The Anti-Inflammatory Potential of Statins in Oncology: A Focus on C-Reactive Protein (CRP), Interleukin-6 (IL-6), and Tumor Necrosis Factor-Alpha (TNF-α) Modulation

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Abstract

Statins, widely known for their cholesterol-lowering effects, have demonstrated promising therapeutic potential in modulating chronic inflammation, a pivotal contributor to cancer progression. Elevated inflammatory biomarkers, including C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) are frequently observed cancer patients and are associated with unfavorable prognoses. This narrative review synthesizes findings from 42 recent publications (2019–2024) retrieved via PubMed, Scopus, and Web of Science, focusing on statins' impact on these biomarkers in oncologic contexts. The studies encompass both preclinical and clinical investigations examining statin type, dosage, cancer subtype, biomarker modulation, and synergy with conventional therapies. Findings indicate that lipophilic statins, such as simvastatin and atorvastatin, substantially reduce IL-6 and TNF-α levels by inhabiting the mevalonate pathway and RhoA activation, thereby downregulating transcription factors such as NF-κB. These downstream effects indirectly contribute to CRP suppression. Additionally, statins have demonstrated the capacity to enhance the efficacy of chemotherapeutic agents, particularly platinum compounds, doxorubicin, and taxanes, by sensitizing tumor cell sensitivity, reducing resistance, and promoting apoptosis. Despite these encouraging outcomes, most data derive from preclinical studies and small-scale clinical trials, often lacking standardized effect size reporting and longitudinal clinical endpoints. This review concludes that statins may serve as effective adjunctive agents in oncology through their anti-inflammatory properties. However, large-scale randomized controlled trials are essential to establish their long-term clinical utility, safety profile, and optimal application in cancer treatment

Keyword: *Statins, Cancer, Inflammation, IL-6, C-reactive protein*

INTRODUCTION

Statins, formally known as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are widely prescribed as the first-line treatment for hypercholesterolemia and cardiovascular disease (CVD) due to their ability to reduce low-density lipoprotein (LDL), total cholesterol, and triglyceride levels. Beyond their lipid-lowering capacity, statins exhibit multiple pleiotropic effects, including anti-inflammatory, immunomodulatory, antithrombotic, and endothelial-stabilizing properties. These attributes have sparked growing interest in their potential utility beyond cardiovascular health, particularly in oncology (Jiang et al., 2021; Nickel et al., 2021).

Chronic inflammation is now recognized as a fundamental driver in carcinogenesis, playing a central role in tumor initiation, promotion, and progression. This connection, first noted in the 19th century, has since been substantiated by molecular evidence illustrating how persistent inflammation alters the cellular microenvironments, damages DNA, and facilitates immune evasion within tumors (Xiang et al., 2023; Zhao et al., 2021). The tumor microenvironment (TME), composed of immune cells, inflammatory mediators, and stromal components, supports tumor growth through sustained secretion of pro-inflammatory cytokines.

Among these, C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) are pivotal biomarkers of cancer-associated inflammation. Elevated levels of these markers indicate systemic inflammatory activity and are associated with poor prognosis in outcomes across various malignancies (Gallo, 2021; Hamzawy et al., 2017). Notably, IL-6 stimulates hepatic production of CRP, while TNF-α interacts with both molecules to perpetuate inflammatory signaling. These interrelated pathways form a self-sustaining inflammatory loop within the TME, that may be amenable to pharmacologic intervention (Basith et al., 2012; Z. Wang et al., 2015).

Emerging evidence suggests that statins may attenuate this inflammatory axis, positioning them as potential adjuncts in cancer therapy. Observational and experimental studies have reported reductions in IL-6 and CRP levels among statin users, though findings specific to oncologic settings remain inconclusive (Koushki et al., 2021; Murphy et al., 2020). An earlier Indonesian study highlighted CRP and other biomarkers as predictors of clinical outcomes, including COVID-19 mortality, underscoring their relevance beyond infectious disease and warranting deeper investigation in oncology.

This growing body of research signals that statin therapy may influence key inflammatory biomarkers in cancer contexts, particularly CRP, IL-6, and TNF-α. A landmark meta-analysis of randomized controlled trials across various chronic diseases confirmed that statins significantly reduce CRP, IL-6, and TNF-α—with atorvastatin showing robust effects on IL-6 and TNF-α, and fluvastatin on CRP (Sabeel et al., 2025). A focused meta-analysis in breast cancer patients found that use of lipophilic statins was associated with a 19 % reduction in both breast cancer–specific mortality and recurrence risk (Scott et al., 2025). Mechanistic insights from a Nature Communications–published experiment demonstrated that pitavastatin suppressed the TBK1–IRF3–IL-33 axis in models of chronic pancreatitis, effectively preventing inflammation-driven pancreatic cancer and reducing cancer risk in human (Park et al., 2024). Lastly, epidemiological data from ulcerative colitis patients reported that long-term

statin users exhibited lower incidence and mortality of colorectal cancer—suggesting inflammation-driven protective effects in IBD-associated malignancies (Bugos, 2023)

While the anti-inflammatory mechanisms of statins are well-documented in cardiovascular disease, their effects within the cancer setting remain less defined. The current literature lacks a focused synthesis examining the modulation of CRP, IL-6, and TNF-α in oncology, particularly in relation to the tumor-promoting role of chronic inflammation. This narrative review addresses this gap critically evaluating statins' impact on cancer-related inflammation, with particular emphasis on these key biomarkers. Understanding these interactions may inform the potential role as statins in integrative cancer management.

METHODS

This review applied a narrative approach to synthesize and critically evaluate the most recent evidence on the anti-inflammatory effects of statins in oncology, with specific focus on their modulation of C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). Literature was retrieved from PubMed and ScienceDirect databases, which were selected due to their extensive indexing of biomedical, pharmacological, and oncology-related research. Studies published between January 2002 and May 2024 were considered, with a primary emphasis on research published after 2019. The search strategy included Boolean combinations of keywords such as "statins," "cancer," "inflammation," "C-reactive protein," "IL-6," "TNF-α," and "tumor microenvironment," with field tags [Title/Abstract] and [MeSH Terms] used in PubMed. Filters applied included English language, human studies, and article types limited to original research and meta-analyses.

Studies were selected through a two-step screening process: initial review of titles and abstracts, followed by full-text evaluation. Of the 376 articles initially retrieved, 284 were screened after duplicates were removed, and 42 met the final inclusion criteria. Eligible studies were required to report original data on the impact of statin therapy on inflammatory biomarkers in cancer-related contexts. Articles focusing exclusively on cardiovascular conditions or lacking biomarker outcomes were excluded. The selected studies were then categorized by design: in vitro studies examining statin effects on cancer cell lines, in vivo studies using animal cancer models, and clinical studies evaluating statins in cancer patients. From each included study, key data were extracted, including cancer type, statin type and dose, duration of treatment, outcome measures related to CRP, IL-6, or TNF-α, and overall relevance to inflammation modulation. While this review does not perform quantitative synthesis, findings were integrated to capture overarching trends in statins' anti-inflammatory activity,

and limitations inherent in narrative methods—including potential selection bias and heterogeneity are acknowledged.

RESULTS

Statins and Their Effects on Key Inflammatory Biomarkers in Cancer

This review included 42 studies comprising 15 in vitro experiments, 11 in vivo investigations, and 16 clinical trials evaluating the impact of statins on inflammatory biomarkers within cancer contexts.

C-Reactive Protein (CRP)

Numerous studies demonstrate that statin therapy can reduce CRP levels by 20% to 60%, with notable reductions evident within two weeks of initiating simvastatin or atorvastatin. A meta-analysis of 29 randomized controlled trials (RCTs) revealed that statins significantly lowered both CRP and hs-CRP levels compared to placebo (He et al., 2023). These effects were consistent across various statin types, though lipophilic statins such as atorvastatin appeared more effective in reducing CRP levels. Some studies also observed dose-dependent effects, with higher statin doses associated with greater CRP reductions.

Interleukin-6 (IL-6)

As a central cytokine in tumor-related inflammation, IL-6 was consistently reduced in both preclinical and clinical settings following statin administration. A pooled analysis of 14 RCTs reported modest but statistically significant decreases in IL-6 levels with statin therapy. In vitro studies further showed that fluvastatin and simvastatin could reduce IL-6 mRNA expression by over 50%, particularly in lipopolysaccharide-stimulated cell lines. These effects were sensitive to both dosage and duration of therapy.

Tumor Necrosis Factor-Alpha (TNF-α)

Statins were also found to downregulate TNF-α, with consistent findings across preclinical and limited clinical studies. A meta-analysis of 10 RCTs demonstrated a significant reduction in TNF-α following statin treatment. Mechanistic studies suggested that statins inhibit NF-κB activation, which modulates TNF-α expression and its downstream pro-angiogenic and pro-invasive effects in the tumor microenvironment.

DISCUSSION

Mechanistic Insights and Statin–Biomarker Interactions

Statins reduce C-reactive protein (CRP) levels primarily by suppressing interleukin-6 (IL-6)-mediated hepatic synthesis and enhancing endothelial integrity through increased nitric oxide bioavailability and reduced oxidative stress. The reduction in IL-6 itself occurs via inhibition of the mevalonate pathway, specifically through the blockade of RhoA and Rac1 GTPase activation, both essential for the nuclear translocation of transcription factors such as NF-κB and AP-1 (Y. Wang, 2019; Zubor et al., 2020). These transcription factors directly regulate IL-6 and TNF-α, positioning statins upstream within the inflammatory cascade.

Regarding TNF-α, statins inhibit its expression by attenuating TLR4 signaling and downstream activation of IKKβ–NF-κB, which in turn suppresses pro-inflammatory cytokine release and angiogenesis, particularly in tumors with robust VEGFR signaling (Rajasegaran et al., 2023; Yu et al., 2024). The interconnected nature of these pathways underscores the pleiotropic capacity of statins, suggesting their role extends beyond targeting individual cytokine.

Lipophilic statins, such as simvastatin and atorvastatin, exhibit stronger anti-inflammatory effects than hydrophilic counterparts like pravastatin. This distinction is attributed to higher lipid solubility, which facilitates enhanced cellular uptake, especially within tumor cells and immune compartments (Althanoon et al., 2020). Notably, the degree of biomarker suppression appears to vary across cancer types. For instance, substantial reductions in IL-6 and CRP have been reported in breast and colorectal cancer models (Maryam et al., 2023), whereas findings in hematologic malignancies remains inconsistent—potentially due to differences in tumor metabolism, microenvironmental hypoxia, and statin pharmacokinetics (Zhu et al., 2021).

These mechanistic insights support the conceptualization of statins as pleiotropic agents targeting inflammatory pathways implicated in cancer progression. Their utility may be maximized in cancers with strong inflammatory signatures or VEGF-driven angiogenesis. Most mechanistic evidence is derived from preclinical models; translational applicability is uncertain. Furthermore, differences in dosing, statin type, and biomarker measurement limit comparability across studies. Future studies should investigate statin–biomarker interactions longitudinally in humans, stratify findings by statin class and cancer type, and incorporate molecular pathway validation techniques, such as transcriptomic or proteomic approaches.

Synergistic Effects with Standard Cancer Therapies

The anti-cancer potential of statins is further reinforced by their synergistic interactions with conventional therapies. Statins have been shown to enhance tumor cell sensitivity to chemotherapeutic agents such as cisplatin, paclitaxel, and doxorubicin, partly through inhibition of MDR1 efflux pumps and induction of apoptotic signaling pathways (Emran et al., 2022; Pun et al., 2021).

In preclinical models, co-administration of statins with radiotherapy has led to increased tumor regression, largely attributed to the downregulation in hypoxia-inducible factor-1α (HIF-1α) and improved vascular perfusion (Wadhwa et al., 2022). Additionally, statins may potentiate immunotherapy efficacy by enhancing T-cell infiltration, reducing myeloid-derived suppressor cells (MDSCs), and modulating PD-L1 expression, though robust clinical data in this domain remain limited (Obeagu, 2025).

Collectively, these findings highlight the promise of statins as low-cost, widely accessible adjuncts capable of augmenting both chemotherapeutic and immunotherapeutic responses, particularly in tumors characterized by high inflammatory or immune-suppressive burden. These synergistic interactions suggest statins could serve as low-cost adjuvants to improve the efficacy of existing cancer therapies, particularly in resistant tumors or in patients who are suboptimal responders to standard regimens. Synergistic effects are mostly demonstrated in preclinical settings. Clinical evidence remains fragmentary, and trials often lack appropriate immunological or molecular endpoints to measure these effects. Conduct well-designed RCTs testing statins in combination with specific chemotherapeutic or immunotherapeutic agents, ideally with mechanistic correlative studies. Subgroup analyses by cancer site, inflammatory profile, and immune status are also warranted.

Clinical and Research Implications

Despite accumulating evidence, translation into clinical practice remains tentative due to the limited number of large-scale randomized controlled trials (RCTs). While many studies report statistically significant reductions in inflammatory biomarkers, their clinical relevance, particularly regarding progression-free survival (PFS) or overall survival (OS)—remains underexplored. Effect sizes, confidence intervals, and study heterogeneity are rarely reported, limiting meta-analytic synthesis and generalizability (Möller et al., 2024).

Additional confounding factors, including baseline lipid levels, metabolic comorbidities, and polypharmacy, are frequently overlooked. Patient variability in statin metabolism (e.g., CYP3A4 variants), as well as drug–drug interactions with anticancer regimens, may also influence treatment response.

Although statins are safe, inexpensive, and widely accessible, their application in oncology must be both evidence-based and patient-specific. They may offer the greatest value in inflammation-driven malignancies or among elderly patients with multimorbidity. However, current clinical trials are underpowered, short-term, and rarely report progression-free survival (PFS) or overall survival (OS) as primary endpoints. Publication bias and lack of transparency in trial protocols (e.g., unpublished negative results) may skew perception of efficacy.

CONCLUSIONS

This narrative review highlights the potential of statins to reduce cancer-associated inflammation specifically by lowering CRP, IL-6 and TNF-α levels. Available evidence also suggests that statins exert synergistic effects with existing cancer therapies. Nonetheless, statins are not currently recommended to be used as a treatment for cancer prevention due to the lack of high-quality human clinical trials. However, this opens the possibility of more clinical trials and studies to be conducted to explore new paths for cancer treatment and confirm statins' benefits in this context.

Future research should prioritize rigorously designed, large-scale clinical trials to elucidate statins' mechanisms in oncology, with particular emphasis on long-term outcomes and optimal dosing strategies. Moreover, stratifying patients by cancer type, stage, and molecular profile may offer deeper insights into their therapeutic potential.

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