancer, Rectal Neoplasms, Rectal Tumor, Statin, Colorectal Neoplasms, Colorectal Cancer, and Colonic Neoplasms." For advanced searches, combinations of the keywords were searched using Boolean operators (AND, OR) and for manual searches, the list of study sources was screened. Supplementary file 1 presents the search strategy in some database.

PICO elements

- Population: studies related to individuals who had used statins.
- Intervention: statin treatment.
- Comparison: individuals who had not used statins.
- Outcomes: the effect of statins on risk of colorectal, colon, and rectal cancers.

Inclusion criteria

This study investigated cohort and case-control studies that examined the relationship between statin treatment and the risk of colorectal cancer.

Exclusion criteria

Studies with descriptive results, studies lacking the required data for analysis, studies that had investigated the effect of a combination of drugs (including statin) on colorectal cancer, repeated studies, studies on the effect of statins on several types of cancers (including colorectal cancer), studies without an acceptable quality based on the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) quality assessment checklist, and studies that their full texts were not available.

Qualitative evaluation

Two authors independently evaluated the quality of the studies using the STROBE quality assessment checklist (21). The list consisted of 22 questions with an obtainable score between 0 to 44. Studies with scores lower than 16 were considered low quality and were excluded.

Data extraction

Two researchers extracted the data from studies to minimize the possibility of error in data collection. The researchers prepared a checklist for data extraction, which included the researchers' name, publication date of the article, study design, comparison group, location of the study, patients' mean age, sample size, the relationship between statin use and the incidence of colorectal-colon and rectal cancers, and their upper and lower limits.

Statistical analysis

The odds ratio (OR) was utilized to examine the relationship between statin use and risk of colorectal cancer. The log OR of each study was calculated and used to combine the study results. The I^2 index was used to evaluate the heterogeneity of the studies. The fixed and random effects models were used for low and high heterogeneities, respectively. Data analysis was conducted using STATA version 14, and P values lower than 0.05 ($P < 0.05$) indicated the significance of statistical tests.

Results

At first, searches using the mentioned databases identified 1162 articles. After examining the titles, 495 repeated studies were removed. The abstracts of the 667 articles were examined, and 75 studies were excluded for being unrelated. The remaining 592 studies were reviewed, 24 were removed due to the unavailability of their full texts, and 538 were excluded because of other exclusion criteria. Eventually, 30 high-quality articles entered the process of systematic review and meta-analysis (Figure 1).

Among the 30 articles, 15 were cohort, and 15 were case-control studies (Table 1).

The current meta-analysis investigated 30 studies with a combination of 2 436 650 samples (509 870 individuals were in the statin group, and 1 927 680 individuals were

in the comparison group). Figure 2 shows that statin administration reduced the risk of colorectal cancer by 11% (OR: 0.89; 95% CI: 0.84, 0.95).

According to Figure 3, statin administration in the group of individuals aged 50 to 59 reduced the risk of colorectal cancer by 22% (R: 0.78; 95% CI: 0.63, 0.95), group aged 60 to 69 by 14% (OR: 0.86; 95% CI: 0.75, 0.98), and group aged 70 to 79 by 8% (R: 0.92; 95% CI: 0.87, 0.98).

According to Figure 4, the impact of statin administration on the reduction of the risk of colorectal cancer for cohort and case-control studies were (OR: 0.89; 95% CI: 0.79, 0.99) and (OR: 0.90; 95% CI: 0.83, 0.98), respectively.

Statin administration reduced the risk of colorectal cancer in men (OR: 0.71; 95% CI: 0.58, 0.87) and females (OR: 0.84; 95% CI: 0.77, 0.92) by 29% and 16%, respectively (Figures 5 and 6).

The bias diagram showed that the source search phase was completed, and there was no publication bias (*P*=0.880; Figure 7).

According to Table 2, statin administration reduced the risk of colorectal cancer in male and female patients by 59% and 36%, respectively. It also diminished the risk of rectal cancer by 16% (OR: 0.84; 95% CI: 0.74, 0.94).

Discussion

The results of the current meta-analysis revealed that statin administration reduced the risk of colorectal cancer by 11% and rectal cancer by 16%, indicating statin's protective and preventive role in the mentioned cancers. Statin use reduced the risk of CRS in patients aged 50 to 59 by 22%, 60 to 69 by 14%, and 70 to 79 by 8%. According to the findings, the statin's protective role against colorectal cancer reduced with the increase in patients' age, and patients aged 50 to 59 were the best candidates for statin administration. However, statin treatment considerably decreased the risk of colorectal malignancy at older ages.

Furthermore, statin administration reduced the risk of colorectal cancer in men and women by 29% and 16%, respectively. It also reduced the risk of colon cancer in men and women by 59% and 36%, respectively. We can conclude that the statins' preventive effect against colorectal and colon cancers is higher in men than women and statin administration is more effective for male patients.

The findings of the meta-analysis by Li et al, including five case-control and 11 cohort studies, showed that statin treatment reduced the general mortality rate following colorectal cancer (HR = 0.81, 95% CI 0.76 to 0.86) and the colorectal cancer-specific mortality (HR = 0.78, 95% CI: 0.72 to 0.85) (48). Statin administration in our study also reduced the risk of colorectal cancer, consistent with Li and colleagues' results which also reported decreased cancer mortality rate.

In a meta-analysis by Harewood et al on 29 studies, results indicated aspirin's protective role against proximal colon cancer (RR 0.80, 95% CI: 0.73–0.8); however, there was no significant relationship between the oral contraceptives (RR 1.06, 95% CI: 0.98–1.14) or statin administration (RR 0.94, 95% CI: 0.67–1.31) and the

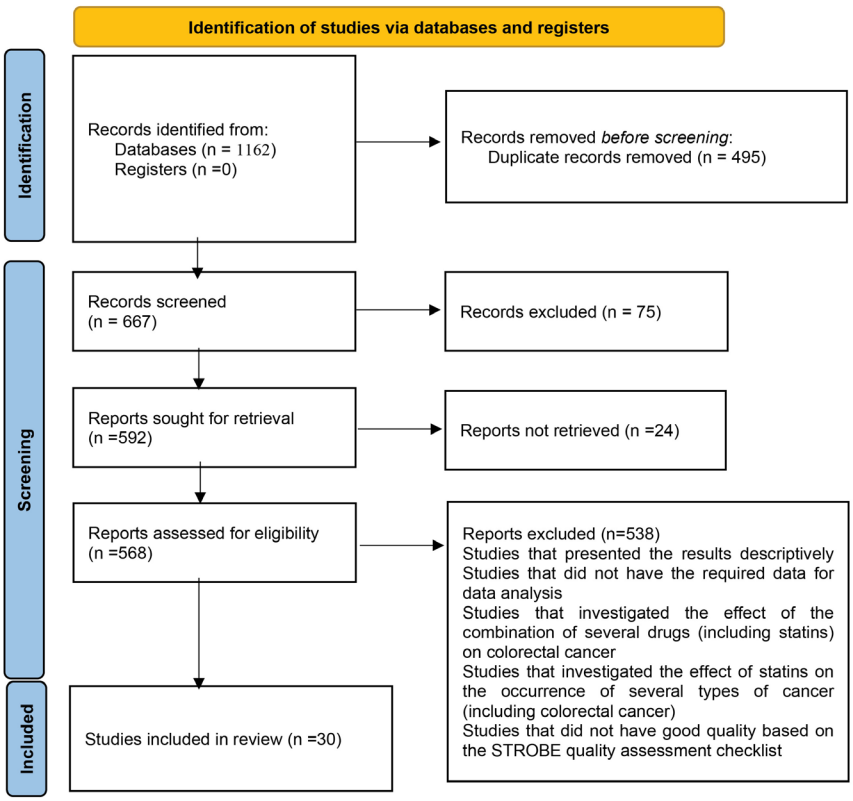

Figure 1. The process of entering the studies into the systematic review and meta-analysis.

Table 1. Summary of the information available in the reviewed articles

First author	Country	Type of study	Sample size people who take statins	The average age of people who take statins (year)	Sample size people who do not take statins	The average age of people who do not take statins (year)	During of study
Ouahoud S, 2022(17)	Netherlands	Cohort	69272	64	94753	63	January 2000 and December 2007
Rodríguez-Miguel A, 2022(18)	Spain	Case-Control	15491	68.6	60000	68.6	From 2001–2014
Hsu SH, 2022(22)	Taiwan	Cohort	2857	40 to 64	393664	40 to 64	January 2007 to December 2009
Zhang Y, 2022(23)	USA	Cohort	843	30-55	2081	30-55	
Kim DS, 2022(24)	South Korea	Cohort	1819	58.1	7779	58.8	during 2005 to June 2013
Erkinantti S, 2021(25)	Finland	Cohort	1349	≥40	24493	≥40	January 1996 and December 2011
Lee JW, 2019(26)	South Korea	Cohort	4050	54.5	8488	51.2	from 2002 to 2015
Rutledge BP, 2019(27)	USA	Cohort	10868	63	121889	63	
Ibáñez-Sanz G, 2019(28)	Spain	Case-Control	25811	74	129117	67	between 2010 and 2015
Ananthakrishnan AN, 2016(29)	USA	Cohort	1376	59	9625	36	from 1998 through 2010
Liu JC, 2016(30)	Taiwan	Cohort	10086	61.55	33716	63.33	between January 2001, and December 2012
Mamtani R, 2016(31)	USA	Case-Control	22163	72.3	86538	72	between 1995 and 2013
Fujimoto M, 2015(19)	Japan	Case-Control	1575	51.8	38402	51.8	January 2005 to July 2013
Sehdev A, 2014(32)	USA	Case-Control	32616	54.44	325086	54.43	between 2004 and 2010
Broughton T, 2013(33)	UK	Case-Control	132	64.2	132	63.8	September 2009 to August 2010
Clancy Z, 2013(34)	Italy	Cohort	215963	18-80	50146	18-80	between January 2003 and December 2009
Simon MS, 2012(35)	USA	Cohort	12030	50-79	147189	50-79	between October 1993, and December 1998
Broughton T, 2012(36)	UK	Case-Control	101	70.3	132	63.8	2009-2010
Lee JE, 2011(37)	USA	Cohort	258		1560		1990-2006
Cheng MH, 2011(38)	Taiwan	Case-Control	1156	68.34	4624	69.29	from January 2005 to December 2008
Robertson DJ, 2010(39)	Denmark	Case-Control	9979	71.2	99790	71.2	between January 1991 and December 2008
Flick ED, 2009(40)	USA	Cohort	24503	45–69	44612	45–69	2002-2003
Hachem C, 2009(41)	USA	Case-Control	6080	74	24320	74	January 2001 –December 2002
Singh H, 2009(20)	Canada	Cohort	1921	40-80	138998	>40	between April 1995 and December 2005
Boudreau DM, 2008(42)	USA	Case-Control	665	69.9	665	70	between January 2000, and December 2003
Yang YX, 2008(43)	USA	Case-Control	4432	67.5	44292	63.6	between May 1987 and April 2002
Hoffmeister M, 2007(44)	Germany	Case-Control	540	>30	614	>30	between January 2003 and June 2004
Setoguchi S, 2007(45)	USA	Cohort	24439	76.4	7284	80.1	between January 1994 and May 2003
Coogan PF, 2007(46)	USA	Case-Control	1809	50–74	1809	50–74	January 2001, through November 2004
Vinogradova Y, 2007(47)	UK	Case-Control	5686	64 –79	24982	64 –79	between 1995 and 2005

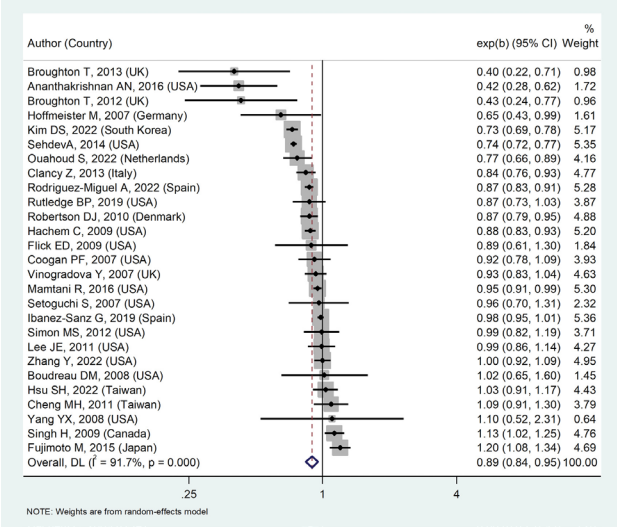

Figure 2. Relationship between statins use and risk of colorectal cancer

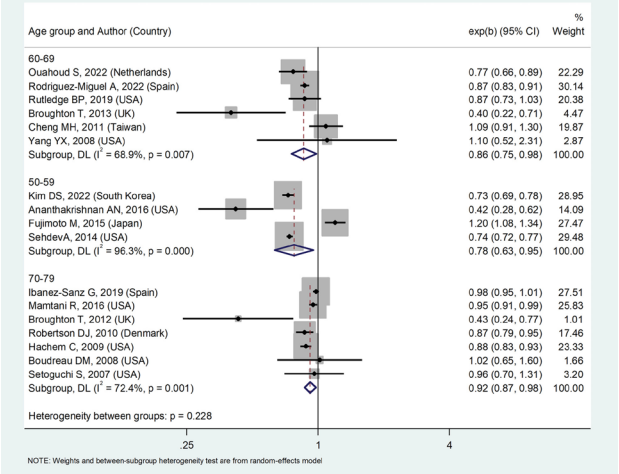

Figure 3. Relationship between statins use and risk of colorectal cancer by age groups.

incidence rate of proximal colon cancer (49). The results of the mentioned study were inconsistent with the present meta-analysis, as in our study, statins effectively reduced the risk of colon cancer. The difference between the number of examined studies, drug doses, duration, and type of administered statin are among the factors which caused the heterogeneity between the studies and may be the cause for the differences between this study and Harewood and colleagues' results.

A meta-analysis by Jung et al of six studies aimed to investigate the relationship between statin use and the risk of colorectal adenoma. Results indicated that statin treatment reduced the risk of advanced colorectal adenoma (RR = 0.83; 95% CI, 0.75–0.92) (50), which was consistent with the results of our study, and the result of the present meta-analysis confirms Jung and colleagues' results.

Based on the results of a meta-analysis by Bonovas et al, which included 18 studies and aimed to examine the relationship between statins administration and the risk

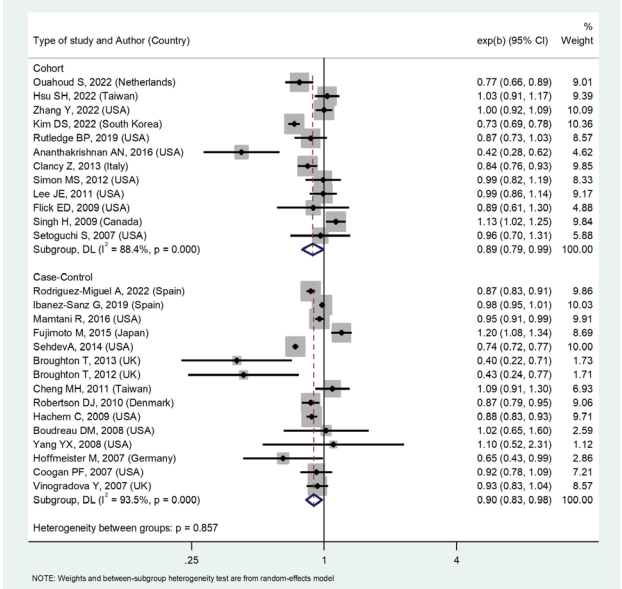

Figure 4. Relationship between statins use and risk of colorectal cancer by type of studies.

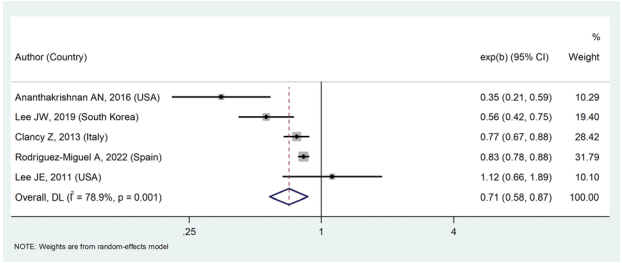

Figure 5. Relationship between statins use and risk of colorectal cancer in male.

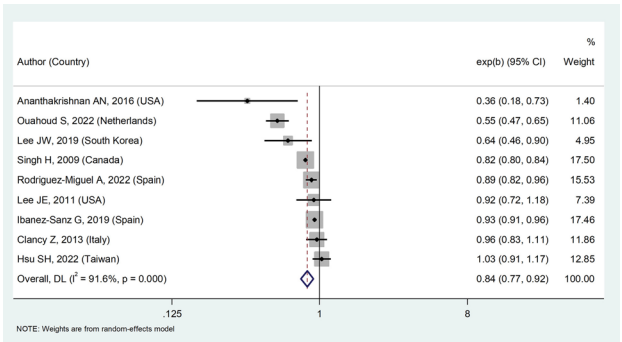

Figure 6. Relationship between statins use and risk of colorectal cancer in female.

of colorectal cancer, there was no evidence indicating the relationship between statin treatment and the risk of colorectal cancer in the cohort studies (RR = 0.96; 95% CI: 0.84 to 1.11; n =3). However, statin reduced the risk of colorectal cancer in case-control studies (RR = 0.91; 95% CI: 0.87 to 0.96; n = 9) (51). Based on the results of a meta-analysis by Lytras et al, there was no statistically significant relationship between the statin treatment and the risk of colorectal cancer (RR = 0.91, 95% CI: 0.83-1.00); however, in case-control studies, statin administration had a protective

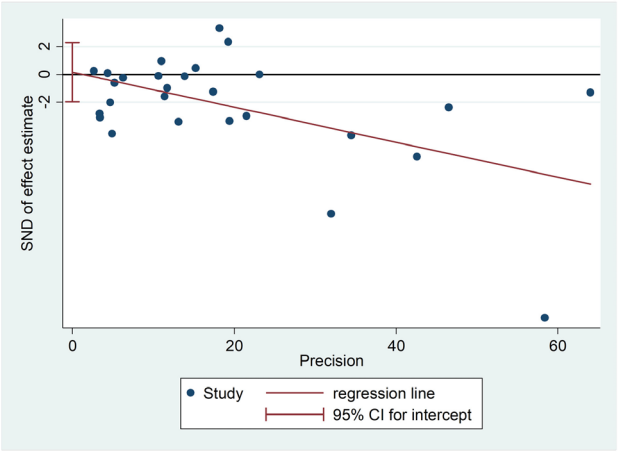

Figure 7. Chart of publication bias.

and preventive role against the incidence of colorectal cancer (RR = 0.92, 95% CI: 0.87-0.98;) (52). A meta-analysis by Liu et al reported that statin administration reduced the risk of colorectal cancer (RR = 0.90, 95% CI: 0.86–0.95). The analysis of subgroups indicated a significant reduction in the risk of colorectal cancer in observational studies (RR = 0.89, 95% CI: 0.84–0.95) and rectum cancer (RR = 0.81, 95% CI: 0.66–0.99) (53). The previous meta-analyses showed that statins' preventive effectiveness in colorectal cancer incidence of case-control studies was statistically significant; however, there was no significant relationship in cohort studies. In the present meta-analysis, however, statin treatment in cohort and case-control studies reduced the risk of colorectal cancer by 11% and 10%, respectively. Considering the fact that the results of the current meta-analysis are up to date and have included recent studies, we can claim that this study has higher reliability than the previous studies.

Conclusion

Results of the current meta-analysis indicated that statin administration prevented the incidence of colorectal, colon, and rectal cancers, and the efficiency of statin treatment in preventing colorectal and colon cancer in men was higher than in women. Furthermore, the efficiency of statin in reducing the risk of colorectal cancer in younger patients was higher. Nevertheless, considering the limitation of the study, there were shortcomings that we suggest to solve in future studies. For instance, we recommend comparing the effect of different statin types and doses on the risk of colorectal cancer in future studies.

Limitation of the meta-analysis

A limited number of studies had mentioned the type of administered statin; therefore, comparing the effect of various statins on the risk of colorectal cancer was not possible. The examined studies did not report the dose of statin administered to the patients; consequently, we could not compare the effect of high and low statin doses on colorectal cancer. Regarding rectal cancer, it was not possible to present the results based on the patients' sex. Many studies had not mentioned the duration of statin treatment; hence, we could not evaluate the effect of statin treatment on the risk of colorectal cancer based on the duration of statin administration.

Table 2. Relationship between statins use and risk of colon and rectal cancer

Subgroups		OR (95% CI)	*P* value	I^2 (%)
Colon cancer	Male	0.41 (0.26, 0.67)	0.142	53.5
	Female	0.64 (0.42, 0.97)	0.167	47.6
Rectal cancer	Total	0.84 (0.74, 0.94)	0.244	26.6

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Authors' contribution

Conceptualization: Mehrdad Abbaszadeh, Alireza Peimanfar.
Data curation: Fahimeh Bayrami, Samaneh Zandifar, Hamid Reza Hemmati.
Formal analysis: Hamid Reza Hemmati, Ali Valadkhani.
Investigation: Alireza Peimanfar.
Methodology: Mehrdad Abbaszadeh, Samaneh Zandifar.
Project administration: Alireza Peimanfar.
Resources: Mehrdad Abbaszadeh, Samaneh Zandifar.
Supervision: Mehrdad Abbaszadeh, Alireza Peimanfar.
Validation: Mehrdad Abbaszadeh, Alireza Peimanfar, Hamid Reza Hemmati.
Visualization: Mehrdad Abbaszadeh, Alireza Peimanfar.
Writing–original draft: Mehrdad Abbaszadeh, Fahimeh Bayrami, Ali Valadkhani, Alireza Peimanfar.
Writing–review and editing: Mehrdad Abbaszadeh, Ali Valadkhani, Samaneh Zandifar, Alireza Peimanfar, Fahimeh Bayrami, Hamid Reza Hemmati.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This investigation has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (ID: CRD42023450984) and Research Registry website with (Unique Identifying Number (UIN) reviewregistry1779). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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Supplementary files

Supplementary file 1. Search strategy in some databases.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209-49. doi: 10.3322/caac.21660.
2. American Cancer Society (ACS). Global Cancer Facts & Figures. 4th ed. Atlanta: ACS; 2018. Available from: https://wwwcancerorg/content/dam/cancer-org/research/cancer-facts-and-statistics/global-cancer-facts-and-figures/global-

cancer-facts-and-figures-4th-editionpdf.
3. American Cancer Society. Cancer Facts & Figures 2019. 2019. Available from: https://wwwcancerorg/searchhtml?q=cancer+Facts+%26+Figures+2019.
4. Lee CH, Cheng SC, Tung HY, Chang SC, Ching CY, Wu SF. The risk factors affecting survival in colorectal cancer in Taiwan. Iran J Public Health. 2018;47:519-30.
5. Ding X, Zhang W, Li S, Yang H. The role of cholesterol metabolism in cancer. Am J Cancer Res. 2019;9:219-27.
6. Brenner H, Kloor M, Pox CP. Colorectal cancer. Lancet. 2014;383:1490-502. doi: 10.1016/s0140-6736(13)61649-9.
7. Binefa G, Rodríguez-Moranta F, Teule A, Medina-Hayas M. Colorectal cancer: from prevention to personalized medicine. World J Gastroenterol. 2014;20:6786-808. doi: 10.3748/wjg.v20.i22.6786.
8. Wang D, Dubois RN. The role of COX-2 in intestinal inflammation and colorectal cancer. Oncogene. 2010;29:781-8. doi: 10.1038/onc.2009.421.
9. Moreira L, Castells A. Cyclooxygenase as a target for colorectal cancer chemoprevention. Curr Drug Targets. 2011;12(13):1888-94. doi: 10.2174/138945011798184218.
10. Davì G, Patrono C. Platelet activation and atherothrombosis. N Engl J Med. 2007;357:2482-94. doi: 10.1056/NEJMra071014.
11. Murai T. Cholesterol lowering: role in cancer prevention and treatment. Biol Chem. 2015;396:1-11. doi: 10.1515/hsz-2014-0194.
12. Faubion SS, Kapoor E, Moyer AM, Hodis HN, Miller VM. Statin therapy: does sex matter? Menopause. 2019;26:1425-35. doi: 10.1097/gme.0000000000001412.
13. Li P, Wu H, Zhang H, Shi Y, Xu J, Ye Y, et al. Aspirin use after diagnosis but not prediagnosis improves established colorectal cancer survival: a meta-analysis. Gut. 2015;64:1419-25. doi: 10.1136/gutjnl-2014-308260.
14. Nielsen SF, Nordestgaard BG, Bojesen SE. Statin use and reduced cancer-related mortality. N Engl J Med. 2012;367:1792-802. doi: 10.1056/NEJMoa1201735.
15. Stryjkowska-Góra A, Karczmarek-Borowska B, Góra T, Krawczak K. Statins and cancers. Contemp Oncol (Pozn). 2015;19:167-75. doi: 10.5114/wo.2014.44294.
16. Thomas JP, Loke YK, Alexandre L. Efficacy and safety profile of statins in patients with cancer: a systematic review of randomised controlled trials. Eur J Clin Pharmacol. 2020;76:1639-51. doi: 10.1007/s00228-020-02967-0.
17. Ouahoud S, Jacobs RJ, Kodach LL, Voorneveld PW, Hawinkels L, Weil NL, et al. Statin use is associated with a reduced incidence of colorectal cancer expressing SMAD4. Br J Cancer. 2022;126:297-301. doi: 10.1038/s41416-021-01604-6.
18. Rodríguez-Miguel A, Fernández-Antón E, Barreira-Hernández D, García-Rodríguez LA, Gil M, García-Lledó A, et al. Statins and colorectal cancer risk: a population-based case-control study and synthesis of the epidemiological evidence. J Clin Med. 2022;11:1528. doi: 10.3390/jcm11061528.
19. Fujimoto M, Higuchi T, Hosomi K, Takada M. Association between statin use and cancer: data mining of a spontaneous reporting database and a claims database. Int J Med Sci. 2015;12:223-33. doi: 10.7150/ijms.10656.
20. Singh H, Mahmud SM, Turner D, Xue L, Demers AA, Bernstein CN. Long-term use of statins and risk of colorectal cancer: a population-based study. Am J Gastroenterol. 2009;104:3015-23. doi: 10.1038/ajg.2009.574.
21. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61:344-9. doi: 10.1016/j.jclinepi.2007.11.008.
22. Hsu SH, Syu DK, Wang YC, Liu CK, Chen MC. Metformin, statin use, and female colorectal cancer: a population-based cohort study in Taiwan. J Clin Med. 2022;11:4469. doi: 10.3390/jcm11154469.
23. Zhang Y, Wu K, Chan AT, Meyerhardt JA, Giovannucci EL. Long-term statin use, total cholesterol level, and risk of colorectal cancer: a prospective cohort study. Am J Gastroenterol. 2022;117:158-66. doi: 10.14309/ajg.0000000000001543.
24. Kim DS, Kim HJ, Ahn HS. Statins and the risk of gastric, colorectal, and esophageal cancer incidence and mortality: a cohort study based on data from the Korean national health insurance claims database. J Cancer Res Clin Oncol. 2022;148:2855-65. doi: 10.1007/s00432-022-04075-1.
25. Erkinantti S, Marttila M, Sund R, Arffman M, Urpilainen E, Puistola U, et al. Association of metformin, other antidiabetic medications, and statins with incidence of colon cancer in patients with type 2 diabetes. Clin Colorectal Cancer. 2021;20:e113-9. doi: 10.1016/j.clcc.2020.11.003.
26. Lee JW, You NY, Kim Y, Kim Y, Kim J, Kang HT. Statin use and site-specific risk of colorectal cancer in individuals with hypercholesterolemia from the National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS). Nutr Metab Cardiovasc Dis. 2019;29:701-9. doi: 10.1016/j.numecd.2019.04.002.
27. Rutledge BP, Desai P, Liu S, Luo J, Nassir R, Lihong Q, et al. The association between statins and colorectal cancer stage in the Women's Health Initiative. Mol Clin Oncol. 2019;11:252-8. doi: 10.3892/mco.2019.1895.
28. Ibáñez-Sanz G, Guinó E, Pontes C, Quijada-Manuitt M, de la Peña-Negro LC, Aragón M, et al. Statin use and the risk of colorectal cancer in a population-based electronic health records study. Sci Rep. 2019;9:13560. doi: 10.1038/s41598-019-49877-5.
29. Ananthakrishnan AN, Cagan A, Cai T, Gainer VS, Shaw SY, Churchill S, et al. Statin use is associated with reduced risk of colorectal cancer in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol. 2016;14:973-9. doi: 10.1016/j.cgh.2016.02.017.
30. Liu JC, Hao WR, Hsu YP, Sung LC, Kao PF, Lin CF, et al. Statins dose-dependently exert a significant chemopreventive effect on colon cancer in patients with chronic obstructive pulmonary disease: a population-based cohort study. Oncotarget. 2016;7:65270-83. doi: 10.18632/oncotarget.11263.
31. Mamtani R, Lewis JD, Scott FI, Ahmad T, Goldberg DS, Datta J, et al. Disentangling the association between statins, cholesterol, and colorectal cancer: a nested case-control study. PLoS Med. 2016;13:e1002007. doi: 10.1371/journal.pmed.1002007.
32. Sehdev A, Shih YC, Huo D, Vekhter B, Lyttle C, Polite B. The role of statins for primary prevention in non-elderly colorectal cancer patients. Anticancer Res. 2014;34:5043-50.
33. Broughton T, Singtonn J, Beales IL. Statin use is associated with a reduced incidence of colorectal adenomatous polyps. Int J Colorectal Dis. 2013;28:469-76. doi: 10.1007/s00384-012-1601-9.
34. Clancy Z, Keith SW, Rabinowitz C, Ceccarelli M, Gagne JJ, Maio V. Statins and colorectal cancer risk: a longitudinal study. Cancer Causes Control. 2013;24:777-82. doi: 10.1007/s10552-013-0160-x.
35. Simon MS, Rosenberg CA, Rodabough RJ, Greenland P, Ockene I, Roy HK, et al. Prospective analysis of association between use of statins or other lipid-lowering agents and colorectal cancer risk. Ann Epidemiol. 2012;22:17-27. doi: 10.1016/j.annepidem.2011.10.006.
36. Broughton T, Singtonn J, Beales IL. Statin use is associated with a reduced incidence of colorectal cancer: a colonoscopy-controlled case-control study. BMC Gastroenterol. 2012;12:36.

doi: 10.1186/1471-230x-12-36.
37. Lee JE, Baba Y, Ng K, Giovannucci E, Fuchs CS, Ogino S, et al. Statin use and colorectal cancer risk according to molecular subtypes in two large prospective cohort studies. Cancer Prev Res (Phila). 2011;4:1808-15. doi: 10.1158/1940-6207.capr-11-0113.
38. Cheng MH, Chiu HF, Ho SC, Tsai SS, Wu TN, Yang CY. Statin use and the risk of colorectal cancer: a population-based case-control study. World J Gastroenterol. 2011;17:5197-202. doi: 10.3748/wjg.v17.i47.5197.
39. Robertson DJ, Riis AH, Friis S, Pedersen L, Baron JA, Sørensen HT. Neither long-term statin use nor atherosclerotic disease is associated with risk of colorectal cancer. Clin Gastroenterol Hepatol. 2010;8:1056-61. doi: 10.1016/j.cgh.2010.08.010.
40. Flick ED, Habel LA, Chan KA, Haque R, Quinn VP, Van Den Eeden SK, et al. Statin use and risk of colorectal cancer in a cohort of middle-aged men in the US: a prospective cohort study. Drugs. 2009;69:1445-57. doi: 10.2165/00003495-200969110-00004.
41. Hachem C, Morgan R, Johnson M, Kuebeler M, El-Serag H. Statins and the risk of colorectal carcinoma: a nested case-control study in veterans with diabetes. Am J Gastroenterol. 2009;104:1241-8. doi: 10.1038/ajg.2009.64.
42. Boudreau DM, Koehler E, Rulyak SJ, Haneuse S, Harrison R, Mandelson MT. Cardiovascular medication use and risk for colorectal cancer. Cancer Epidemiol Biomarkers Prev. 2008;17:3076-80. doi: 10.1158/1055-9965.epi-08-0095.
43. Yang YX, Hennessy S, Propert K, Hwang WT, Sarkar M, Lewis JD. Chronic statin therapy and the risk of colorectal cancer. Pharmacoepidemiol Drug Saf. 2008;17:869-76. doi: 10.1002/pds.1599.
44. Hoffmeister M, Chang-Claude J, Brenner H. Individual and joint use of statins and low-dose aspirin and risk of colorectal cancer: a population-based case-control study. Int J Cancer. 2007;121:1325-30. doi: 10.1002/ijc.22796.
45. Setoguchi S, Glynn RJ, Avorn J, Mogun H, Schneeweiss S. Statins and the risk of lung, breast, and colorectal cancer in the elderly. Circulation. 2007;115:27-33. doi: 10.1161/circulationaha.106.650176.
46. Coogan PF, Smith J, Rosenberg L. Statin use and risk of colorectal cancer. J Natl Cancer Inst. 2007;99:32-40. doi: 10.1093/jnci/djk003.
47. Vinogradova Y, Hippisley-Cox J, Coupland C, Logan RF. Risk of colorectal cancer in patients prescribed statins, nonsteroidal anti-inflammatory drugs, and cyclooxygenase-2 inhibitors: nested case-control study. Gastroenterology. 2007;133:393-402. doi: 10.1053/j.gastro.2007.05.023.
48. Li L, Cui N, Hao T, Zou J, Jiao W, Yi K, et al. Statins use and the prognosis of colorectal cancer: a meta-analysis. Clin Res Hepatol Gastroenterol. 2021;45:101588. doi: 10.1016/j.clinre.2020.101588.
49. Harewood R, Disney R, Kinross J, von Wagner C, Cross AJ. Medication use and risk of proximal colon cancer: a systematic review of prospective studies with narrative synthesis and meta-analysis. Cancer Causes Control. 2021;32:1047-61. doi: 10.1007/s10552-021-01472-8.
50. Jung YS, Park CH, Eun CS, Park DI, Han DS. Statin use and the risk of colorectal adenoma: a meta-analysis. J Gastroenterol Hepatol. 2016;31:1823-30. doi: 10.1111/jgh.13393.
51. Bonovas S, Filioussi K, Flordellis CS, Sitaras NM. Statins and the risk of colorectal cancer: a meta-analysis of 18 studies involving more than 1.5 million patients. J Clin Oncol. 2007;25:3462-8. doi: 10.1200/jco.2007.10.8936.
52. Lytras T, Nikolopoulos G, Bonovas S. Statins and the risk of colorectal cancer: an updated systematic review and meta-analysis of 40 studies. World J Gastroenterol. 2014;20:1858-70. doi: 10.3748/wjg.v20.i7.1858.
53. Liu Y, Tang W, Wang J, Xie L, Li T, He Y, et al. Association between statin use and colorectal cancer risk: a meta-analysis of 42 studies. Cancer Causes Control. 2014;25:237-49. doi: 10.1007/s10552-013-0326-6.