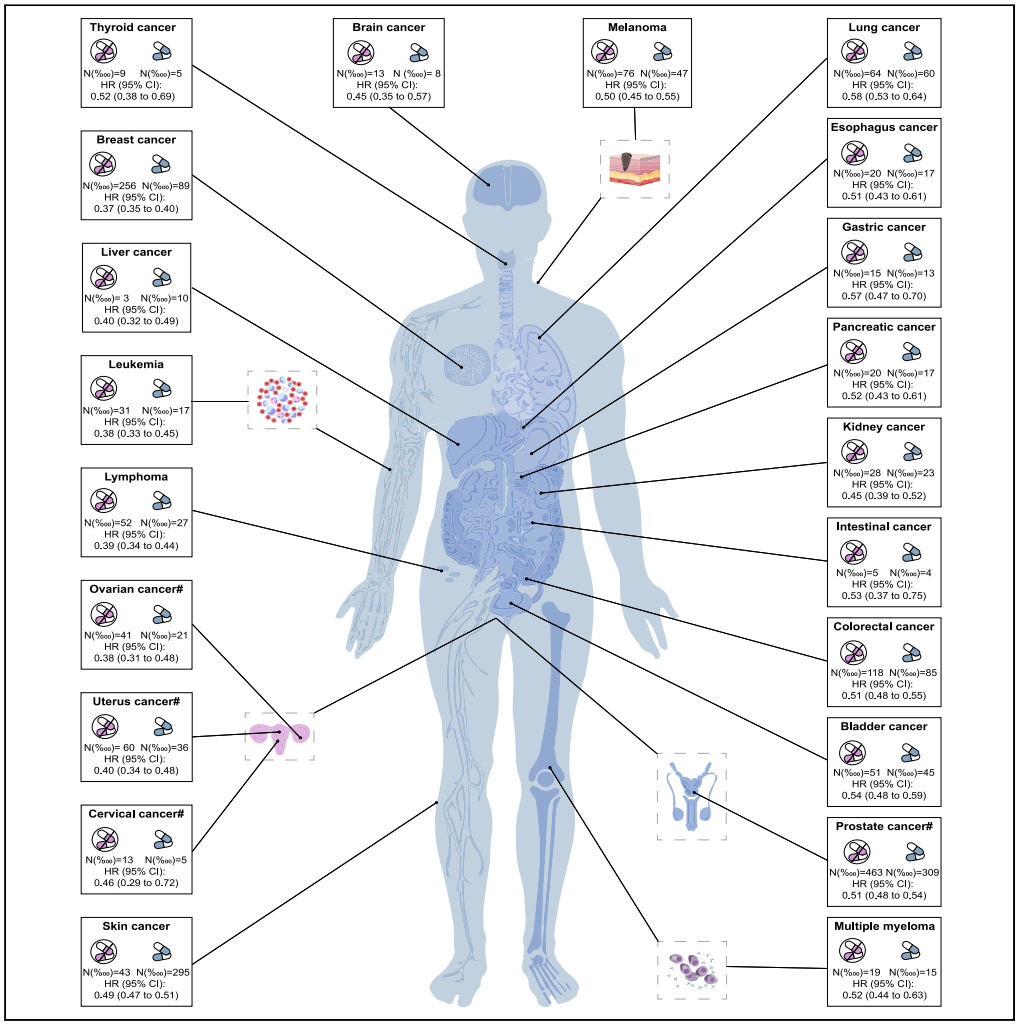
iScience

CellPress
OPEN ACCESS

Article

Longitudinal cohort study highlights cancer-preventive benefits of lipid-lowering drugs



Zinuo Yuan, Chunhui Ding, Jingjing Duan, ..., Yongfeng Song, Jiajun Zhao, Xiude Fan

syf198506@163.com (Y.S.)
jjzhao@sdu.edu.cn (J.Z.)
fanxiudexjtu@163.com (X.F.)

Highlights

Identification of association for lipid-lowering drugs in 21 kinds of cancers

Enhancement of current research on anticancer efficiency of lipid-lowering drugs

Insights into promising drugs for cancer prevention

Yuan et al., iScience 27, 110680
September 20, 2024
https://doi.org/10.1016/j.isci.2024.110680

iScience

CellPress
OPEN ACCESS

Article

Longitudinal cohort study highlights cancer-preventive benefits of lipid-lowering drugs

Zinuo Yuan,[1,2,3,4,5,6,7] Chunhui Ding,[1,2,3,4,5,6,7] Jingjing Duan,[1,2,3,4,5,6,7] Ruonan Lian,[2,3,4,5,6,7] Yingzhou Shi,[1,2,3,4,5,6,7] Junming Han,[2,3,4,5,6,7] Hang Dong,[1,2,3,4,5,6,7] Yongfeng Song,[1,2,3,4,5,6,7,*] Jiajun Zhao,[1,2,3,4,5,6,7,*] and Xiude Fan[2,3,4,5,6,7,8,*]

SUMMARY

Cancer prevention is a serious global challenge. We aimed to investigate the relationship between lipid-lowering drugs and cancers. We included participants based on the UK Biobank. Lipid-lowering drug use was defined as new users before enrollment and the primary outcome was cancer incidence. The Cox proportional hazards regression model was used to evaluate the association between drug use and outcome. We also performed a meta-analysis. We found that lipid-lowering drugs were associated with decreased risk of 21 types of cancers, including melanoma, skin cancer, and reproductive, hematological, urinary, digestive, nervous, and endocrine system cancers (all $p < 0.0010$). Our meta-analysis documented that lipid-lowering drugs reduced the risk of prostate, liver, and gastric cancers, especially (all $p < 0.050$). Overall, lipid-lowering drugs had protective associations with cancer incidence, suggesting the possible cancer prevention effects even in the general population.

INTRODUCTION

Cancer remains a prominent global health concern, with a rising incidence rate projected to reach 28.4 million new cases worldwide by 2040, marking a substantial 47% increase from 2020.[1] Addressing cancer prevention has posed a significant challenge on a global scale. In recent decades, scientists have conducted extensive and relentless research on various drugs that could potentially be utilized for cancer prevention. For example, antiviral drugs and anti-estrogen drugs such as Tamoxifen and Raloxifene have exhibited promising results in preventing specific cancer types.[2,3] Aspirin and metformin have been investigated for their potential to reduce the risk of colorectal and lung cancer.[4,5] Furthermore, the role of antioxidants in lowering cancer susceptibility has been elucidated through numerous preclinical and clinical studies.[6,7] Despite these advancements, current drug interventions still face significant challenges, with the actual impact on cancer prevention falling short of the ideal. Therefore, it is crucial to explore innovative and more effective strategies in cancer prevention.

Hyperlipidemia may impact cell growth and differentiation by promoting chronic inflammatory and oxidative stress, creating an environment conducive to cancer development.[8] As one of the most widely prescribed drugs globally, lipid-lowering drugs targeting blood lipids may help reduce cancer risk. Apart from their acknowledged therapeutic value in lowering blood lipids, lipid-lowering drugs may also contribute to anti-cancer processes through pleiotropic mechanisms.[9–11] Some preclinical studies have suggested that lipid-lowering drugs could inhibit cancer by modulating cell signaling pathways, reducing chronic inflammation, mitigating oxidative stress, and inducing pro-apoptosis.[12–14] Consequently, lipid-lowering drugs have attracted significant attention as potential strategies for combating cancer.

Emerging evidence suggests that the use of lipid-lowering drugs may reduce the risk of specific cancers, such as gastric, liver, and uterine cancers.[11,15] A study by Carter et al. using the Mendelian randomization method also concluded that statins decrease cancer risk.[16] Nevertheless, certain studies suggested that statins have no effect on the risk of particular site-specific cancers.[17–19] Additionally, even investigations in rodents have indicated that exposure to lipid-lowering drugs at doses similar to those used in humans can increase the risk of cancer.[20] Most previously published studies have mainly focused on the effects of statins, and the results have been controversial when evaluating the risk of

[1]Department of Endocrinology, Shandong Provincial Hospital, Shandong University, Jinan, Shandong 250021, China
[2]Key Laboratory of Endocrine Glucose & Lipids Metabolism and Brain Aging, Ministry of Education; Department of Endocrinology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong 250021, China
[3]Shandong Clinical Research Center of Diabetes and Metabolic Diseases, Jinan, Shandong 250021, China
[4]Shandong Institute of Endocrine and Metabolic Diseases, Jinan, Shandong 250021, China
[5]"Chuangxin China" Innovation Base of Stem Cell and Gene Therapy for Endocrine Metabolic Diseases, Jinan, Shandong 250021, China
[6]Shandong Engineering Laboratory of Prevention and Control for Endocrine and Metabolic Diseases, Jinan, Shandong 250021, China
[7]Shandong Engineering Research Center of Stem Cell and Gene Therapy for Endocrine and Metabolic Diseases, Jinan, Shandong 250021, China
[8]Lead contact
*Correspondence: syf198506@163.com (Y.S.), jjzhao@sdu.edu.cn (J.Z.), fanxiudexjtu@163.com (X.F.)
https://doi.org/10.1016/j.isci.2024.110680

different cancer types. The role of lipid-lowering drugs in cancer remains inconclusive, and the potential impact of these drugs on cancer prevention still cannot be adequately explained. Given the pleiotropic effects of lipid-lowering drugs, not only for patients with dyslipidemia, a comprehensive study of their cancer prevention effects in the general population will offer important insights for the development of more effective cancer prevention strategies in the future.

In this context, a comprehensive retrospective cohort was utilized to explore the efficacy of lipid-lowering medications in cancer prevention at 21 different locations. Additionally, a meta-analysis was performed to synthesize and enhance the current body of research on this topic for future scholarly inquiry.

RESULTS

Characteristics of the study population

Details of the characteristics of the study population were summarized in Table 1. A total of 383,784 participants were identified from the UK Biobank with 114,451 (29.8%) categorized as new users and most of them were white. Among new users, the mean age was 72.97 $\pm$ 6.42 years which was significantly higher than non-users ($p < 0.0010$) and 59,385 (51.9%) were males. While the majority of non-users were female. Compared to non-users, new users had higher levels of glucose (5.24 vs. 5.01), cholesterol (5.95 vs. 5.67), triglyceride (2.00 vs. 1.60), and low-density lipoprotein cholesterol (LDL-C) (3.77 vs. 3.53) (all $p < 0.0010$). Similarly, as for anthropometry, new users had higher body mass index (BMI) (28.29 vs. 26.82), waist circumference (WC) (93.53 vs. 88.16), hip circumference (HC) (104.43 vs. 102.74), and blood pressure (BP) (systolic BP: 144.63 vs. 136.79; diastolic BP: 84.07 vs. 81.25) (all $p < 0.0010$). The new user group also had a higher prevalence of overweight (44.9% vs. 41.4%) and obesity (30.0% vs. 20.2%) compared to non-users ($p < 0.0010$). Participants using lipid-lowering drugs were more likely to be smokers (previous: 38.5% vs. 31.9% and current: 11.7% vs. 9.3%) and drinkers (previous: 3.8% vs. 3.2%) (all $p < 0.0010$) (Table 1).

Association of lipid-lowering drugs and risk of cancers in patients with hyperlipidemia

We observed that participants with hyperlipidemia were more likely to have melanoma, pancreatic, colorectal, gastric, liver, skin, kidney, cervical, uterus, and ovarian cancer on baseline (all $p < 0.050$) (Figure S1). Subsequently, during the follow-up period, we found that new users had a lower risk of leukemia, lymphoma, multiple myeloma, melanoma, prostate, ovarian, uterus, cervical, breast, lung, live, esophagus, gastric, intestinal, colorectal, skin, bladder, kidney, thyroid, pancreatic, and brain cancer in patients with hyperlipidemia (all $p < 0.050$) (Figure 1A).

Association of lipid-lowering drugs and risk of cancers in general participants

We found that new users had a lower risk of leukemia, lymphoma, multiple myeloma, melanoma, breast, liver, esophagus, colorectal, skin, bladder, kidney, thyroid, pancreatic, and brain cancer (all $p < 0.0010$) with a median follow-up period of 12.8 years. However, there was no statistically significant association between lipid-lowering drug use and the risk of lung (HR 0.94, 95% CI 0.86–1.03, $p = 0.169$), gastric (HR 0.88, 95% CI 0.73–1.07, $p = 0.195$), and intestinal cancer (HR 0.81, 95% CI 0.58–1.14, $p = 0.23$) before adjustment (Table S1). After adjusting for potential confounders, new users had 0.58-fold, 0.57-fold, and 0.53-fold (all $p < 0.0010$) lower risk of lung, gastric and intestinal cancer. Notably, for sex-specific cancers, compared with non-users, new users had a 49% lower risk of prostate cancer in males after adjustment ($p < 0.0010$). Lipid-lowering drug use was associated with 61% ($p < 0.0010$), 59% ($p < 0.0010$), and 54% ($p = 0.0010$) lower risk of ovarian, uterus, and cervical cancers in females, respectively. When focusing on the classification of some cancers, we found that lipid-lowering drug use was associated with a lower risk of both myeloid (HR 0.35, 95% CI 0.27–0.47) and lymphoid leukemia (HR 0.37, 95% CI 0.30–0.46), both Hodgkin (HR 0.41, 95% CI 0.28–0.62) and NHL (HR 0.39, 95% CI 0.34–0.44) (all $p < 0.0010$) (Figure 1B). Lower risks of prostate, ovarian, uterus, cervical, breast, intestinal, and colorectal cancer persisted even after adjusting for cancer-specific covariates (all $p < 0.050$) (Figure S2).

Subgroup and sensitivity analysis of the main study

In females, using lipid-lowering drugs was associated with decreased risk of leukemia, lymphoma, multiple myeloma, lung, liver, esophagus, intestinal, colorectal, skin, bladder, kidney, thyroid, pancreatic, and brain cancer (all $p < 0.050$). Similar results were observed in males except for intestinal cancer (HR 0.63, 95% CI 0.40–1.00, $p = 0.052$). Interestingly, the effect of lipid-lowering drugs on melanoma risk seemed greater in females than males (Figure 2A). Short-term use of lipid-lowering drugs reduced the risk of all cancers we studied. Furthermore, long-term use was associated with the risk of cancers, except for intestinal (HR 0.61, 95% CI 0.37–1.00, $p = 0.050$) and thyroid cancer (HR 0.80, 95% CI 0.55–1.18, $p = 0.27$). Long-term use of lipid-lowering drugs decreased the risk of prostate, uterus, breast, colorectal, skin, bladder, and kidney cancer greater than short-term use (all $p < 0.050$) (Figure 2B). For intestinal cancer, lipid-lowering drug use was associated with a lower cancer risk in patients with normal BMI and overweight. However, only new users with overweight and obese had decreased gastric cancer compared to non-users (Figure 2C). Similar results were observed when redefining the new users as participants with more than one prescription or when comparing statins users and non-statin users (all $p < 0.050$) (Figure 3). Notably, there was no significant difference between fibrate users and non-fibrate users in males (Table S2). Interestingly, compared with non-users, using lipid-lowering drugs decreased the mortality of overall cancer in total patients (HR 0.25, 95% CI 0.23–0.27, $p < 0.0010$) (Figure S3).

Association of lipid-lowering drugs and mortality of overall cancer

Interestingly, compared with non-users, using lipid-lowering drugs decreased the mortality of overall cancer in total patients (HR 0.25, 95% CI 0.23–0.27, $p < 0.0010$). Similar results were observed in subgroup and sensitivity analysis (Figure S3). We found that compared with non-users,

Table 1. Descriptive characteristics of participants in UK Biobank by lipid-lowering drug use

	Non-users (n = 269333)	New users (n = 114451)	*p-value*
Age, years, mean±SD	68.58 (8.22)	72.97 (6.92)	<0.0010
Comorbidity index, mean±SD	0.09 (0.37)	0.16 (0.52)	<0.0010
Blood examination			
Glucose, mmol/L, mean ± SD	5.01 (0.94)	5.24 (1.40)	<0.0010
Cholesterol, mmol/L, mean ± SD	5.67 (1.05)	5.95 (1.24)	<0.0010
Triglyceride, mmol/L, mean ± SD	1.60 (0.92)	2.00 (1.13)	<0.0010
LDL-C, mmol/L, mean ± SD	3.53 (0.80)	3.77 (0.94)	<0.0010
Anthropometry			
BMI, kg/cm^2, mean ± SD	26.82 (4.62)	28.29 (4.80)	<0.0010
WC, cm, mean ± SD	88.16 (13.03)	93.53 (13.10)	<0.0010
HC, cm, mean ± SD	102.74 (9.00)	104.43 (9.30)	<0.0010
SBP, mmHg, mean ± SD	136.79 (19.51)	144.63 (19.99)	<0.0010
DBP, mmHg, mean ± SD	81.25 (10.79)	84.07 (10.97)	<0.0010
Sex			<0.0010
Female, n (%)	159120 (59.1)	55066 (48.1)	
Male, n (%)	110213 (40.9)	59385 (51.9)	
Race			<0.0010
White, n (%)	253800 (94.2)	106918 (93.4)	
Mixed, n (%)	1838 (0.7)	545 (0.5)	
Asian or Asian British, n (%)	4403 (1.6)	3285 (2.9)	
Black or Black British, n (%)	4841 (1.8)	1913 (1.7)	
Chinese, n (%)	981 (0.4)	270 (0.2)	
Other ethnic groups, n (%)	2464 (0.9)	1085 (0.9)	
Do not know or not answer, n (%)	1006 (0.4)	435 (0.4)	
BMI			<0.0010
BMI<18.5, n (%)	1729 (0.6)	320 (0.3)	
18.5≤BMI<25, n (%)	101691 (37.8)	28407 (24.8)	
25≤BMI<30, n (%)	111436 (41.4)	51393 (44.9)	
BMI≥30, n (%)	54477 (20.2)	34331 (30.0)	
Smoking			<0.0010
Never, n (%)	157415 (58.4)	56516 (49.4)	
Previous, n (%)	85991 (31.9)	44076 (38.5)	
Current, n (%)	24979 (9.3)	13336 (11.7)	
Prefer not to answer, n (%)	948 (0.4)	523 (0.5)	
Drinking			<0.0010
Never, n (%)	10906 (4.0)	5703 (5.0)	
Previous, n (%)	8602 (3.2)	4331 (3.8)	
Current, n (%)	249472 (92.6)	104230 (91.1)	
Prefer not to answer, n (%)	353 (0.1)	187 (0.2)	

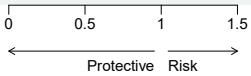
SD: standard deviation; LDL-C: low-density lipoprotein cholesterol; WC: waist circumference; HC: hip circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index.

using lipid-lowering drugs decreased the mortality of overall cancer in females (HR 0.23, 95% CI 0.20–0.26) and males (HR 0.26, 95% CI 0.23–0.28) (all $p < 0.0010$). In addition, the use of lipid-lowering drugs reduced the risk of cancer death regardless of the duration of medication, patients' BMI, and infection of coronavirus disease 2019 (COVID-19) (all $p < 0.0010$). Even there were similar results when redefining the new users as participants with more than one prescription or comparing statins users and non-statin users (all $p < 0.050$) (Figure S3).

A

Cancers	Non−users (N)	Non−users(Incidence)	New users (N)	New users(Incidence)	HR (95% CI)	P−value
Prostate cancer#	64925	2975 (458)	40419	1237 (306)	0.51 (0.48 to 0.55)	<0.001
Ovarian cancer#	80899	368 (45)	36457	79 (22)	0.40 (0.31 to 0.52)	<0.001
Uterus cancer#	81726	557 (68)	36506	144 (39)	0.42 (0.35 to 0.51)	<0.001
Cervical cancer#	81562	90 (11)	36580	18 (5)	0.51 (0.30 to 0.87)	0.013
Breast cancer	150993	3915 (259)	80733	757 (94)	0.37 (0.34 to 0.40)	<0.001
Lung cancer	153263	1039 (68)	82864	470 (57)	0.55 (0.49 to 0.62)	<0.001
Liver cancer	153318	215 (14)	83026	76 (9)	0.39 (0.30 to 0.51)	<0.001
Esophagus cancer	153283	350 (23)	82976	134 (16)	0.46 (0.37 to 0.56)	<0.001
Gastric cancer	153300	248 (16)	82981	108 (13)	0.57 (0.45 to 0.72)	<0.001
Intestinal cancer	153307	73 (5)	83007	37 (4)	0.62 (0.41 to 0.94)	0.026
Colorectal cancer	152754	1952 (128)	82171	728 (89)	0.53 (0.49 to 0.58)	<0.001
Leukemia	153195	465 (30)	82849	137 (17)	0.39 (0.32 to 0.47)	<0.001
Myeloid leukemia	153263	168 (11)	82984	52 (6)	0.42 (0.30 to 0.58)	<0.001
Lymphoid leukemia	153253	275 (18)	82899	73 (9)	0.35 (0.26 to 0.45)	<0.001
Lymphoma	153053	812 (53)	82686	221 (27)	0.38 (0.33 to 0.45)	<0.001
Hodgkin lymphoma	153281	73 (5)	82991	21 (3)	0.41 (0.25 to 0.68)	0.001
Non−hodgkin lymphoma	153084	773 (50)	82712	207 (25)	0.38 (0.32 to 0.44)	<0.001
Multiple myeloma	153274	301 (20)	82957	117 (14)	0.50 (0.40 to 0.62)	<0.001
Skin cancer	151402	6910 (456)	79486	2376 (299)	0.51 (0.48 to 0.53)	<0.001
Melanoma	152882	1179 (77)	82360	391 (47)	0.51 (0.45 to 0.57)	<0.001
Bladder cancer	153088	836 (55)	82489	372 (45)	0.52 (0.46 to 0.59)	<0.001
Kidney cancer	153228	463 (30)	82812	193 (23)	0.47 (0.39 to 0.56)	<0.001
Thyroid cancer	153255	148 (10)	82967	49 (6)	0.54 (0.39 to 0.76)	<0.001
Pancreatic cancer	153315	374 (24)	83014	130 (16)	0.44 (0.36 to 0.55)	<0.001
Brain cancer	153297	236 (15)	83010	63 (8)	0.41 (0.31 to 0.55)	<0.001

Hyperlipidemia



B

Cancers	Non−users (N)	Non−users (Incidence)	New users (N)	New users (Incidence)	HR (95% CI)	P−value
Prostate cancer#	109099	5003 (459)	57001	1779 (312)	0.51 (0.48 to 0.54)	<0.001
Ovarian cancer#	148263	608 (41)	49020	100 (21)	0.38 (0.31 to 0.48)	<0.001
Uterus cancer#	149737	900 (60)	49011	180 (37)	0.40 (0.34 to 0.48)	<0.001
Cervical cancer#	149363	192 (13)	49121	24 (5)	0.46 (0.29 to 0.72)	0.001
Breast cancer	264880	6803 (257)	111185	1006 (90)	0.37 (0.35 to 0.40)	<0.001
Lung cancer	268796	1691 (63)	114157	687 (60)	0.58 (0.53 to 0.64)	<0.001
Liver cancer	268883	359 (13)	114386	110 (10)	0.40 (0.32 to 0.49)	<0.001
Esophagus cancer	268828	527 (20)	114315	191 (17)	0.51 (0.43 to 0.61)	<0.001
Gastric cancer	268842	393 (15)	114328	150 (13)	0.57 (0.47 to 0.70)	<0.001
Intestinal cancer	268877	128 (5)	114364	45 (4)	0.53 (0.37 to 0.75)	<0.001
Colorectal cancer	268000	3142 (117)	113225	976 (86)	0.51 (0.48 to 0.55)	<0.001
Leukemia	268687	810 (30)	114134	201 (18)	0.38 (0.33 to 0.45)	<0.001
Myeloid leukemia	268796	300 (11)	114326	67 (6)	0.35 (0.27 to 0.47)	<0.001
Lymphoid leukemia	268795	485 (18)	114212	118 (10)	0.37 (0.30 to 0.46)	<0.001
Lymphoma	268434	1379 (51)	113880	313 (27)	0.39 (0.34 to 0.44)	<0.001
Hodgkin lymphoma	268831	136 (5)	114337	33 (3)	0.41 (0.28 to 0.61)	<0.001
Non−hodgkin lymphoma	268486	1302 (48)	113916	296 (26)	0.39 (0.34 to 0.44)	<0.001
Multiple myeloma	268824	524 (19)	114278	174 (15)	0.52 (0.44 to 0.63)	<0.001
Skin cancer	26561	11506 (433)	109379	3233 (296)	0.49 (0.47 to 0.51)	<0.001
Melanoma	268200	2034 (76)	113500	532 (47)	0.50 (0.45 to 0.55)	<0.001
Bladder cancer	268497	1337 (50)	113627	525 (46)	0.54 (0.48 to 0.59)	<0.001
Kidney cancer	268760	747 (28)	114091	258 (23)	0.45 (0.39 to 0.52)	<0.001
Thyroid cancer	268777	251 (9)	114304	61 (5)	0.52 (0.38 to 0.69)	<0.001
Pancreatic cancer	268879	545 (20)	114373	190 (17)	0.52 (0.43 to 0.61)	<0.001
Brain cancer	268862	360 (13)	114371	86 (8)	0.45 (0.35 to 0.57)	<0.001

General participants

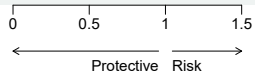


Figure 1. Association between lipid-lowering drugs and cancer risk

(A) In total follow participants.

(B) In participants with hyperlipidemia. Incidence: number of cancer occurrences per 10000 patients. #: Only in females or males. HR: hazard ratio; CI: confidence interval. Adjusted for age, sex, BMI, race, smoking status, drinking status, comorbidity index, and other drugs.

Meta-analysis of the association of lipid-lowering drugs and the risk of cancers

The meta-analysis on cancer incidence included 39 publications with varying numbers of studies focusing on different types of cancer (prostate:13, breast:11, colorectal:9, pancreas:6; liver:4, lung:4, gastric:4, ovarian:4, melanoma:3, bladder:2, kidney:2, uterus:2, NHL:2). The included studies were from 9 countries in the US, Korea, French, Japan, the UK, China, Israel, Finnish, and Canada. Our study results were also included in the analyses. Based on the Newcastle-Ottawa Scale (NOS), 35 studies received scores ≥7, indicating a low risk of bias (Table S2). Notably, we observed lower incidence of the prostate (HR 0.85, 95% CI 0.73–0.97, n = 13, p = 0.020), liver (HR 0.58, 95% CI 0.48–0.70, n = 4, p < 0.0010), and gastric (HR 0.64, 95% CI 0.45–0.90, n = 4, p = 0.010) cancer when using lipid-lowering drugs. Conversely, there was no statistically significant association in breast, colorectal, pancreatic, lung, kidney, bladder, NHL, uterus, ovarian cancer, and melanoma (all p > 0.050) (Figure 4). Considerable inter-study heterogeneity was noted, with no significant publication bias in Egger's test or funnel plots (Figure S4; Table S3). Sensitivity analysis confirmed the stability of the results for prostate, liver, and gastric cancer (Figure S5).

DISCUSSION

In summary, this study was a comprehensive and prospective study to evaluate the effect of lipid-lowering drugs on a total of 21 kinds of cancers with a large sample size. Based on UK Biobank, we observed that the use of lipid-lowering drugs, particularly statins, was associated with

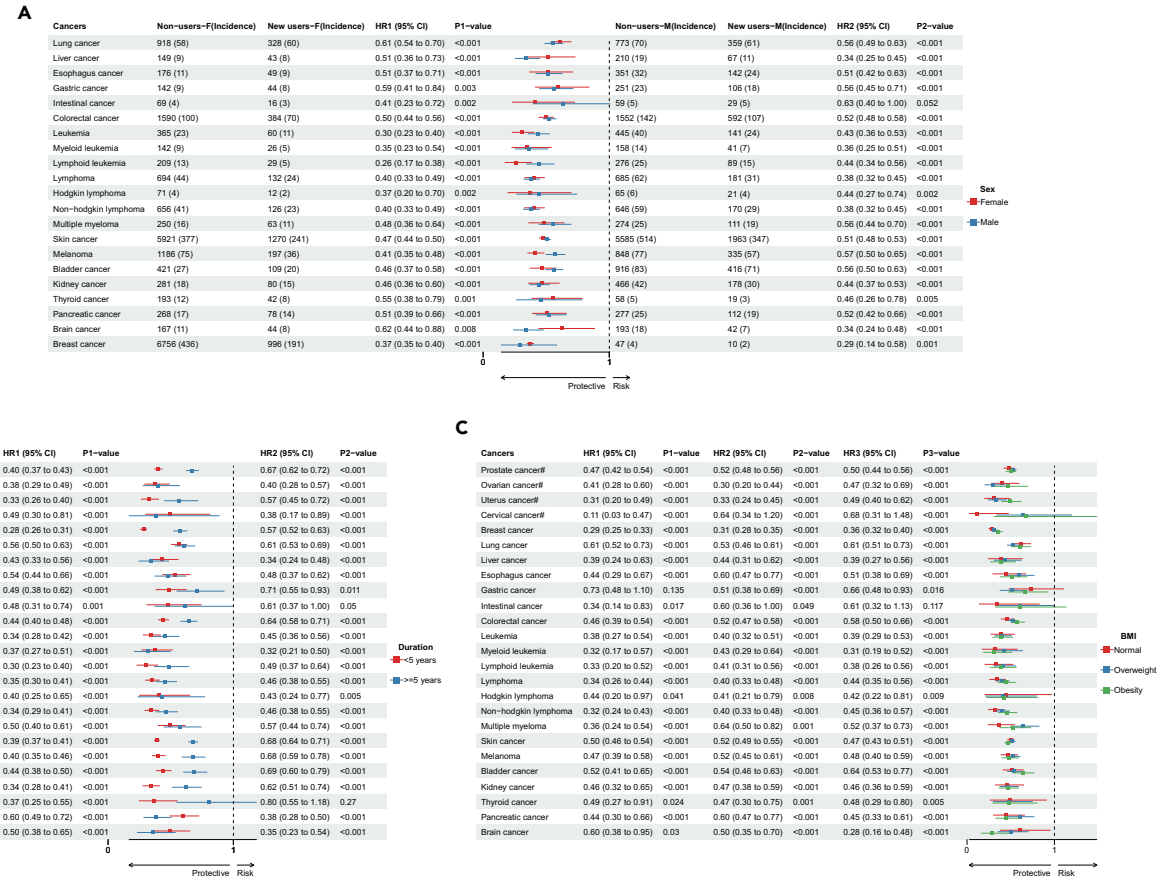


Figure 2. Association between lipid-lowering drugs and cancer risk

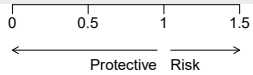
(A) By sex.

(B) By duration.

(C) By BMI. Incidence: number of cancer occurrences per 10000 patients. #: Only in females or males. HR: hazard ratio; CI: confidence interval; BMI: body mass index. Models: (1) Model 1 was adjusted for age and sex; (2) Model 2 was also adjusted for BMI, race, smoking status, and drinking status; (3) Model 3 was further adjusted for the comorbidity index and other drugs identified.

A

Cancers	Non−users(Incidence)	New users(Incidence)	HR (95% CI)	P−value
Prostate cancer#	5108 (451)	1674 (317)	0.53 (0.50 to 0.56)	<0.001
Ovarian cancer#	616 (40)	92 (21)	0.40 (0.32 to 0.51)	<0.001
Uterus cancer#	913 (59)	167 (38)	0.43 (0.36 to 0.51)	<0.001
Cervical cancer#	192 (12)	24 (5)	0.54 (0.34 to 0.84)	0.007
Breast cancer	6875 (251)	934 (92)	0.40 (0.37 to 0.43)	<0.001
Lung cancer	1737 (62)	641 (61)	0.60 (0.55 to 0.66)	<0.001
Liver cancer	368 (13)	101 (10)	0.40 (0.32 to 0.51)	<0.001
Esophagus cancer	537 (19)	181 (17)	0.54 (0.46 to 0.65)	<0.001
Gastric cancer	399 (14)	144 (14)	0.62 (0.51 to 0.75)	<0.001
Intestinal cancer	130 (5)	43 (4)	0.57 (0.40 to 0.82)	0.002
Colorectal cancer	3210 (116)	908 (87)	0.53 (0.49 to 0.58)	<0.001
Leukemia	827 (30)	184 (18)	0.39 (0.33 to 0.46)	<0.001
Myeloid leukemia	310 (11)	57 (5)	0.33 (0.25 to 0.44)	<0.001
Lymphoid leukemia	491 (18)	112 (11)	0.40 (0.32 to 0.49)	<0.001
Lymphoma	1399 (50)	293 (28)	0.41 (0.36 to 0.47)	<0.001
Hodgkin lymphoma	137 (5)	32 (3)	0.46 (0.30 to 0.68)	<0.001
Non−hodgkin lymphoma	1323 (48)	275 (26)	0.40 (0.35 to 0.46)	<0.001
Multiple myeloma	543 (20)	155 (15)	0.51 (0.43 to 0.62)	<0.001
Skin cancer	11725 (427)	3014 (300)	0.51 (0.49 to 0.53)	<0.001
Melanoma	2077 (75)	489 (47)	0.51 (0.46 to 0.56)	<0.001
Bladder cancer	1371 (49)	491 (47)	0.56 (0.50 to 0.62)	<0.001
Kidney cancer	761 (27)	244 (23)	0.47 (0.41 to 0.55)	<0.001
Thyroid cancer	256 (9)	56 (5)	0.53 (0.39 to 0.72)	<0.001
Pancreatic cancer	554 (20)	181 (17)	0.55 (0.46 to 0.66)	<0.001
Brain cancer	366 (13)	80 (8)	0.46 (0.36 to 0.60)	<0.001
More than one				



B

Cancers	Non−users(Incidence)	New users(Incidence)	HR (95% CI)	P−value
Prostate cancer#	5010 (459)	1772 (312)	0.51 (0.48 to 0.54)	<0.001
Ovarian cancer#	608 (41)	100 (20)	0.39 (0.31 to 0.48)	<0.001
Uterus cancer#	901 (60)	179 (37)	0.40 (0.34 to 0.48)	<0.001
Cervical cancer#	192 (13)	24 (5)	0.46 (0.30 to 0.73)	<0.001
Breast cancer	6808 (257)	1001 (90)	0.37 (0.35 to 0.40)	<0.001
Lung cancer	1692 (63)	686 (60)	0.58 (0.53 to 0.64)	<0.001
Liver cancer	359 (13)	110 (10)	0.40 (0.32 to 0.50)	<0.001
Esophagus cancer	528 (20)	190 (17)	0.51 (0.43 to 0.61)	<0.001
Gastric cancer	393 (15)	150 (13)	0.58 (0.47 to 0.70)	<0.001
Intestinal cancer	128 (5)	45 (4)	0.53 (0.37 to 0.76)	<0.001
Colorectal cancer	3144 (117)	974 (86)	0.51 (0.48 to 0.55)	<0.001
Leukemia	812 (30)	199 (17)	0.38 (0.32 to 0.45)	<0.001
Myeloid leukemia	301 (11)	66 (6)	0.35 (0.26 to 0.46)	<0.001
Lymphoid leukemia	486 (18)	117 (10)	0.37 (0.30 to 0.46)	<0.001
Lymphoma	1379 (51)	313 (28)	0.39 (0.34 to 0.44)	<0.001
Hodgkin lymphoma	136 (5)	33 (3)	0.42 (0.28 to 0.62)	<0.001
Non−hodgkin lymphoma	1302 (48)	296 (26)	0.39 (0.34 to 0.44)	<0.001
Multiple myeloma	525 (20)	173 (15)	0.52 (0.44 to 0.62)	<0.001
Skin cancer	11522 (433)	3217 (295)	0.49 (0.47 to 0.51)	<0.001
Melanoma	2040 (76)	526 (46)	0.49 (0.44 to 0.54)	<0.001
Bladder cancer	1340 (50)	522 (46)	0.53 (0.48 to 0.59)	<0.001
Kidney cancer	748 (28)	257 (23)	0.45 (0.39 to 0.52)	<0.001
Thyroid cancer	252 (9)	60 (5)	0.51 (0.38 to 0.68)	<0.001
Pancreatic cancer	546 (20)	189 (17)	0.51 (0.43 to 0.61)	<0.001
Brain cancer	360 (13)	86 (8)	0.45 (0.35 to 0.57)	<0.001
Statin				

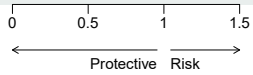


Figure 3. Sensitivity analysis

(A) More than one prescription.

(B) Statins. Incidence: number of cancer occurrences per 10000 patients. #: Only in females or males. HR: hazard ratio; CI: confidence interval. Models: (1) Model 1 was adjusted for age and sex; (2) Model 2 was also adjusted for BMI, race, smoking status, and drinking status; (3) Model 3 was further adjusted for the comorbidity index and other drugs identified.

reduced risk of melanoma, skin cancer, and reproductive (prostate, ovarian, uterus, cervical, breast), hematological (leukemia, lymphoma, multiple myeloma), urinary (bladder, kidney), digestive (esophagus, gastric, intestinal, colorectal, liver), respiratory (lung), nervous (brain cancer), endocrine system (thyroid, pancreatic) cancers even in patients with hyperlipidemia. Our meta-analysis documented that lipid-lowering drugs reduced the risk of prostate, liver, and gastric cancer, especially. According to our findings, lipid-lowering drugs reduced the overall risk of cancer death. Further investigations with extensive sample sizes and long follow-up periods are needed to explore the effect on deaths from each type of cancer. Moreover, previous studies found that statins may have a potentially beneficial effect on COVID-19, possibly by directly affecting the endocytosis or replication process of the virus.[21] Consequently, we conducted a stratification analysis and found that lipid-lowering drugs had a similar reduction in cancer risk regardless of COVID-19 infection.

Cancer has emerged as a major global health challenge in today's society, imposing not only psychological and financial burdens on patients and families but also placing a substantial burden on society as a whole.[22] As a result, the importance of cancer prevention is increasing. Preventive strategies are deemed more advantageous than treatment due to the prolonged and expensive nature of cancer therapy, which yields varying success rates. By adopting preventive measures such as maintaining healthy lifestyles and undergoing screening tests, the risk of developing cancer can be reduced, leading to improved overall health, longevity, and quality of life while simultaneously decreasing healthcare costs and societal burden.[23,24] However, the effectiveness of current prevention methods is not optimal.

Numerous studies have been conducted on the relationship between lipid-lowering therapy and cancer prevention, yielding conflicting findings. For instance, a study involving an American cohort found no significant correlation between statins and prostate, breast, lung, colorectal, pancreatic, kidney, and bladder cancers, while indicating a reduced risk for NHL and melanoma.[17] Another study reported that statin use was associated with decreased risk of prostate, uterus, liver, and gastric cancers.[15] A large prospective study conducted in Korea with 587705 participants demonstrated that statins were associated with a decreased risk of breast and cervix uteri cancer but showed no association with uterus and ovarian cancer.[25] Furthermore, Murtola et al. and Lopez et al. also observed that statin use was associated with a decreased risk of prostate cancer, which aligns with our cohort findings.[26,27] Similarly, other studies on liver and kidney cancer have reported the anti-cancer effects of lipid-lowering drugs, consistent with our results.[28,29] Our study, in contrast to previous research focused on a single type of cancer, observed multiple cancer outcomes and conducted independent follow-ups for each cancer, thereby eliminating the impact of unobserved medication before cohort entry. However, only statins have been shown to potentially reduce the risk of cancer. A meta-analysis found no significant results for the use of fibrates in the respiratory tract, breast, colon, gastrointestinal tract, prostate, genitourinary tract cancers, or melanoma.[30] It is possible that distinct mechanisms exist for the prevention of different types of cancer. For instance, a review suggested that statins affect lung cancer stem cells by inhibiting RhoA, YAP/TAZ, reducing the effect of oncogenic genes, and down-regulating Oct4/Nano G, thereby reducing the risk of lung cancer. Additionally, evidence suggests that there may be sex-specific differences in the protective effects of statins against lung cancer, possibly attributed to immune responses, mutated oncogenes, or even lifestyle habits such as smoking among men and women.[31]

In our study, when only adjusting for age and sex, we did not observe a significant protective effect of lipid-lowering drugs on lung, gastric, intestinal, and bladder cancers. However, it had a protective effect when further adjusted. Given that the majority of our cohort was White, we thought that further adjusted factors (BMI, smoking, drinking) might play a role. In our subgroup analysis of BMI, lipid-lowering drugs reduced the risk of gastric cancer in overweight and obese participants, while reducing the risk of intestinal cancer in normal-weight and overweight participants. This verified the reliability of the confounding factors we adjusted to some extent. Tobacco smoke contains more than 40 carcinogens and is therefore considered one of the major risk factors for cancers.[32] Thus, smoking is an important confounding factor that needs to be adjusted. Moreover, a meta-analysis found that drinkers had a significantly increased risk of prostate cancer and even had a significant dose-response relationship.[33] Some studies suggested they may affect the risk of other types of cancer.[34,35] The confounding factors adjusted in our study are necessary.

An important metabolic characteristic of cancer cells is a disruption in lipid metabolism, which is essential for the proliferation of various types of cancer cells and plays a role in all aspects of tumorigenesis. Therefore, targeting lipid metabolism presents a promising strategy for cancer prevention.[36] One potential mechanism involves the increased demand for mevalonate (MVA) as a marker of carcinogenesis, making the MVA pathway a prime target for cancer. Statins, by inhibiting HMGCR, can reduce MVA levels, affecting both cholesterol-mediated and non-cholesterol-mediated pathways.[37] Dysregulation of cholesterol homeostasis, is associated with the emergence of cancer through various pathways, including inflammasome and microRNA-mediated pathways.[38,39] For some statins such as rosuvastatin that rarely reach the extrahepatic tissues, in the absence of the statin, reduced cholesterol in these cells might remove the negative feedback on cholesterol biogenesis, stimulating the cholesterol pathway.[40] Thus, it may be more related to non-cholesterol-mediated pathways in the development of these cancers. Statins can inhibit cancer cell growth by targeting isoprene intermediates FPP and geranyl pyrophosphate (GPP), which play a crucial role in modifying intracellular G proteins such as Rho, Rac, and Ras involved in cell proliferation, differentiation, and apoptosis. By inhibiting this process, statins ultimately inhibit cancer cell growth. This mechanism is particularly significant in specific tumor types such as lung, colorectal, and pancreatic cancer.[41–44] Furthermore, lipid-lowering drugs may have a preventive effect on cancer by mitigating chronic inflammation, a crucial factor in the pathogenesis of numerous malignancies. Research indicates that the use of lipid-lowering drugs can attenuate systemic

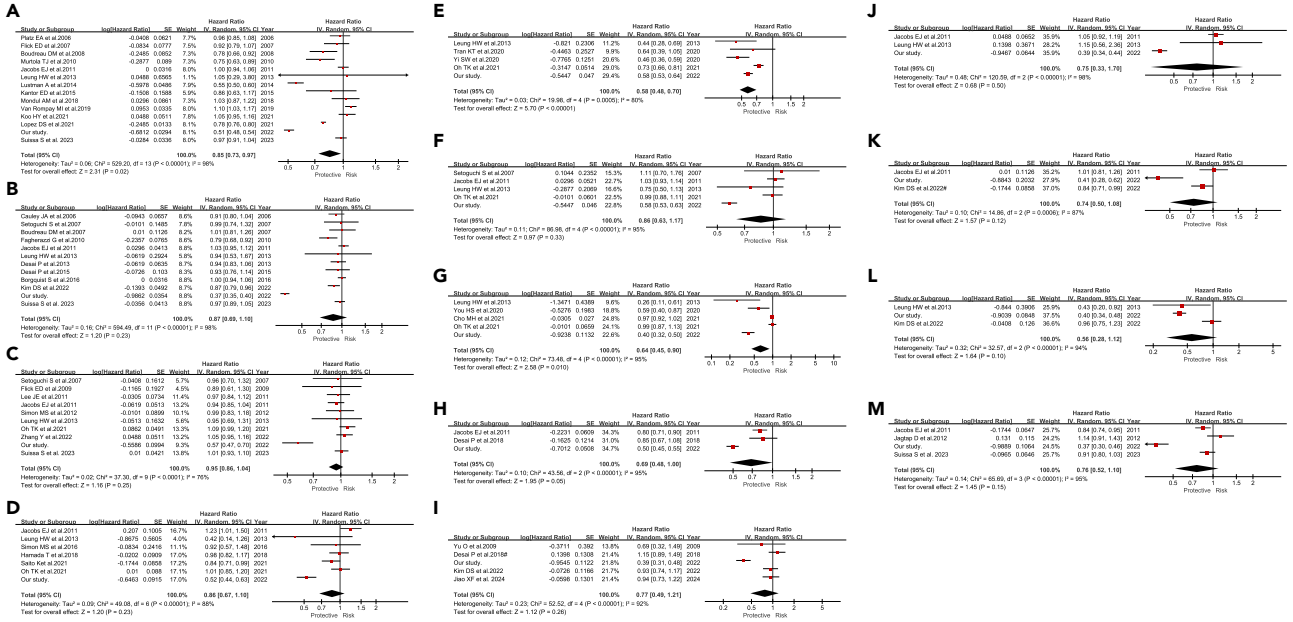


Figure 4. Studies included in the meta-analysis on association between lipid-lowering drugs and cancer risk

(A): prostate cancer; (B): breast cancer; (C): colorectal cancer; (D): pancreatic cancer; (E): liver cancer; (F): lung cancer; (G): gastric cancer; (H): non-Hodgkin lymphoma; (I): ovarian cancer; (J): bladder cancer; (K): kidney cancer; (L): uterus cancer; (M): melanoma. IV: Inverse Variance; CI: confidence interval.

chronic inflammation by suppressing the release of inflammatory mediators and modulating immune response. This mechanism can impede the proliferation and metastasis of cancer cells, thereby contributing to cancer prevention.[45] Studies have demonstrated that fibrates can effectively prevent the formation of certain tumor cells through their anticoagulant and anti-inflammatory characteristics.[46] In addition, lipid-lowering drugs may prevent certain hormone-dependent cancers by regulating estrogen levels and hormone receptor activity. Recently, cholesterol has been identified as a natural estrogen-related receptor (ERR)-α ligand using a combined biochemical strategy. It underscored the association between elevated cholesterol levels and certain cancer phenotypes characterized by overexpression of ERRα, such as breast, prostate, and colorectal cancers, where metabolic adaptations affect many cancer processes.[47] This emphasizes the potential use of cholesterol-lowering drugs such as statins.[48] Furthermore, by regulating cholesterol levels and improving blood circulation, statins can also improve cellular oxidative stress and antioxidant capacity, reduce the occurrence of DNA damage and gene mutations, and thus reduce the risk of cancer.[49] Separately, statins may possess distinct mechanisms to prevent different cancers. For example, studies conducted on mouse models showed that statins inhibited the expression of matrix metalloproteinases (MMPs), very late antigens (VLAs), CDK phosphorylation, and cyclin, meanwhile, inhibited Rho/LIM kinase (LIMK)/serum response factor (SRF)/c-Fos signaling pathway and promoted the expression of cyclin-dependent kinase (CDK) inhibitors to reduce the risk of melanoma.[50]

We also compare our study with the other. The study by Carter et al. utilized the Mendelian randomization method to investigate the relationship between HMGCR inhibition and the risk of overall cancer and site-specific cancers. They found that statins reduce cancer risk which suggests that any reduction in cancer risk from statins in practice is likely to be modest.[16] Similar results were also found in our study that the use of lipid-lowering drugs reduced the risk of 21 types of cancers and further research is needed on the role of subclasses of lipid-lowering drugs. Nonetheless, it is worth noting that we also evaluated the association between lipid-lowering drugs and the mortality of overall cancer and found that using lipid-lowering drugs decreased the mortality of overall cancer in total patients, which was not explored in the study of Carter et al. In addition, we conducted a separate analysis on the role of the fibrates which was not included in the variant gene regions used in the study of Carter et al., and found that fibrates were not associated with a lower risk of cancer in males, highlighting a divergence in results. Furthermore, our study was stratified and showed that the effects of lipid-lowering drugs on site-specific cancers were different in sex and BMI groups, which will be more conducive to the precise application of lipid-lowering drugs for cancer prevention in the future. To enhance the generalizability of our findings across different ethnicities and nationalities, we conducted a meta-analysis including the results of our study based on the UK population and other cohort studies and found that there was a reduced risk of the prostate, liver, and gastric cancer in participants using lipid-lowering drugs, especially. Although our meta-analysis was not so comprehensive, the integration of publications similar to our type of study can minimize methodological heterogeneity and provide some reference for the existing controversy between lipid-lowering drugs and cancer.

Our advantage was the use of a large prospective sample cohort in the UK over a long period of follow-up and the analysis was limited to a single type of cancer. Besides, each cancer was followed up individually. Besides, we used linked GP data and death registry data rather than self-reported data to make the assessment of exposure and outcome more accurate. In summary, lipid-lowering drugs protect from cancer incidence, suggesting the possible cancer prevention effects even in the general population. As an important part of public health policy,

cancer prevention is important, reducing the incidence of cancer in the community as a whole, improving overall health, and reducing the need for medical resources. It is worth noting that our study offers the possibility of new preventive measures to reduce the incidence of cancer in the future. It may be a promising strategy to consider repurposing lipid-lowering drugs for cancer prevention.

Limitations of the study

It should be noted that there were several limitations. First, we did not further classify the detailed drug due to the number of patients taking a different medication and we were unable to obtain information on the use of some drug types such as ezetimibe and PCSK9 inhibitors. However, we did our best to conduct subgroup and sensitivity analyses. Second, there were some possible confounders not in the model (e.g., exercises, diet, familial history of cancer) due to the limited information collected by the UK Biobank. However, we adjusted potentially important confounders (e.g., comorbidity index, use of other drugs). Third, detailed clinical data such as the stage of cancers and dosage of drugs were unable to be included in the analysis. Fourth, the analyses may be particularly affected by selection bias caused by the selective discontinuation of drug use in the terminal phase of cancers. Also, confounding indications for lipid-lowering drugs must be taken into consideration in further studies. Fifth, this study predominantly included only white populations. The applicability of these findings may be restricted. Furthermore, since drug information was based on prescriptions, it was impossible to ascertain whether participants adhered to the prescribed drug or not. Finally, limited by the number of articles retrieved, only 13 kinds of cancers were included in our meta-analysis, and studies on each cancer were relatively small which included quite a bit of cancer that has not been studied before. Some methods, such as Egger's test, may lack analytical power due to the small sample sizes. Hence, the results should be interpreted with caution and it is necessary to design more rigorous research in the future to further explore and validate our findings.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

- KEY RESOURCES TABLE
- RESOURCE AVAILABILITY
  - Lead contact
  - Materials availability
  - Data and code availability
- EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS
  - Data source
  - Participants
- METHOD DETAILS
  - Ascertainment of medications and outcomes
  - Ascertainment of covariates
  - Meta-analysis
- QUANTIFICATION AND STATISTICAL ANALYSIS

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2024.110680.

ACKNOWLEDGMENTS

This study was supported by the National Natural Science Foundation of China (82130025), National Key Research and Development Program of China (2021YFA0805100), the National Natural Science Foundation of China (82200659), and the Natural Science Foundation of Shandong Province (ZR20220H002). We kindly acknowledge the participants and researchers who participated in this study.

AUTHOR CONTRIBUTIONS

JZ created the study protocol. XF and ZY contributed to the analysis plan. ZY contributed to the data analysis and wrote the first draft of the article. All authors critically revised and approved the article and agreed with the submission and publication.

DECLARATION OF INTERESTS

The authors declare no competing interests.

Received: April 28, 2024
Revised: June 23, 2024
Accepted: August 2, 2024
Published: August 6, 2024

REFERENCES

1. Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A., and Bray, F. (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA. Cancer J. Clin. *71*, 209–249. https://doi.org/10.3322/caac.21660.
2. Vogel, V.G., Costantino, J.P., Wickerham, D.L., Cronin, W.M., Cecchini, R.S., Atkins, J.N., Bevers, T.B., Fehrenbacher, L., Pajon, E.R., Jr., Wade, J.L., 3rd, et al. (2006). Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA *295*, 2727–2741. https://doi.org/10.1001/jama.295.23.joc60074.
3. Kamolratanakul, S., and Pitisuttithum, P. (2021). Human Papillomavirus Vaccine Efficacy and Effectiveness against Cancer. Vaccines *9*, 1413. https://doi.org/10.3390/vaccines9121413.
4. Ye, S., Lee, M., Lee, D., Ha, E.H., and Chun, E.M. (2019). Association of Long-term Use of Low-Dose Aspirin as Chemoprevention With Risk of Lung Cancer. JAMA Netw. Open *2*, e190185. https://doi.org/10.1001/jamanetworkopen.2019.0185.
5. Drew, D.A., Cao, Y., and Chan, A.T. (2016). Aspirin and colorectal cancer: the promise of precision chemoprevention. Nat. Rev. Cancer *16*, 173–186. https://doi.org/10.1038/nrc.2016.4.
6. Han, X., Li, J., Brasky, T.M., Xun, P., Stevens, J., White, E., Gammon, M.D., and He, K. (2013). Antioxidant intake and pancreatic cancer risk: the Vitamins and Lifestyle (VITAL) Study. Cancer *119*, 1314–1320. https://doi.org/10.1002/cncr.27936.
7. Wright, M.E., Mayne, S.T., Stolzenberg-Solomon, R.Z., Li, Z., Pietinen, P., Taylor, P.R., Virtamo, J., and Albanes, D. (2004). Development of a comprehensive dietary antioxidant index and application to lung cancer risk in a cohort of male smokers. Am. J. Epidemiol. *160*, 68–76. https://doi.org/10.1093/aje/kwh173.
8. Zhao, H., Wu, L., Yan, G., Chen, Y., Zhou, M., Wu, Y., and Li, Y. (2021). Inflammation and tumor progression: signaling pathways and targeted intervention. Signal Transduct. Target. Ther. *6*, 263. https://doi.org/10.1038/s41392-021-00658-5.
9. Gazzerro, P., Proto, M.C., Gangemi, G., Malfitano, A.M., Ciaglia, E., Pisanti, S., Santoro, A., Laezza, C., and Bifulco, M. (2012). Pharmacological actions of statins: a critical appraisal in the management of cancer. Pharmacol. Rev. *64*, 102–146. https://doi.org/10.1124/pr.111.004994.
10. Oesterle, A., Laufs, U., and Liao, J.K. (2017). Pleiotropic Effects of Statins on the Cardiovascular System. Circ. Res. *120*, 229–243. https://doi.org/10.1161/CIRCRESAHA.116.308537.
11. Bonovas, S. (2014). Statins: do they have a potential role in cancer prevention and modifying cancer-related outcomes? Drugs *74*, 1841–1848. https://doi.org/10.1007/s40265-014-0309-2.
12. Sassano, A., and Platanias, L.C. (2008). Statins in tumor suppression. Cancer Lett. *260*, 11–19. https://doi.org/10.1016/j.canlet.2007.11.036.
13. Weis, M., Heeschen, C., Glassford, A.J., and Cooke, J.P. (2002). Statins have biphasic effects on angiogenesis. Circulation *105*, 739–745. https://doi.org/10.1161/hc0602.103393.
14. Gauthaman, K., Fong, C.Y., and Bongso, A. (2009). Statins, stem cells, and cancer. J. Cell. Biochem. *106*, 975–983. https://doi.org/10.1002/jcb.22092.
15. Leung, H.W.C., Chan, A.L.F., Lo, D., Leung, J.H., and Chen, H.L. (2013). Common cancer risk and statins: a population-based case-control study in a Chinese population. Expert Opin. Drug Saf. *12*, 19–27. https://doi.org/10.1517/14740338.2013.744392.
16. Carter, P., Vithayathil, M., Kar, S., Potluri, R., Mason, A.M., Larsson, S.C., and Burgess, S. (2020). Predicting the effect of statins on cancer risk using genetic variants from a Mendelian randomization study in the UK Biobank. Elife *9*, e57191. https://doi.org/10.7554/eLife.57191.
17. Jacobs, E.J., Newton, C.C., Thun, M.J., and Gapstur, S.M. (2011). Long-term use of cholesterol-lowering drugs and cancer incidence in a large United States cohort. Cancer Res. *71*, 1763–1771. https://doi.org/10.1158/0008-5472.Can-10-2953.
18. Mondul, A.M., Joshu, C.E., Barber, J.R., Prizment, A.E., Bhavsar, N.A., Selvin, E., Folsom, A.R., and Platz, E.A. (2018). Longer-term Lipid-lowering Drug Use and Risk of Incident and Fatal Prostate Cancer in Black and White Men in the ARIC Study. Cancer Prev. Res. (Philadelphia, Pa.) *11*, 779–788. https://doi.org/10.1158/1940-6207.CAPR-17-0396.
19. Borgquist, S., Tamimi, R.M., Chen, W.Y., Garber, J.E., Eliassen, A.H., and Ahern, T.P. (2016). Statin Use and Breast Cancer Risk in the Nurses' Health Study. Cancer Epidemiol. Biomarkers Prev. *25*, 201–206. https://doi.org/10.1158/1055-9965.EPI-15-0654.
20. Newman, T.B., and Hulley, S.B. (1996). Carcinogenicity of lipid-lowering drugs. JAMA *275*, 55–60.
21. Pawlos, A., Niedzielski, M., Gorzelak-Pabiś, P., Broncel, M., and Wozniak, E. (2021). COVID-19: Direct and Indirect Mechanisms of Statins. Int. J. Mol. Sci. *22*, 4177. https://doi.org/10.3390/ijms22084177.
22. McGuire, S. (2016). World Cancer Report 2014. Geneva, Switzerland: World Health Organization, International Agency for Research on Cancer, WHO Press, 2015. Adv. Nutr. *7*, 418–419. https://doi.org/10.3945/an.116.012211.
23. Colditz, G.A., Atwood, K.A., Emmons, K., Monson, R.R., Willett, W.C., Trichopoulos, D., and Hunter, D.J. (2000). Harvard report on cancer prevention volume 4: Harvard Cancer Risk Index. Risk Index Working Group, Harvard Center for Cancer Prevention. Cancer Causes Control. *11*, 477–488. https://doi.org/10.1023/a:1008984432272.
24. World Health Organization. Cancer prevention. https://www.who.int/cancer/prevention/en/.
25. Kim, D.S., Ahn, H.S., and Kim, H.J. (2022). Statin use and incidence and mortality of breast and gynecology cancer: A cohort study using the National Health Insurance claims database. Int. J. Cancer *150*, w20211706603.
26. Murtola, T.J., Tammela, T.L., Määttänen, L., Huhtala, H., Platz, E.A., Ala-Opas, M., Stenman, U.H., and Auvinen, A. (2010). Prostate cancer and PSA among statin users in the Finnish prostate cancer screening trial. Int. J. Cancer *127*, w20100137427.
27. Lopez, D.S., Polychronopoulou, E., Tsilidis, K.K., Khera, M., Su, L.J., Fowke, J.H., Peek, M.K., Kuo, Y.F., Markides, K., and Canfield, S. (2021). Independent and Joint Effects of Testosterone Replacement Therapy and Statins use on the Risk of Prostate Cancer Among White, Black, and Hispanic Men. Cancer Prev. Res. (Philadelphia, Pa.) *14*, 719–728. https://doi.org/10.1158/1940-6207.Capr-21-0040.
28. Kim, D.S., Kim, H.J., and Ahn, H.S. (2022). Association Between Statins and the Risk of Kidney Cancer Incidence and Mortality Using the Korean National Health Insurance Claims Database. Cancer Control *29*, 10732748221111293. https://doi.org/10.1177/10732748221111293.
29. Yi, S.W., Kim, S.H., Han, K.J., Yi, J.J., and Ohrr, H. (2020). Higher cholesterol levels, not statin use, are associated with a lower risk of hepatocellular carcinoma. Br. J. Cancer *122*, 630–633. https://doi.org/10.1038/s41416-019-0691-3.
30. Bonovas, S., Nikolopoulos, G.K., and Bagos, P.G. (2012). Use of fibrates and cancer risk: a systematic review and meta-analysis of 17 long-term randomized placebo-controlled trials. PLoS One *7*, e45259. https://doi.org/10.1371/journal.pone.0045259.
31. Marcianò, G., Palleria, C., Casarella, A., Rania, V., Basile, E., Catarisano, L., Vocca, C., Bianco, L., Pelaia, C., Cione, E., et al. (2022). Effect of Statins on Lung Cancer Molecular Pathways: A Possible Therapeutic Role. Pharmaceuticals *15*, 589. https://doi.org/10.3390/ph15050589.
32. Zyczkowski, M., Bogacki, R., and Paradysz, A. (2014). [The impact of smoking on diseases of the genitourinary system]. Wiad. Lek. *67*, 540–547.
33. Zhao, J., Stockwell, T., Roemer, A., and Chikritzhs, T. (2016). Is alcohol consumption a risk factor for prostate cancer? A systematic review and meta-analysis. BMC Cancer *16*, 845. https://doi.org/10.1186/s12885-016-2891-z.
34. Yen, H., Dhana, A., Okhovat, J.P., Qureshi, A., Keum, N., and Cho, E. (2017). Alcohol intake and risk of nonmelanoma skin cancer: a systematic review and dose-response meta-analysis. Br. J. Dermatol. *177*, 696–707. https://doi.org/10.1111/bjd.15647.
35. Ye, X.H., Huai, J.P., Ding, J., Chen, Y.P., and Sun, X.C. (2013). Smoking, alcohol consumption, and the risk of extrahepatic cholangiocarcinoma: a meta-analysis. World J. Gastroenterol. *19*, 8780–8788. https://doi.org/10.3748/wjg.v19.i46.8780.
36. Liu, Q., Luo, Q., Halim, A., and Song, G. (2017). Targeting lipid metabolism of cancer cells: A promising therapeutic strategy for cancer. Cancer Lett. *401*, 39–45. https://doi.org/10.1016/j.canlet.2017.05.002.
37. Zaky, M.Y., Fan, C., Zhang, H., and Sun, X.F. (2023). Unraveling the Anticancer Potential of Statins: Mechanisms and Clinical Significance. Cancers *15*, 4787. https://doi.org/10.3390/cancers15194787.
38. Moossavi, M., Parsamanesh, N., Bahrami, A., Atkin, S.L., and Sahebkar, A. (2018). Role of the NLRP3 inflammasome in cancer. Mol. Cancer *17*, 158. https://doi.org/10.1186/s12943-018-0900-3.
39. Bae, J.Y., Lee, S.W., Shin, Y.H., Lee, J.H., Jahng, J.W., and Park, K. (2017). P2X7 receptor and NLRP3 inflammasome activation in head and neck cancer.

Oncotarget *8*, 48972–48982. https://doi.org/10.18632/oncotarget.16903.

40. White, C.M. (2002). A review of the pharmacologic and pharmacokinetic aspects of rosuvastatin. J. Clin. Pharmacol. *42*, 963–970.
41. Gonyeau, M.J., and Yuen, D.W. (2010). A clinical review of statins and cancer: helpful or harmful? Pharmacotherapy *30*, 177–194. https://doi.org/10.1592/phco.30.2.177.
42. Adjei, A.A. (2001). Blocking oncogenic Ras signaling for cancer therapy. J. Natl. Cancer Inst. *93*, 1062–1074. https://doi.org/10.1093/jnci/93.14.1062.
43. Ukomadu, C., and Dutta, A. (2003). p21-dependent inhibition of colon cancer cell growth by mevastatin is independent of inhibition of G1 cyclin-dependent kinases. J. Biol. Chem. *278*, 43586–43594. https://doi.org/10.1074/jbc.M307194200.
44. Frick, M., Dulak, J., Cisowski, J., Józkowicz, A., Zwick, R., Alber, H., Dichtl, W., Schwarzacher, S.P., Pachinger, O., and Weidinger, F. (2003). Statins differentially regulate vascular endothelial growth factor synthesis in endothelial and vascular smooth muscle cells. Atherosclerosis *170*, 229–236. https://doi.org/10.1016/s0021-9150(03)00299-5.
45. Platz, E.A., Leitzmann, M.F., Visvanathan, K., Rimm, E.B., Stampfer, M.J., Willett, W.C., and Giovannucci, E. (2006). Statin drugs and risk of advanced prostate cancer. J. Natl. Cancer Inst. *98*, 1819–1825. https://doi.org/10.1093/jnci/djj499.
46. Berstein, L.M. (2005). Clinical usage of hypolipidemic and antidiabetic drugs in the prevention and treatment of cancer. Cancer Lett. *224*, 203–212. https://doi.org/10.1016/j.canlet.2004.11.011.
47. Casaburi, I., Chimento, A., De Luca, A., Nocito, M., Sculco, S., Avena, P., Trotta, F., Rago, V., Sirianni, R., and Pezzi, V. (2018). Cholesterol as an Endogenous ERRalpha Agonist: A New Perspective to Cancer Treatment. Front. Endocrinol. *9*, 525. https://doi.org/10.3389/fendo.2018.00525.
48. Nelson, E.R. (2018). The significance of cholesterol and its metabolite, 27-hydroxycholesterol in breast cancer. Mol. Cell. Endocrinol. *466*, 73–80. https://doi.org/10.1016/j.mce.2017.09.021.
49. Feleszko, W., Zagozdzon, R., Gołab, J., and Jakóbisiak, M. (1998). Potentiated antitumour effects of cisplatin and lovastatin against MmB16 melanoma in mice. Eur. J. Cancer *34*, 406–411. https://doi.org/10.1016/s0959-8049(97)10034-x.
50. Tsubaki, M., Takeda, T., Kino, T., Obata, N., Itoh, T., Imano, M., Mashimo, K., Fujiwara, D., Sakaguchi, K., Satou, T., and Nishida, S. (2015). Statins improve survival by inhibiting spontaneous metastasis and tumor growth in a mouse melanoma model. Am. J. Cancer Res. *5*, 3186–3197.
51. Learn more about UK Biobank. https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank.
52. The Ethics Advisory Committee (EAC). https://www.ukbiobank.ac.uk/ethics/.
53. UK Biobank. https://www.ukbiobank.ac.uk/.
54. Data providers and dates of data availability. https://biobank.ndph.ox.ac.uk/showcase/exinfo.cgi?src=Data_providers_and_dates.
55. Hippisley-Cox, J., and Coupland, C. (2010). Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. BMJ (Clinical research ed.) *340*, c2197. https://doi.org/10.1136/bmj.c2197.
56. Charlson, M.E., Pompei, P., Ales, K.L., and MacKenzie, C.R. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J. Chronic Dis. *40*, 373–383. https://doi.org/10.1016/0021-9681(87)90171-8.
57. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
58. Hata, Y., Mabuchi, H., Saito, Y., Itakura, H., Egusa, G., Ito, H., Teramoto, T., Tsushima, M., Tada, N., Oikawa, S., et al. (2002). Report of the Japan Atherosclerosis Society (JAS) Guideline for Diagnosis and Treatment of Hyperlipidemia in Japanese adults. J. Atheroscler. Thromb. *9*, 1–27. https://doi.org/10.5551/jat.9.1.
59. Alberti, K.G.M.M., Zimmet, P., and Shaw, J.; IDF Epidemiology Task Force Consensus Group (2005). The metabolic syndrome–a new worldwide definition. Lancet (London, England) *366*, 1059–1062. https://doi.org/10.1016/S0140-6736(05)67402-8.

STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
The UK Biobank data	UK Biobank Limited	https://www.ukbiobank.ac.uk/
Main dataset	UK Biobank Limited	https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access
Primary care data	UK Biobank Limited	https://www.ukbiobank.ac.uk/enable-your-research/about-our-data/covid-19-data
Death data	UK Biobank Limited	https://www.ukbiobank.ac.uk/enable-your-research/about-our-data/covid-19-data
Software and algorithms		
R-4.2.0	R Foundation for Statistical Computing	https://www.r-project.org/
IBM SPSS Statistics 26.0	International Business Machines Corporation	https://www.ibm.com/products/spss-statistics
Navicat Premium 16	Navicat	https://www.navicat.com.cn/
RevMan 5.4	Cochrane RevMan	https://training.cochrane.org/online-learning/core-software/revman
Adobe illustrator 2022	Adobe company	https://www.adobe.com/cn
Stata 17.0	StataCorp LLC	https://www.stata.com/
forestploter_1.1.1	Alimu Dayimu et al.	https://cran.r-project.org/web/packages/forestploter/index.html
ggplot2_3.4.4	Hadley Wickham et al.	https://cran.r-project.org/web/packages/ggplot2/index.html
gridExtra_2.3	Baptiste Auguie et al.	https://cran.r-project.org/web/packages/gridExtra/index.html
readxl_1.4.3	Hadley Wickham et al.	https://cran.r-project.org/web/packages/readxl/index.html
formattable_0.2.1	Kun Ren et al.	https://cran.r-project.org/web/packages/formattable/index.html

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the Lead Contact, Xiude Fan (fanxiudexjtu@163.com).

Materials availability

No new reagents or materials were generated in this study.

Data and code availability

- This study used data from the UK Biobank (application number 89483). For details, please contact access@ukbiobank.ac.uk. All other data reported in this paper will be shared by the lead contact upon request.
- This paper does not report original code.
- Any additional information required to reanalyze the data reported in this work paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Data source

A prospective cohort study was conducted using data from the UK Biobank cohort. The UK Biobank is a large-scale longitudinal biomedical database that recruited over half a million volunteers aged 40 to 69 years from across the UK from 2006 to 2010. Participants provided biological samples of blood, urine, and saliva for genotyping and biochemical analysis. The ethical approval was from its own Ethics Advisory Committee (EAC). It provides detailed information on informed consent and public involvement of participants.[51,52] The UK Biobank has approval from the North West Multi-centre Research Ethics Committee (MREC) as a Research Tissue Bank (RTB) approval. This RTB approval was granted initially in 2011 and it is renewed on a 5-yearly cycle: hence UK Biobank successfully applied to renew it in 2016 and 2021 (2021 NWREC RTB Application and Approval). UK Biobank will in due course apply for renewal effective in 2026 (https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank/about-us/ethics). Each participant attended a baseline assessment at the center in England, Scotland, or

Wales. Volunteers were surveyed about their lifestyle (including nutrition, drug use, etc.) and genetic relationships. Information on their health and medical status was tracked over time.[53]

The UK Biobank is linked with primary care data, also known as the General Practitioner (GP) data, for participants, all of whom provided consent for linkage to their health-related records. The initial release of GP data contains data for approximately 409,000 participants which included information such as clinical events and prescription information with TPP (https://www.tpp-uk.com/) or EMIS (https://www.emishealth.com/) as the data system supplier.[54] Using the GP data, we identified new users of lipid-lowering drugs by Dictionary of Medicines and Devices (DM + D) and local EMIS codes for the different data system suppliers. The death data was received from the UK Biobank-linked death data which was from the NHS Digital system for participants in England and Wales, and the NHS Central Register (NHSCR) for participants in Scotland. This data included the date of death, primary and contributing causes of death, coded using the ICD-10 system.[54] An overview of all of the linked health data available from the UK Biobank can be found in the Essential Information section of Showcase.[53]

Participants

We conducted an open cohort study using data from the UK Biobank to investigate the effects of lipid-lowering drugs on various cancer types. Participants were enrolled between January 1, 2006, and December 31, 2010, and were followed up until the earliest of cancer diagnosis, death, or study end on December 31, 2021. For each specific cancer type, we independently included and excluded participants from the cohort. Participants who had been diagnosed with the specific cancer before the assessment center visit, lacked baseline data for analysis or were lost to follow-up were excluded from the analyses. Notably, for uterine and cervical cancer, women who had undergone hysterectomy were excluded, while for ovarian cancer, women who had undergone bilateral oophorectomy were excluded. For the overall cancer mortality cohort, we included participants with any cancer diagnosis at the time of enrollment or diagnosed during the follow-up period (as shown in Figure S3). This cohort began on the date of enrollment or time of the first diagnosis of cancer (if diagnosed after enrollment). The analysis method and model were consistent with the main study. Additional details were outlined in Figure S6.

The demographic characteristics obtained from UK Biobank data field (Table S5) are: age, sex (female and male), race (white, mixed, Asian or Asian British, black or black British, Chinese, other ethnic groups, do not know or not answer), smoking status (never, previous, current, prefer not to answer), and drinking status (never, previous, current, prefer not to answer), blood examination (glucose: mmol/L, cholesterol: mmol/L, triglyceride: mmol/L, LDL-C: mmol/L), anthropometry (BMI: kg/cm^2, WC: cm, HC: cm, systolic blood pressure [SBP: mmHg], diastolic blood pressure [DBP: mmHg]), history of bowel cancer screening (yes or no), prostate specific antigen (PSA) test (yes or no), breast cancer screening/mammogram (yes or no), cervical smear test (yes or no), oral contraceptive pill (yes or no), hormone-replacement therapy (HRT) (yes or no) and age when periods started (menarche). The collection and detection methods of the examination items above can be found in detail on the website.[53]

METHOD DETAILS

Ascertainment of medications and outcomes

Using the linked primary care data, also known as the General Practitioner (GP) data, the participants were categorized as non-users and new users. Refer to definitions from previous studies, new users were considered to have no lipid-lowering drug prescription before enrollment but have lipid-lowering drug prescriptions in follow-up to reduce the "cumulative effect" of not being observed.[55] Whereas participants were considered non-users if they never had a lipid-lowering drug prescription. The lipid-lowering drugs identified from the GP data were statins and fibrates. Furthermore, the duration was defined as the interval between the first prescription and the date of discontinuing drug use. The date of discontinuing drug use was defined as the date 90 days after the last prescription.[55] Our primary outcomes were the risks of 21 site-specific cancers identified by the International Classification of Disease (ICD)-10 codes. The codes used were shown in Table S4.

Ascertainment of covariates

Potential confounders were obtained from the touchscreen questionnaire, GP data, hospital admission, and blood biochemistry assay. The details can be found on the website of UK Biobank.[53] We identified the potential confounding diseases to calculate the comorbidity index using ICD-10 codes (Table S4) and other potential confounding drugs that probably affect the association between lipid-lowering drugs and cancers.[56] Potential confounding diseases: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes mellitus, hemiplegia, moderate or severe renal disease, diabetes mellitus with chronic complications, moderate or severe liver disease and acquired immune deficiency syndrome (AIDS). Potential confounding drugs: aspirin, hypoglycemic drugs (metformin, sulfonylureas, glucagon-like peptide-1 [GLP-1], dipeptidyl peptidase-4 [DDP-4], and insulin), hypotensive drugs (angiotensin-converting enzyme inhibitors [ACEI], angiotensin receptor blockers [ARB], calcium channel blockers [CCB], β-blockers and hydrochlorothiazide).

Meta-analysis

We searched PubMed and Sinomed databases to identify all articles on the effect of lipid-lowering drug use on the risk of cancers until June 6, 2024. Medical Subject Headings (MeSH) (or subject term) and free terms related to "lipid-lowering drugs", "cancer", "incidence" and "proportional hazards models" were employed. The studies included in the meta-analysis met the following criteria: (1) prospective design, (2) lipid-lowering drugs or statins as the exposure, (3) cancer incidence as the outcome, (4) availability of hazard ratios (HRs) and confidence

intervals (CIs), and (5) description of covariables in the models. In total, 458 records were identified through searching. We excluded 113 records for animals, non-English articles, clinical trials, reviews, meta-analyses, and case reports. After further screening, 39 studies were included in the meta-analysis, including our own study. The detailed search strategy and selection flow chart were presented in Table S6 and Figure S7. The corresponding information was obtained by reading the full text and then using the NOS to assess the risk of bias.[57] We extracted the following information: title, author, country, year of publication, duration of follow-up or the start and end time of the research, drug assessment method, outcome assessment method, covariables in the fully adjusted model, types of cancer, subgroup, HRs, and CIs. Details and NOS scores were placed in Tables S7 and S8. The I^2 statistic and Cochran's Q test were used to assess the heterogeneity among included studies. Pooled estimates of HRs and CIs were computed using the Inverse Variance method and random-effects model if heterogeneity was found ($I^2 > 50\%$ or $p < 0.050$) and were reported as forest plots. Otherwise, the fixed-effects model was used.

Furthermore, we conducted sensitivity analyses using one by one-by-one elimination method if applicable (included studies >5) by which the stability of the results was assessed by eliminating one study at a time and recombining others for analysis. Publication bias was evaluated using Egger's test with a funnel plot. Besides, we performed meta-regression to explore possible sources of heterogeneity if applicable (included studies >5), including length of follow-up (≥10 years and <10 years), drug assessment method (self-report, prescription records, medication codes), outcome assessment method (self-report, medical record, cancer registries), country, sample size, adjustment for potential confounders and study quality (NOS score).

QUANTIFICATION AND STATISTICAL ANALYSIS

We used the t-test and Chi-square test for continuous and categorical variables to compare the baseline characteristics of participants according to drug use status (non-uses and new users), respectively. The multivariable Cox proportional hazards regression model with HRs and 95% CIs was employed. The main study aimed to evaluate the association between lipid-lowering drugs and the risk of cancers. The target variables (incidence of specific cancers) were binary and took only two values, 0 or 1. Furthermore, we adjusted for the potential confounders in the multivariable Cox proportional hazards regression model to examine the associations between lipid-lowing drugs and outcomes: (1) Model 1 was adjusted for age and sex; (2) Model 2 was also adjusted for BMI, race, smoking status, drinking status; (3) Model 3 was further adjusted for comorbidity index and other drugs we identified; (4) Model 4 was additionally adjusted for cancer-specific confounders. Cancer-specific confounders adjusted in Model 4: PSA test for prostate cancer; age when periods started (menarche), oral contraceptive pill, and HRT for ovarian and uterus cancers; cervical smear test (yes or no), age when periods started (menarche), oral contraceptive pill, and HRT for cervical cancer; breast cancer screening/mammogram for breast cancer; bowel cancer screening for intestinal and colorectal cancers.

We also performed stratified analyses by (1) sex (except for sex-specific cancers): male and female; (2) duration of drug use: <5 years and ≥5 years; (3) BMI groups: normal weight: 18.5–25 kg/m^2, overweight: 25–30 kg/m^2, obesity: >30 kg/m^2. We performed sensitivity analyses to examine the robustness of our findings. First, we repeated the analysis by redefining new users as participants with more than one prescription to assess the association between lipid-lowering drugs and the occurrence of cancers. Second, we compared statins users and non-statins users to repeat the analysis because statin users made up a large portion of the lipid-lowering drugs in our study. Statins users were defined as prescribing statins and the others were considered non-statins users. Third, we compared fibrates users and non-fibrates users. Fibrates users were defined as prescribing fibrates and the others were considered non-fibrates users. Since there was no consistent definition of hyperlipidemia at present, we referred to relevant studies and defined it as meeting any of the following conditions: (1) patients with a diagnosis of hyperlipidemia based on ICD-10 codes (E78); (2) baseline cholesterol level >5.72 mmol/L; (3) baseline triglyceride level >1.7 mmol/L.[58,59] Navicat Premium 16 was used to extract the linked GP data. All analyses were conducted using IBM SPSS Statistics 26.0 and R tools 4.2. RevMan 5.4 and Stata 17.0 were used for meta-analysis. Two-sided $p < 0.050$ were considered statistically significant. Our study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guideline.