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Research

Efficacy of Statins Use in the Treatment of Colorectal Cancer Patients Systemic Review and Meta-Analysis

Reyad Al-Moktar Ekhmaj*[1], Wafa Mahmoud Alshaiby[2], Einass Ragab Ibraheim[3]

[1]University of Zawia, Faculty of Medicine, Department of Surgery, Zawia, Libya.
[2'3]University of Zawia, Faculty of Pharmacy, Department of Pharmacology, Zawia, Libya.

*Author for Correspondence: Dr. Reyad Al-Moktar Ekhmaj
Email: reyadekhmaj@gmail.com

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Abstract

Numerous observational studies conducted in the past few years have confirmed the link between statin use and colorectal cancer by preserving and lowering the death rate. Statins may have an impact on cancer cells' ability to proliferate, migrate, and survive. Since the 1990s, the idea of utilizing statins to treat cancer has gained traction. Statins have been used in cohort studies, in vitro and in vivo tests, and on tumor-related inflammation and oxidative stress to show their anticancer effects. Method: we systematically searched for studies about the statin used in colorectal cancer patients in electronic databases, including PubMed, Web of Science, academic Google Scholar, and science direct, covering the last eight years up until 2022. A total of 8 studies, which include 506,346 individuals, of whom, 100,225 were statins users. The collected data assessed by using Statistical Package for the Social Sciences (SPSS). Result: Our analysis selected studies presented with outcome based on relative ratios (RRs) and 95% confidence intervals (CIs) of colorectal cancer-specific mortality. The use of statin was potentially associated with a decline in colorectal cancer-specific mortality in cancer patients (RR; 0.92; 95% CI, 0.90 to 0.95; random-effects model: RR0.90; 95% CI, 0.79 to 0.96). The meta-analysis showed that ongoing statin therapy was associated with a 20% decrease in the risk of colorectal cancer-specific mortality compared to patients without ongoing statin therapy (adjusted HR 0.75, 95%CI 0.65-0.85, P < .002). Conclusion: The risk of colorectal cancer was lower in statin user versus nonuser, accumulating evidence suggests that statins may have a role in colorectal cancer prevention and treatment. Among Lipid lowering medication (LLM) users, adherence to this drug is associated with a decrease in cancer-specific mortality.

Keywords: colorectal cancer, colorectal cancer- specific mortality, statins.

INTRODUCTION

The condition known as colorectal cancer (CRC) occurs when cells in the colon or rectum proliferate uncontrollably. Depending on where it starts, cancer that starts in the colon is referred to as colon cancer, and cancer that starts in the rectum is referred to as rectal cancer. The large bowel, also known as the colon, is the intestine. The path from the colon to the anus is called the rectum [1,2,3].

Colon cancer can strike anyone at any age, but it usually strikes older people. Usually, it starts off as little cell clusters inside the colon called polyps. Although most polyps are benign, some may eventually develop into colon cancer [4, 5]. Polyps frequently show no symptoms. Screening tests are available to healthcare providers to identify precancerous polyps before they develop into malignant tumors. If colon cancer is not identified or treated, it may spread to other body parts [4,6].

Colon cancer (CRC) accounts for 0.94 million deaths and 1.93 million incidence cases globally in 2020 [10], or 10% of global cancer incidence (total 19.29 million new cases) and 9.4% of all cancer-related deaths (total 9.96 million deaths), according to GLOBOCAN 2020 data. Colon cancer is the third-most deadly and most common type of cancer [7,8,9]. Globally, colorectal cancer (CRC) is the primary cause of cancer-related fatalities for both sexes; More than 5.25 million people globally (5-year prevalence) are living with colorectal cancer (CRC), which is marginally less common than breast cancer (7.79 million cancer cases)[11]. The pathophysiology of colorectal cancer (CRC) has been better understood, and treatment options have been expanded. These include endoscopic resection, surgical local excision, targeted therapy, radiation therapy, ablative therapies, chemotherapy, and immunotherapy. Combined, these treatments have doubled the overall survival of colorectal cancer to three years[13]. However, even in the majority of highly industrialized nations, notable variations in the CRC survival rate have been noted. The notable variations in survival rates may be partially explained by the diagnosis made at various clinical stages of colorectal cancer [14].

Most CRC patients are already in the advanced stage, when malignancies are aggressive, malignant, and metastatic. CRC is typically asymptomatic. When symptoms do occur, such as rectal bleeding, anemia, or abdominal pain, the majority of patients are already in this stage.

One factor contributing to the difference in survival and the high number of CRC fatalities globally is an advanced diagnosis. Therefore, starting more than ten years ago, population-based screening programs have been widely proposed and put into place in certain highly developed nations with the goal of increasing therapy outcomes and moving the distribution of CRC to earlier stages [9, 11, 12]. It is impossible to change some of the most significant risk variables, such as age and family history. Colorectal cancer can occur as a result of both environmental and inherited risk factors[13]. One of the most significant factors influencing the risk of colorectal cancer appears to be dietary factors. Disease-regional variation can be partially explained by diet. Diets heavy in red meat, saturated fat, and high-calorie, low-fiber foods seem to put people at risk. Fruits, vegetables, fiber, folate, and calcium may all offer protection. Tall stature and obesity, especially abdominal obesity, may be risk factors. Numerous studies have demonstrated that physical activity lowers the incidence of colorectal cancer. Hormone replacement therapy after menopause may potentially offer protection.

Additionally, individuals with Crohn's disease or ulcerative colitis, two types of inflammatory bowel diseases (IBD), may experience long-term inflammation of the large intestine, which raises the risk of cancer [14,15,16,17].

Statins and Mechanisms of Action

Numerous observational studies conducted in the past few years have confirmed the link between statin use and colorectal cancer by preserving and lowering the death rate.

Statins may have an impact on cancer cells' ability to proliferate, migrate, and survive. Since the 1990s, the idea of utilizing statins to treat cancer has gained traction. Statins have been used in cohort studies, in vitro and in vivo tests, and on tumor-related inflammation and oxidative stress to show their anticancer effects (i.e., proliferation and migration impairment). However, these acts' biological processes remain incompletely understood.

By lowering circulating lipids, particularly the cholesterol found in low-density lipoprotein (LDL), statins have an anti-neoplastic impact. This process results from the specificity of statins as inhibitors of the mevalonate pathway, which is in charge of the synthesis of non-sterol isoprenoids and cholesterol from scratch. In particular, statins prevent HMG-CoA from being converted to mevalonate by blocking HMG-CoA reductase (HMGCR), a limiting enzyme involved in cholesterol synthesis and the rate-limiting enzyme of the mevalonate pathway. It is widely known that statins have an enzyme affinity hundreds of times greater than that of the natural substrate, which lowers the synthesis of mevalonate and, as a result, lowers the intracellular cholesterol concentration (Fig. 1). There's a chance that farnesyl pyrophosphate, which promotes cell adhesion, protein activation, and proliferation, will also be impacted [19]. Sterol regulatory element-binding protein transcription is triggered, under normal circumstances, by low intracellular cholesterol through a homeostatic feedback mechanism (SREBP). The lowering of serum cholesterol levels is the outcome of SREBP activation. In some cancer cells, this feedback pathway is defective, and making them vulnerable to HMGCR inhibition in human cancer [20, 21]. Statins prevent the production of mevalonate and the downstream isoprenoids (geranylgeranyl pyrophosphate and farnesyl pyrophosphate), as well as other products of the mevalonate pathway. Many cellular proteins, particularly small GTPases like Ras and Rho, have their membrane location and function determined in part by post-translational isoprenylation [25].

It was confirmed by Fujiwara et al. (2017) that the induction of apoptosis in hematological tumor cells by statins could be caused via mitochondrial apoptotic signaling pathways. These are activated with the aid of suppressing mevalonate or geranylgeranyl pyrophosphate biosynthesis due to mobileular cycle arrest within G1-phase because of suppressing the prenylation of the rapamycin (Ras) pathways [27].

The role of statins in inhibiting the growth of the majority of cancer cells, which results in G1-phase arrest and may even reduce cell migration, is another plausible mechanism that has already been shown. Because statins may decrease the expression of matrix metalloproteinase-9 (MMP-9) in endothelial cells, which results in decreased capability in invasive cells, they can also suppress tumor angiogenesis. According to some research, statins restrict the growth of cancer cells by reducing the expression of the proteins Ras, Rho, and c-Myc and/or by inducing senescence in cancer cell lines. Additionally, statins have been demonstrated to reduce angiogenesis by amplifying TNF-alpha's inhibitory effect on tumor growth and vascularization. Fig. 1 displays a schematic representation of the mevalonate pathway along with a few capacity results on tumor cells.

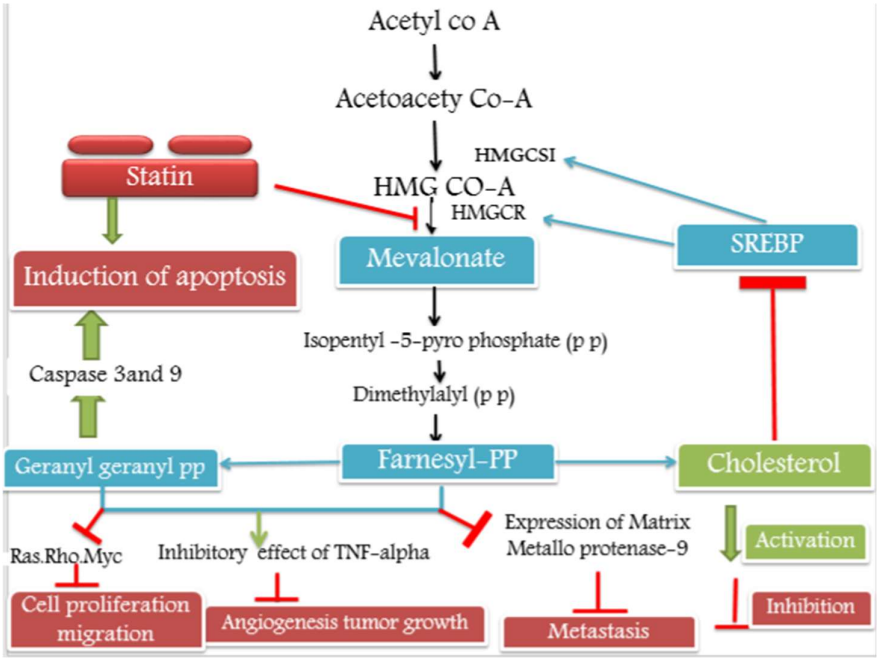

Fig 1: Diagram illustrating the mevalonate pathway's possible impacts on tumor cells.

Acetyl-CoA is converted by the mevalonate pathway into cholesterol and a few non-sterol isoprenoids that are important for cell division and survival. Because statins inhibit mevalonate production, they also inhibit farnesylation and geranylgeranylation. This leads to: 1) a decrease in the expression of the proteins Ras, Rho, and c-Myc, which inhibits the proliferation and migration of tumor cells; 2) a decrease in the expression of matrix metalloproteinase-9, a protein associated with the metastasis of tumor cells; 3) an increase in the inhibitory effect of TNF alpha on angiogenesis; 4) activation of caspase-9 and caspase-3, which triggers the death of cells; and 5) Statins have also been demonstrated to have a direct impact on cell apoptosis [22].

Additional research confirmed that, compared to benign tumors of the same origin, the effects of statins are more pronounced and visible in highly metastatic malignant tumor cells. Probably because malignant tumors proliferate more quickly and require a greater amount of isoprenoids from mevalonate to alter signaling in order for cells to survive [23]. Our goal is to summarize the posted research on the impact of statins on colorectal carcinogenesis.

METHODOLOGY

Search strategy

We conducted a comprehensive search using PubMed, Web of Science, academic Google Scholar, and science direct to find any potential connections between statins and colorectal cancer. The articles were identified by applying a highly sensitive search technique to identify reviews containing a combination of controlled terms and textual phrases related to: (1) statins (flaviastatin, mevastatin, rosuvastatin, atorvasatin, hydroxymethylglutaryl-CoA reductase inhibitor, pravastatin, simvastatin, atorvasatin, rosuvastatin, fluvastatin,

and mevastatin). (2) Colorectal cancers. Additional recursive searches and cross-references have been carried out, along with manual searches of articles found following an initial search and the use of a "comparable articles" function. Regarding the correlation between statin use and the increased chance of survival for CRC patients, it has been established or can be inferred from published studies covering the last eight years up until 2022, as shown in Table 1.

Selection Criteria

This meta-analysis took into account observational studies (case control or cohort) or randomized control trials (RCTs) that assessed the relationship between statin intake and colorectal cancer risk in addition to meta-analysis study as it included number of studies that we couldn't access. If there was insufficient available data to determine an estimate of relative risk (RR) and CI, the articles were not included in the analyses. The statistics presented were exclusively from the most current report, where there were several publications from the same population.

RCTs were deemed eligible if they assessed the effectiveness of statin medication in comparison to placebo or no treatment at all, had at least 465 participants enrolled, showed no differences in other interventions between the experimental and control groups, and disclosed the incidence of colorectal cancer during the study [28]. The data extracted from the eligible articles: author's name, year of publication, sample size, number of statins users, risk estimates and corresponding 95% confidence intervals (95% CIs).

Inclusion criteria

We covered the subsequent varieties of articles: randomized medical trials, case control, cohort research, and meta-analysis that assessed or reported the most common colorectal, colon, and rectal cancer occurrence in topics taking or not taking statins, studies published in English, studies with access and abstract or full text was available.

Exclusion criteria

Excluded studies: irrelevant studies (studies conducted on colorectal cancer cases but used other drugs rather than statins), studies no longer posted in English, studies without sufficient data (studies that didn't present the colorectal cancer specific mortality values for whom using statins before or after diagnosis), studies with unclear statistical analysis, and duplicated studies [24].

Statistical analysis

The relevant findings were based on statin use before or after cancer diagnosis and mortality specifically related to colorectal cancer. Hazard ratios (HRs) evaluating the impact of statins on outcomes in patients with colorectal cancer were pooled using this technique. Risk estimates for mortality specific to colorectal cancer were computed before risk estimates for mortality from other causes, if studies were reported. We took into consideration statistical analyses carried out using the Statistical Package for the Social Sciences (SPSS) if there were colorectal cancer-specific mortality estimates based on statin use prior to cancer diagnosis [26].

RESULTS

After the eight studies were selected the multivariate (sample number, relative ratio, study design, and confidence interval) was collected from each study and recorded on spreadsheet to be analyzed, as shown in Table 1.

Table 1: Observational in data studies

Study	Study Location	Study Design	Participants	Statins users	RR	CI %95
Timothy L Lash, Anders H Riis,2017 [29]	Danish	Cohort study	21,152	6,557	0.78	0.75 to 1.01
Liusheng Li ,2021 [30]	China	Cohort study	387,518	41,134	0.81	0.72 to 0.85
Angeliki Kotti 2019 [31]	Swedish	Cohort	465	465	0.62	0.39–0.96
Thomas F. Imperiale 2022 [32]	United States	retrospective cohort	29,866	10,780	0.83	0.76–0.87
Ronan T Gray 2012 [33]	Scottish	cohort	8,391	5,045	0.79	1.00-1.36
ChiaraMelloni, Gretchen G 2019 [34]	United States	cohort	29,498	11,340	0.69	0.66-0.72
Jia-Li Feng ,	Australian	cohort	11,719	11,492	0.90	0.93-0.97

Xiwen Qin2020 [35]						
Jae-Woo Lee,2019 [36]	Korea	cohort	17,737	13,412	0.70	0.25-0.72

CRC, Colorectal cancer; RR, Relative Risk.

Table 1, display that, the meta-analysis encompassed these eight studies with 506,346 individuals, of whom, 100,225 were statins users. This time, reduction in the risk of colorectal cancer (RR; 0.92;95% CI, 0.90 to 0.95; random-effects model: RR0.90;95% CI,0.79 to 0.96). The corresponding 8 statistics was 18%, both indicating little variability between studies.

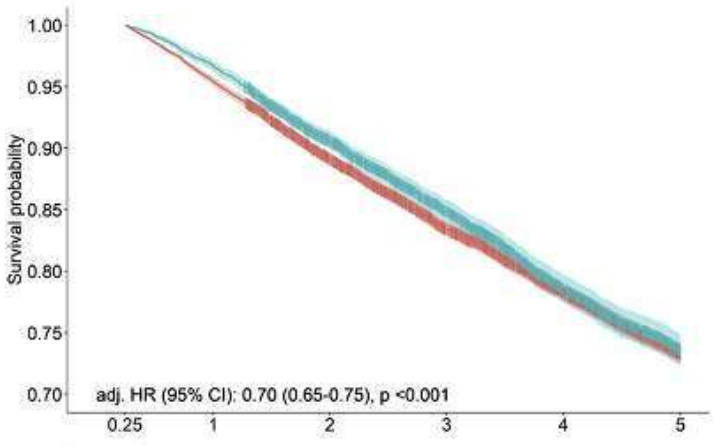

Fig 2: Kaplan- plot for all-cause mortality

The Cox regression analysis also showed that ongoing statin therapy was associated with a 20% decrease in the risk of cancer-specific mortality compared to patients without ongoing statin therapy (adjusted HR 0.75, 95% (CI 0.65-0.85, P < .002).

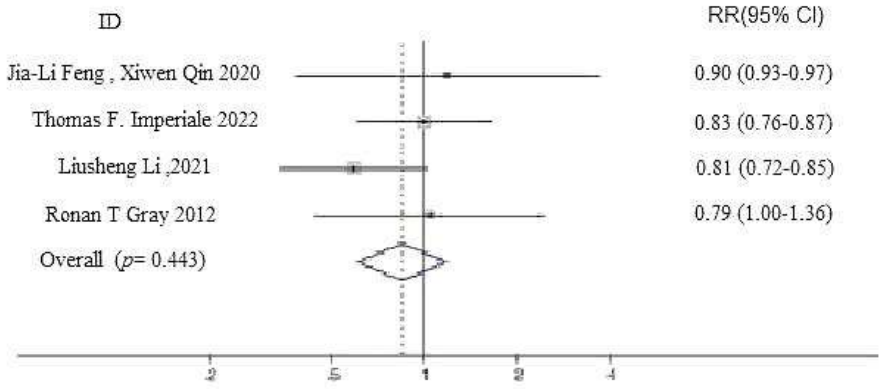

Fig 3: Group analysis of the Relative Risk (RR)

The group analysis of the association between Relative Risk (RR) and mortality of colorectal cancer (CRC) patients, the result of Relative Risk did not markedly alter.

DISCUSSION

Patients on statins had a persistent lower specific death risk for colorectal cancer, according to the study. Eight studies, published in {2021,2022}, {2016,2017,2019,2019,2020}, {retrospective case control study, cohort studies and one meta-analysis}, as shown in Table 1, were included in this analysis. A total of 506,346 people were included in these studies, of whom, 100,225 were statins users. This time, there was a decrease in the chance

of colorectal cancer (RR; 0.92; 95% CI, 0.90 to 0.95; RR0.90; 95% CI, 0.79 to 0.96 in the random-effects model). 18% was the matching 8 statistics, both of which showed minimal variation between investigations.

And Additionally, according to the Cox regression analysis, individuals receiving continuous statin medication had a 20% lower chance of dying from cancer than those not receiving it (adjusted HR 0.75, 95% CI 0.65-0.85, P <.002) fig. 2. The group analysis of the association between Relative Risk (RR) and mortality of colorectal cancer (CRC) patients, the result of Relative Risk did not markedly alter fig. 3.

Statins, which lower cholesterol by inhibiting HMG-CoA reductase, the rate-limiting enzyme of the mevalonate pathway for the de novo production of cholesterol, are widely used to lower cholesterol levels and are linked to a decline in the prevalence of cardiovascular events. Additionally, statins may have an impact on the onset and spread of cancer. It was recently shown that statins were engaged in the beginning and progression of cancer by preventing the conversion of HMG-CoA into mevalonate, to alter and activate proteins and to cause tumor-specific apoptosis.

Cohort study was done by Timothy L. Lash, etc. (in 2017). From 2001 to 2011, they monitored 21,152 patients with stage I–III colorectal cancer diagnoses. And calculated the correlation between the use of statins in the preceding year and cancer recurrence, cancer-specific mortality, and all-cause mortality rates. Statin use was not associated with a reduced rate of colorectal cancer recurrence, but it was associated with a reduced rate of cancer-specific mortality, statin use in the year preceding recurrence was associated with a reduced risk of cancer-specific mortality (A HR = 0.83, 95% CI: 0.74, 0.92). [29]

Liusheng Li et al. conducted another meta-analysis in 2021. Eleven prospective cohort studies (consisting of 40659 statin users and 344459 non-statin users) and five retrospective case-control studies (including 475 statin users and 1925 non-statin users) were included in the study. Using a random effects model, the study indicated that the usage of statins may be substantially linked with a lower overall mortality in CRC (HR = 0.81, 95% CI 0.76 to 0.86, I2 = 61.9%, p value for Q test <0.001). Furthermore, a random effects model suggested that the use of statins was protective for the prognosis of colorectal cancer (CR = 0.78, 95% CI 0.72 to 0.85, I2 = 57.3%, p value for Q test = 0.007). This suggests that statin use may be significantly related with lower cancer-specific mortality in colorectal cancer. However, the relationship between statins use and CRC prognosis requires repeated and large prospective studies to be verified [30].

A cohort study was done by Monica Parks and David Wang et al (2014). The purpose of this study was to evaluate the relationship between statins and cancer-specific and all-cause mortality in 7,657 patients newly diagnosed with stage I-III colorectal cancer were identified from the National Cancer Data Repository (NCDR), United Kingdom Clinical Practice Research Datalink (CPRD) and the Office of National Statistics (ONS). Patients were excluded for previous NCDR cancer diagnoses, stage IV disease, or if they died in the first year following diagnosis Average follow-up after diagnosis was 5 years. Compared to non-statin users, statin users had similar stage and grade of cancer but were more likely to be male, be older, to have a higher BMI, to have smoked, to have other comorbidities, and to use other medications. At the conclusion of this study, the authors found that statin use after diagnosis of colorectal cancer was associated with a 28% reduction in cancer-specific mortality in a dose-dependent relationship. Furthermore, statin use was also associated with reduced all-cause mortality [37].

Another cohort study was done by Pourlotfi, Arvid M.D et al (2021). All adult patients undergoing elective surgery for colon cancer between January 2007 and September 2016 were included in the study. Patients who had received and collected a prescription for statins pre- and postoperatively were allocated to the statin-positive cohort. A total of 22,337 patients underwent elective surgery for colon cancer during the study period, of whom 6,494 (29%) were classified as statin users. Statin users displayed a significant survival benefit despite being older, having a higher comorbidity burden, and being less fit for surgery Multivariate analysis illustrated significant reductions in the incidence risk for 90-day all-cause mortality (Incidence Rate Ratio = 0.12, $p < 0.001$) [38].

Recently, cohort study was done by Dong-sook Kim et al (2022), they compared patients aged 45–70 years' statin users for at least 6 months to non-statin users matched by age and sex. Out of 1,008,101 people, 20,473 incident cancers, 3938 cancer deaths occurred and 7669 incident cancers, 1438 cancer death in matched cohort There were associations between statin use and colorectal cancer mortality (HR 0.43, 95% CI 0.36–0.51) [39].

Meta-analysis was done by Shanliang Zhong et al (2015), Thirty-nine cohort studies and two case-control studies involving 990,649 participants were included. The results showed that patients who used statins after diagnosis had a HR of 0.81 (95% CI: 0.72–0.91) for all-cause mortality compared to non-users. Those who used statin after diagnosis (vs. non-users) had a HR of 0.77 (95% CI: 0.66–0.88) for cancer-specific mortality. Prediagnostic exposure to statin was associated with both all-cause mortality (HR = 0.79, 95% CI: 0.74–0.85) and cancer-specific mortality (HR = 0.69, 95% CI: 0.60–0.79. In conclusion, the average effect of statin use, both post diagnosis and pre diagnosis, is beneficial for overall survival and cancer-specific survival [40].

In population based cohort study was done by Michael Hoffmeister, Lina Jansen…et al (in 2015), use of statins and other risk or protective factors were assessed in standardized interviews with 2697 patients from

southern Germany with a diagnosis of incident CRC between 2003 and 2009 Follow-up included assessment of therapy details, recurrence, vital status, and cause of death. Information about Patients were age 68 years on average, 412 used statins (15%), and 769 died during follow-up (29%). After a median follow-up time of 3.4 years, use of statins was not associated with overall (HR = 1.10, 95% CI = 0.85 to 1.41), CRC-specific (HR = 1.11, 95% CI = 0.82 to 1.50) survival.

Analyses in relevant subgroups also showed no association of statin use with overall and CRC-specific survival, and no associations were observed after stratifying for major pathological subtypes. Among stage I and II patients, statin use was associated with better recurrence-free but not with better CRC-specific survival. Statin use was not associated with reduced mortality among CRC patients [41].

In another case control study was done by Fatim Lakha et al (in 2012), the Analysis was carried out on 309 cases and 294 controls from the Scottish Study of Colorectal Cancer (SOCCS) statins were found to show a statistically significant association for three of the four statin variables and were found to not show a statistically significant association with either all-cause or CRC-specific mortality (OR 0.49; 95%CI 0.49-1.36; p-value = 0.17 and OR 0.33; 95%CI 0.08-1.35; P-value = 0.12, respectively) [42].

CONCLUSION

The risk of colorectal cancer was lower in statin users versus nonusers; accumulating evidence suggests that statins may have a role in colorectal cancer prevention and treatment. Among Lipid-lowering medication (LLM) users, adherence to this drug is associated with a decrease in cancer-specific mortality. In summary, the outcomes of this meta-evaluation propose that using statin may reduce cancer-specific mortality and provide promising hope for adjuvant treatment of CRC. Further clinical studies particularly randomized control trials are required to confirm this association and clarify the mechanism by which statins interact with the cancer.

Limitations

The limitation of this study is that it only included articles published in English, this is led to the exclusion of other related studies published in other language. Moreover, some of the studies were excluded due to inadequate quality, such as those didn't compare the between statins users and non-users. Another important limitation was the inability to access the web of science database. This affected on the number of the studies included in this analysis.

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