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Article

Lipid-Lowering Drug Use and Cancer Incidence and Mortality in the ARIC Study

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Abstract

Background: Lipid-lowering drugs, particularly statins, are associated with reduced incidence of certain cancers in some studies. Associations with cancer mortality are not well studied, and whether associations are similar across race is unknown. **Methods:** We conducted a prospective analysis of 12 997 cancer-free participants in the Atherosclerosis Risk in Communities Study who were never users at visit 1 (1987-1989). Ever use, duration of use, and age at first use were modeled as time-dependent variables using Cox regression to estimate associations with total, obesity- and smoking-associated, bladder, breast, colorectal, lung, and prostate cancer incidence and mortality. **Results:** We ascertained 3869 cancer cases and 1661 cancer deaths in 237 999 or more person-years. At 6 years of follow-up, 70.8% of lipid-lowering drug use was a statin. Compared with never use, ever use was associated with lower total, obesity- and smoking-associated cancer mortality and with colorectal cancer mortality (hazard ratio [HR] = 0.50, 95% confidence interval [CI] = 0.32 to 0.79) and incidence (HR = 0.69, 95% CI = 0.53 to 0.92). Inverse associations were consistent by sex and race. Shorter-term use was associated with bladder cancer incidence in men (<10 years: HR = 1.67, 95% CI = 1.02 to 2.73). First use at age 60 years or older was inversely associated with: total mortality, obesity- and smoking-associated mortality, and colorectal cancer mortality; and total incidence, obesity- and smoking-associated incidence, and breast, colorectal, and prostate cancer incidence. **Conclusions:** This study provides additional evidence for inverse associations between lipid-lowering drug use and cancer incidence and mortality but a positive association with bladder cancer incidence in men. Evaluation of the impact of chemoprevention strategies that include lipid-lowering drugs on population-level cancer burden is needed.

Statins, one of the most commonly prescribed medications in the United States, have potent cholesterol-lowering properties and an attractive safety profile (1). In 2013, in the United States, 28% of adults aged 40 years or older were taking statins (2). The cholesterol-lowering effects of statins are achieved through inhibiting the 3-hydroxy-3-methylglutaryl coenzyme reductase enzyme in the mevalonate pathway, crucial to cholesterol synthesis. Recent attention to cancer cell energetics and metabolism has implicated the mevalonate pathway in carcinogenesis (3,4). Intermediate and downstream products in this pathway are necessary for essential cellular functions including membrane integrity, cell signaling, protein synthesis, and cell cycle progression (4). However, the exact mechanism through which statins may reduce cancer risk, whether through lower cholesterol or through the pleiotropic actions, is uncertain (3,5). Statins were associated with reduced total, colorectal, gastric, esophageal, and liver cancer risk in meta-analyses including both observational studies and randomized trials of statins and cardiovascular outcomes (6) but were not associated with total cancer incidence or mortality in meta-analyses of randomized trials only with median follow-up of 5 years or less for cancer outcomes (6,7). Observational evidence is most consistent for a reduced risk of lethal and fatal prostate cancer (8), including in the Atherosclerosis Risk in Communities (ARIC) study with follow-up through 2012 (9).

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Although our hypothesis of an inverse association between statins and several cancer sites is through common biologic mechanisms, some studies have reported increased risks of total incident cancer in older adults (6). Given the heterogeneity in the association, statins could have differential effects throughout the natural history of cancer and the life course. The current evidence on statins and cancer is mainly for cancer incidence rather than mortality and is limited in accounting for change in lipid profiles and for other metabolic perturbations that are associated with total and site-specific cancer (eg, diabetes), in considering the timing of the first use of lipid-lowering drugs and in evaluating these associations in persons who are Black.

Thus, we determined associations of lipid-lowering drug use, duration of use, and age of first use with total, obesity- and smoking-associated, and site-specific cancer incidence and mortality overall, in men and women, and in Black and White participants. We leveraged decades-long longitudinal data on lipid-lowering drug use, including statins, collected across multiple ARIC study contacts.

Methods

Study Population

ARIC is a prospective cohort study that enrolled 15 792 men and women aged 45-64 years (27.0% Black, 72.7% White) in 1987-1989 from 4 field centers: Forsyth County, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland. Participants were invited to 3 follow-up visits every 3 years over 10 years and a fifth visit in 2011-2013. At each visit, participants received an examination by trained personnel and interviews on their medical history, medication use, health-care access and utilization, and demographic and lifestyle factors. For this analysis, we excluded participants with prevalent cancer prior to visit 2, prevalent lipid-lowering drug users at visit 1, who were not Black or White (0.3%) and who had missing visit 2 covariates (n = 29), leaving 12 997 participants (54.8% women, 26.1% Black) in the analytic cohort. Race was self-reported, and race categories (American Indian or Alaskan Indian, Asian or Pacific Islander, Black, and White) were defined by study investigators for the baseline visit in 1989. Hispanic origin was not collected. Participants gave written informed consent, and institutional review boards at each site approved the ARIC study protocol.

Lipid-Lowering Drug Use, Duration of Use, and Age of First Use

Participants taking lipid-lowering drugs (statins, fibrates, bile acid sequestrants, niacin) at visit 2 were categorized as current users or as a never users until first report of lipid-lowering drug use at a visit, or beginning in 2006, on an annual and/or semi-annual follow-up call. Lipid-lowering drug use in ARIC was found to be highly accurate (10). Once participants reported lipid-lowering drug use, they were classified as an ever user until date of censor or cancer event. Duration of use was calculated as time of first reported use from visit 2 until date of censor or cancer event. Age of first use was based on the age in which never users first reported lipid-lowering drug use (younger than 60, 60 years and older) during follow-up.

Cancer Incidence and Death Ascertainment

Incident cancers were ascertained from visit 2 through 2015 via linkage with cancer registries in the 4 states where participants were recruited, abstraction of medical records and archived hospital discharge summaries, and death certificates (11). Cancer mortality, ascertained through 2015 from death certificates, was defined as death from cancer as the underlying cause among participants without a cancer diagnosis at visit 2 (Supplementary Methods, available online).

Covariate Assessment

Data on demographics, lifestyle, and medical conditions were collected during visits, including cancer risk factors (body mass index, smoking status, family history of cancer, total cholesterol, glycemia, and diabetes). Visits 2 through 5 data were used to adjust for confounding in time-updated analyses (Supplementary Methods, available online).

Statistical Analysis

Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence interval (CIs) for current use, duration of use, and age of first use of lipid-lowering drugs modeled as time-dependent and risk of total, obesity- and smoking-associated, and site-specific cancer incidence and mortality adjusting for known or potential risk factors (Supplementary Methods, available online). Participants contributed person-time from visit 2 until cancer diagnosis (or cancer death), death due to another cause, or end-of-study, whichever came first. Analyses were conducted overall, among men and women and among Black and White participants. The Wald-test was used to test for trend across categories of lipid-lowering drug use. Interaction between lipid-lowering drug use and sex and race was assessed using the likelihood ratio test. We confirmed the proportional hazards assumption in multivariable-adjusted models with a global test based on Schoenfeld residuals. Analyses were conducted using Stata 15. Statistical tests were 2-sided with a *P* value less than .05 considered statistically significant.

Results

Study Population

We ascertained 3869 first primary cancers in 237 999 person-years and 1661 cancer deaths in 267 474 person-years. Participant characteristics by lipid-lowering drug use at visit 4 (mean = 6 years of follow-up) are shown in Table 1. At visit 4, after statins had been available in the United States for approximately 10 years, 16% of participants used lipid-lowering drugs; of those, 70.8% used a statin. The 25-year crude cumulative incidence of cancer was 34.6% (95% CI = 33.7% to 35.6%) overall, 33.6% (95% CI = 32.4% to 34.9%) among never users, and 36.6% (95% CI = 34.7% to 38.7%) among ever users, and cancer mortality was 15.3% (95% CI = 14.6% to 16.0%), 15.6% (95% CI = 14.6% to 16.6%), and 14.6% (95% CI = 13.3% to 16.1%), respectively (data not shown).

Lipid-Lowering Drug Use and Cancer Mortality

Among participants without a cancer diagnosis at visit 2, ever use, longer-term use, and first use at age 60 years or older were associated with lower total, obesity- and smoking-associated cancer mortality (Table 2). Consistent inverse associations were observed by sex (Table 2) and race (Table 3). Similar inverse associations were observed for statin use (Supplementary Table 1, available online), access to and utilization of health care (Supplementary Tables 2 and 3, available online), and in never smokers (Supplementary Table 4, available online). Consistent inverse associations were observed among participants with normal total cholesterol at the visit prior to the visit of first reported lipid-lowering drug use overall and in men, although positive associations were observed for longer-term use and first use at age younger than 60 years with cancer mortality in women (Supplementary Table 5, available online).

Ever use was associated with lower colorectal cancer mortality compared with never use (HR = 0.50, 95% CI = 0.32 to 0.79) (Supplementary Table 6, available online). Shorter-term (<10 years) and longer-term (≥10 years) use were associated with 45% and 56% lower colorectal cancer mortality, respectively, compared with never use (P_{trend} = .01) (Supplementary Table 6, available online). Stronger inverse associations for ever use were seen among women. First use at age 60 years or older was associated with lower colorectal cancer mortality. Similar inverse associations were observed in White participants (Supplementary Table 7, available online). Inverse associations were consistent when restricting to participants who had a sigmoidoscopy or colonoscopy (Supplementary Table 8, available online), for statins (Supplementary Table 1, available online), when accounting for access to and utilization of health care, in never smokers, and to participants with normal total cholesterol at the visit prior to the visit of first reported lipid-lowering drug use. However, ever use appeared to be associated with non-statistically significantly higher colorectal cancer mortality in never-smoking men (HR = 1.77, 95% CI = 0.60 to 5.25).

Ever use, duration of use, and age of first use were not statistically significantly associated with other site-specific cancer mortality, although most hazard ratios were in the inverse direction, except for ever use and longer-term use and bladder cancer in men, and first use at age younger than 60 years and breast cancer (Supplementary Table 6, available online).

Lipid-Lowering Drug Use and Cancer Incidence

First use at age 60 years or older was associated with lower total, obesity- and smoking-associated cancer incidence overall, by sex (Table 4), and by race (Table 5). Consistent inverse associations were observed for statins, when accounting for access to and utilization of health care, in never smokers, and in participants with normal total cholesterol at the visit prior to the visit of first-reported lipid-lowering drug use (Supplementary Tables 1-5, available online).

Ever use was associated with lower colorectal cancer incidence (HR = 0.69, 95% CI = 0.53 to 0.92), an association that was consistent by sex and by race (Supplementary Tables 6 and 7, available online). Shorter-term use and first use at age 60 years or older were associated with lower colorectal cancer incidence with similar inverse associations in men and women and in Black and White participants. Similar inverse associations were observed when restricting to participants who had a sigmoidoscopy or colonoscopy (Supplementary Table 8, available online), for statins (Supplementary Table 1, available online), accounting for access to and utilization of health care, in never smokers, and in participants with normal total cholesterol at the visit prior to the visit of first reported lipid-lowering drug use. Among male never smokers, ever use appeared to be associated with non-statistically significant higher colorectal cancer incidence (HR = 1.21, 95% CI = 0.61 to 2.43).

First use at age 60 years or older was associated with lower breast cancer incidence overall (HR = 0.58, 95% CI = 0.45 to 0.74) and by race and with prostate cancer incidence overall (HR = 0.68, 95% CI = 0.55 to 0.83) and by race (Supplementary Tables 6 and 7, available online). First use at age younger than 60 years was non-statistically significantly associated with higher lung cancer incidence in women (HR = 1.45, 95% CI = 0.86 to 2.43).

Ever use and duration of use were not statistically significantly associated with breast, lung, and prostate cancer incidence, although most hazard ratios were in the inverse direction except for ever use and shorter-term use with prostate cancer incidence in Black men and for ever use and shorter-term use with lung cancer incidence in women (Supplementary Tables 6 and 7, available online).

Ever use was associated with higher bladder cancer incidence among men, especially shorter-term use (HR = 1.67, 95% CI = 1.02 to 2.73) (Supplementary Table 6, available online). Consistent patterns of a positive association with bladder cancer incidence in men were observed for statin use (Supplementary Table 1, available online) and when accounting for access to and utilization of health care. Positive associations for ever use were possibly stronger in never-smoking men (HR = 1.94, 95% CI = 0.63 to 6.05) and in men with normal total cholesterol at the visit prior to the visit of first reported lipid-lowering drug use (HR = 2.61, 95% CI = 1.37 to 5.00).

Discussion

In this prospective study of lipid-lowering drug use, we found that ever use, longer-term use, and first use at age 60 years or older were consistently associated with a lower risk of death from total, obesity- and smoking-associated, and most site-specific cancers. For incidence, associations were consistently inverse for first use at age 60 years or older. In general, these findings were consistent for statin use; 71% of lipid-lowering drug users were using a statin by visit 4, representing 80% of the person-time of lipid-lowering drug use. Our findings were not explained by differences in access to and utilization of health care or for colorectal cancer by receiving endoscopic screening or by total cholesterol level prior to starting lipid-lowering drugs.

The ARIC study is an ideal cohort for investigating the association between lipid-lowering drug use and cancer incidence and mortality: follow-up is over 25 years and repeated measures of medication use, total cholesterol and glucose, and anthropometric characteristics were measured by trained study personnel. Thus, we were able to investigate multiple measures—ever, cumulative use (duration of use), and timing of use (age of first use)—in relation to cancer incidence and mortality. Because of ARIC's long follow-up, we were able to focus on a 10-year duration of use intervals. Assessing longer duration of use of medications may inform these drugs as potential cancer chemopreventive agents. For example, the association between longer-term use of aspirin and colorectal cancer (12) suggests

Table 1. Age- and race-adjusted characteristics of ever lipid-lowering drug users and never users overall and by sex in ARIC at visit 4 (1996-1999)[a]

Participant characteristics	Overall		Men		Women	
	Ever user	Never user	Ever user	Never user	Ever user	Never user
Total No.	1728	8858	857	3892	871	4966
Race, %						
Black	16.8	25.1	12.5	21.1	21.1	28.3
White	83.2	74.9	87.5	78.9	78.9	71.7
Mean age (95% CI), y	63.8 (63.6 to 64.1)	62.4 (62.3 to 62.6)	63.6 (63.4 to 63.9)	63.1 (63.0 to 63.3)	62.7 (62.6 to 62.8)	62.2 (62.0 to 62.3)
Education, % (95% CI)						
Less than high school	20.1 (18.3 to 21.9)	19.6 (18.8 to 20.4)	19.1 (17.6 to 20.6)	19.9 (18.9 to 20.8)	20.5 (19.7 to 21.2)	19.5 (18.5 to 20.5)
High school graduate, vocational school, some college	43.3 (41.0 to 45.6)	41.4 (40.4 to 42.4)	35.8 (33.9 to 37.7)	38.3 (37.1 to 39.6)	42.1 (41.2 to 43.1)	45.2 (43.9 to 46.5)
College graduate, some graduate school, graduate degree	36.6 (34.4 to 38.9)	39.0 (38.0 to 40.0)	45.1 (43.2 to 47.0)	41.8 (40.6 to 43.0)	37.4 (40.6 to 43.0)	35.2 (33.9 to 36.5)
Mean BMI (95% CI), kg/m^2	29.2 (29.0 to 29.5)	28.8 (28.7 to 28.9)	28.3 (28.1 to 28.5)	28.7 (28.5 to 28.8)	28.7 (28.6 to 28.8)	29.1 (29.0 to 29.3)
Smoking status, % (95% CI)						
Never smoker	39.2 (36.9 to 41.5)	41.9 (40.9 to 42.9)	19.6 (17.7 to 21.4)	30.9 (29.7 to 32.1)	42.4 (41.4 to 43.3)	53.4 (52.1 to 54.6)
Former smoker	48.2 (45.9 to 50.5)	42.7 (41.7 to 43.7)	64.3 (62.5 to 66.2)	53.4 (52.2 to 54.6)	43.6 (42.6 to 44.5)	32.4 (31.1 to 33.7)
Current smoker	12.5 (10.8 to 14.2)	15.4 (14.6 to 16.1)	16.0 (14.6 to 17.4)	15.6 (14.8 to 16.5)	14.0 (13.3 to 14.7)	14.2 (13.3 to 15.2)
Drinking status, % (95% CI)						
Nondrinker	22.2 (20.3 to 24.0)	20.8 (20.0 to 21.6)	5.4 (3.9 to 6.9)	13.8 (12.8 to 14.8)	22.0 (21.3 to 22.8)	29.2 (28.2 to 30.3)
Former drinker	30.0 (27.8 to 32.1)	29.8 (28.8 to 30.7)	32.7 (30.9 to 34.5)	31.5 (30.3 to 32.6	29.8 (28.9 to 30.7	28.0 (26.8 to 29.2)
Current drinker	47.9 (45.6 to 50.1	49.4 (48.4 to 50.4	61.9 (60.0 to 63.8	54.7 (53.5 to 55.	48.2 (47.2 to 49.1	42.8 (41.5 to 44.0)
Diabetes status, % (95% CI)						
No diabetes	38.1 (35.8 to 40.5)	48.3 (47.3 to 49.4)	32.0 (30.1 to 33.9)	39.2 (37.9 to 40.4)	47.2 (46.3 to 48.2)	55.0 (53.7 to 56.3)
At-risk for diabetes	36.3 (34.1 to 38.6)	35.8 (34.8 to 36.8)	46.7 (44.8 to 48.6)	41.1 (39.9 to 42.3)	35.5 (34.6 to 36.4)	30.0 (34.6 to 36.4)
Undiagnosed diabetes	5.0 (4.0 to 6.0)	5.0 (4.5 to 5.4)	6.1 (5.3 to 7.0)	5.6 (5.0 to 6.1)	4.9 (4.5 to 5.4)	4.3 (3.7 to 4.9)
Diagnosed diabetes	20.0 (18.5 to 21.5)	9.9 (9.2 to 10.5)	14.2 (13.0 to 15.5)	13.1 (12.3 to 13.9)	11.5 (10.9 to 12.1	9.9 (9.0 to 10.7)
Mean total cholesterol (95% CI), mmol/L	5.24 (5.2 to 5.2)	5.18 (5.2 to 5.2)	4.88 (4.8 to 4.9)	5.04 (5.0 to 5.1)	5.21 (5.2 to 5.2)	5.37 (5.3 to 5.4)
Aspirin use, % (95% CI)	91.0 (89.2 to 92.8)	80.1 (79.3 to 80.9)	81.3 (79.8 to 82.8)	81.4 (80.4 to 82.3)	82.3(81.6 to 83.1)	82.4 (81.4 to 83.4)
Statin use, % (95% CI)	70.8 (69.9 to 71.6)	–	70.2 (67.2 to 73.3)	–	71.3 (68.3 to 74.3)	–
HRT use, % (95% CI)	–	–	–	–	39.8 (36.7 to 43.0)	41.9 (40.6 to 43.3)

[a]ARIC = Atherosclerosis Risk in Communities ; BMI = body mass index; CI = confidence interval; HRT = hormone replacement therapy.

Table 2. Association of lipid-lowering medication use with total, obesity-associated and smoking-associated cancer mortality in ARIC (1990-2015)

	Overall			Women			Men		
Model[a]	Cases	Person-time	HR (95% CI)	Cases	Person-time	HR (95% CI)	Cases	Person-time	HR (95% CI)
Total cancer									
Use									
Never user	1153	200 548	1 (Referent)	508	115 539	1 (Referent)	645	85 009	1 (Referent)
Ever user	508	66 925	0.81 (0.72 to 0.91)	229	36 344	0.85 (0.71 to 1.01)	279	30 581	0.77 (0.66 to 0.91)
$P_{interaction}$[b]			–			.32			–
Duration of use									
Never user	1153	200 548	1 (Referent)	508	115 539	1 (Referent)	645	85 009	1 (Referent)
<10 years	343	41 106	0.87 (0.75 to 1.00)	155	22 926	0.88 (0.72 to 1.09)	188	18 180	0.84 (0.69 to 1.01)
≥10 years	165	25 818	0.73 (0.61 to 0.86)	74	13 418	0.79 (0.61 to 1.01)	91	12 401	0.68 (0.54 to 0.86)
P_{trend}[c]			<.001			.06			.001
$P_{interaction}$[b]			–			.31			–
Age of first use									
Never user	1153	200 549	1 (Referent)	508	115 540	1 (Referent)	645	85 009	1 (Referent)
<60 y	88	16 836	0.90 (0.72 to 1.13)	47	8174	1.20 (0.88 to 1.64)	41	8662	0.71 (0.51 to 0.98)
≥60 y	411	48 309	0.80 (0.70 to 0.91)	178	27 101	0.78 (0.64 to 0.95)	233	21 208	0.80 (0.67 to 0.95)
P_{trend}[c]			<.001			.02			.008
$P_{interaction}$[b]			–			.72			–
Obesity-related cancers[d]									
Use									
Never user	691	200 548	1 (Referent)	281	115 539	1 (Referent)	410	85 009	1 (Referent)
Ever user	298	66 925	0.81 (0.69 to 0.94)	119	36 344	0.78 (0.61 to 0.99)	179	30 581	0.82 (0.66 to 1.00)
$P_{interaction}$[b]			–			.96			–
Duration of use									
Never user	691	200 548	1 (Referent)	281	115 539	1 (Referent)	410	85 009	1 (Referent)
<10 y	199	41 106	0.86 (0.71 to 1.03)	78	22 926	0.78 (0.59 to 1.04)	121	18 180	0.89 (0.70 to 1.14)
≥10 y	99	25 818	0.74 (0.59 to 0.92)	41	13 418	0.77 (0.55 to 1.07)	58	12 401	0.72 (0.54 to 0.96)
P_{trend}[c]			.007			.11			.02
$P_{interaction}$[b]			–			.78			–
Age of first use									
Never user	691	200 549	1 (Referent)	281	115 540	1 (Referent)	410	85 009	1 (Referent)
<60 y	48	16 836	0.82 (0.60 to 1.11)	23	8174	1.06 (0.69 to 1.65)	25	8662	0.67 (0.44 to 1.02)
≥60 y	244	48 309	0.80 (0.67 to 0.95)	93	27 101	0.71 (0.54 to 0.92)	151	21 208	0.85 (0.68 to 1.06)
P_{trend}[c]			.007			.01			.10
$P_{interaction}$[b]			–			.62			–
Smoking-related cancers[e]									
Use									
Never user	671	200 548	1 (Referent)	261	115 539	1 (Referent)	410	85 009	1 (Referent)
Ever user	292	66 925	0.81 (0.69 to 0.95)	113	36 344	0.77 (0.60 to 0.99)	179	30 581	0.82 (0.66 to 1.00)
$P_{interaction}$[b]			–			.84			–
Duration of use									
Never user	671	200 548	1 (Referent)	261	115 539	1 (Referent)	410	85 009	1 (Referent)
<10 y	194	41 106	0.85 (0.71 to 1.03)	73	22 926	0.77 (0.57 to 1.03)	121	18 180	0.89 (0.70 to 1.14)
≥10 y	98	25 818	0.75 (0.60 to 0.93)	40	13 418	0.79 (0.56 to 1.11)	58	12 401	0.72 (0.54 to 0.96)
P_{trend}[c]			.01			.16			.02
$P_{interaction}$[b]			–			.63			–
Age of first use									
Never user	671	200 549	1 (Referent)	261	115 540	1 (Referent)	410	85 009	1 (Referent)
<60 y	46	16 836	0.80 (0.59 to 1.09)	21	8174	1.04 (0.66 to 1.64)	25	8662	0.67 (0.44 to 1.02)
≥60 y	240	48 309	0.80 (0.68 to 0.95)	89	27 101	0.71 (0.55 to 0.94)	151	21 208	0.85 (0.68 to 1.06)
P_{trend}[c]			.009			.02			.10
$P_{interaction}$[b]			–			.75			–

[a]All models are adjusted for visit 2 age, sex, joint terms for field center, and race (Black from Jackson, Mississippi; Black from any of the other field centers; White from Forsyth County or Washington County [reference is White from Minneapolis]), education level, body mass index, diabetes status (diagnosed diabetes, undiagnosed diabetes, at risk for diabetes [reference is normal]), aspirin use, smoking status and pack-years, drinking status, and family history of any cancer. ARIC = Atherosclerosis Risk in Communities; CI = confidence interval; HR = hazard ratio.

[b]The 2-sided likelihood ratio test was used to test interaction between lipid-lowering drug use and sex (female, male).

[c]The 2-sided Wald test was used to test for trend across categories of lipid-lowering drug use.

[d]Obesity-related cancers include oropharynx cancer, esophagus cancer, lung and bronchus cancer, postmenopausal breast cancer, liver cancer, gallbladder cancer, pancreas cancer, kidney cancer, stomach cancer, colorectal cancer, endometrial cancer, and ovarian cancer.

[e]Smoking-related cancers include oropharynx cancer, esophagus cancer, lung and bronchus cancer, bladder cancer, liver cancer, pancreatic cancer, stomach cancer, and kidney and other urinary cancer.

Table 3. Association of lipid-lowering medication use with total, obesity-associated and smoking-associated cancer mortality by race in ARIC (1990-2015)

	Black			White		
Model[a]	Cases	Person -time	HR (95% CI)	Cases	Person-time	HR (95% CI)
Total cancer						
Use						
Never user	344	52 727	1 (Referent)	809	147 821	1 (Referent)
Ever user	90	13 484	0.65 (0.50 to 0.84)	418	53 441	0.86 (0.75 to 0.98)
$P_{interaction}$[b]			.03			–
Duration of use						
Never user	344	52 727	1 (Referent)	809	147 821	1 (Referent)
<10 y	69	9386	0.67 (0.50 to 0.91)	274	31 721	0.94 (0.80 to 1.10)
≥10 y	21	4098	0.58 (0.37 to 0.92)	144	21720	0.76 (0.63 to 0.91)
P_{trend}[c]			.009			.003
$P_{interaction}$[b]			.04			–
Age of first use						
Never user	344	52728	1 (Referent)	809	147 821	1 (Referent)
<60 y	15	2952	0.80 (0.47 to 1.36)	73	13 884	0.94 (0.73 to 1.20)
≥60 y	75	10 284	0.63 (0.47 to 0.83)	336	38 026	0.85 (0.73 to 0.98)
P_{trend}[c]			.001			.03
$P_{interaction}$[b]			.03			–
Obesity-related cancers[d]						
Use						
Never user	204	52 727	1 (Referent)	487	14 7821	1 (Referent)
Ever user	48	13 484	0.59 (0.41 to 0.84)	250	53 441	0.87 (0.73 to 1.03)
$P_{interaction}$[b]			.06			–
Duration of use						
Never user	204	52 727	1 (Referent)	487	147 821	1 (Referent)
<10 y	35	9386	0.57 (0.38 to 0.86)	164	31 721	0.95 (0.77 to 1.17)
≥10 y	13	4098	0.64 (0.36 to 1.13)	86	21 720	0.77 (0.60 to 0.97)
P_{trend}[c]			.06			.02
$P_{interaction}$[b]			.11			–
Age of first use						
Never user	204	52 728	1 (Referent)	487	147 821	1 (Referent)
<60 y	9	2952	0.86 (0.43 to 1.69)	39	13 884	0.82 (0.58 to 1.14)
≥60 y	39	10 284	0.54 (0.36 to 0.79)	205	38 026	0.87 (0.72 to 1.05)
P_{trend}[c]			.002			.12
$P_{interaction}$[b]			.04			–
Smoking-related cancers[e]						
Use						
Never user	198	52 727	1 (Referent)	473	147 821	1 (Referent)
Ever user	47	13 484	0.58 (0.41 to 0.84)	245	53 441	0.87 (0.73 to 1.04)
$P_{interaction}$[b]			.07			–
Duration of use						
Never user	198	52 727	1 (Referent)	473	147 821	1 (Referent)
<10 y	34	9386	0.56 (0.37 to 0.85)	160	31 721	0.94 (0.77 to 1.17)
≥10 y	13	4098	0.65 (0.37 to 1.15)	85	21 720	0.78 (0.61 to 0.99)
P_{trend}[c]			.07			.04
$P_{interaction}$[b]			.14			–
Age of first use						
Never user	198	52 728	1 (Referent)	473	147 821	1 (Referent)
<60 y	9	2952	0.88 (0.44 to 1.74)	37	13 884	0.79 (0.56 to 1.12)
≥60 y	38	10 284	0.53 (0.36 to 0.79)	202	38 026	0.88 (0.72 to 1.06)
P_{trend}[c]			.002			.15
$P_{interaction}$[b]			.05			–

[a]All models are adjusted for visit 2 age, sex, field center (Black from Jackson, Mississippi; any of the other field center [reference], and White from Forsyth County and Washington County, Minnesota [reference]), education level, body mass index, diabetes status (diagnosed diabetes, undiagnosed diabetes, at risk for diabetes [reference is normal]), aspirin use, smoking status and pack-years, drinking status, and family history of any cancer. ARIC = Atherosclerosis Risk in Communities; CI = confidence interval; HR = hazard ratio; Ref = referent.

[b]The 2-sided likelihood ratio test was used to test for interaction between lipid-lowering drug use and race (Black, White) in models that included a term for race (Black, White) but did not include joint terms for race and field center, which were adjusted for in the race-specific analyses.

[c]The 2-sided Wald test was used to test for trend across categories of lipid-lowering drug use.

[d]Smoking-related cancers include oropharynx cancer, esophagus cancer, lung and bronchus cancer, bladder cancer, liver cancer, pancreatic cancer, stomach cancer, and kidney and other urinary cancer.

[e]Obesity-related cancers include oropharynx cancer, esophagus cancer, lung and bronchus cancer, postmenopausal breast cancer, liver cancer, gallbladder cancer, pancreas cancer, kidney cancer, stomach cancer, colorectal cancer, endometrial cancer, and ovarian cancer.

Table 4. Association of lipid-lowering medication use with total, obesity-associated and smoking-associated cancer incidence in ARIC (1990-2015)

	Overall			Women			Men		
Model[a]	Cases	Person-time	HR (95% CI)	Cases	Person-time	HR (95% CI)	Cases	Person-time	HR (95% CI)
Total cancer									
Use									
Never user	2780	181 739	1 (Referent)	1269	106 167	1 (Referent)	1511	75 572	1 (Referent)
Ever user	1089	56 260	1.02 (0.94 to 1.10)	494	31 693	0.99 (0.88 to 1.11)	595	24 568	1.05 (0.94 to 1.17)
$P_{interaction}$[b]			–			.66			–
Duration of use									
Never user	2780	181 739	1 (Referent)	1269	106 167	1 (Referent)	1511	75 572	1 (Referent)
<10 y	689	34 219	1.11 (1.01 to 1.23)	318	19 835	1.05 (0.91 to 1.21)	371	14 384	1.17 (1.02 to 1.34)
≥10 y	400	22 041	0.91 (0.82 to 1.02)	176	11 858	0.91 (0.78 to 1.08)	224	10 183	0.92 (0.80 to 1.07)
P_{trend}[c]			.10			.29			.28
$P_{interaction}$[b]			–			.60			–
Age of first use									
Never user	2780	18 8054	1 (Referent)	1269	109 136	1 (Referent)	1511	78 918	1 (Referent)
<60 y	244	15 360	0.93 (0.81 to 1.06)	105	7589	0.98 (0.80 to 1.20)	139	7771	0.91 (0.76 to 1.09)
≥60 y	821	40 850	0.73 (0.67 to 0.80)	377	23 738	0.71 (0.62 to 0.80)	444	17 112	0.75 (0.67 to 0.85)
P_{trend}[c]			<.001			<.001			<.001
$P_{interaction}$[b]			–			.82			–
Obesity-related cancers[d]									
Use									
Never user	1638	189 165	1 (Referent)	996	107 551	1 (Referent)	642	81 614	1 (Referent)
Ever user	646	61 105	0.98 (0.88 to 1.09)	385	32 455	1.01 (0.89 to 1.16)	261	28 650	0.95 (0.80 to 1.12)
$P_{interaction}$[b]			–			.63			–
Duration of use									
Never user	1638	189 165	1 (Referent)	996	107 551	1 (Referent)	642	81 614	1 (Referent)
<10 y	414	37 346	1.07 (0.94 to 1.21)	250	20 321	1.09 (0.93 to 1.29)	164	17 025	1.03 (0.84 to 1.26)
≥10 y	232	23 759	0.88 (0.77 to 1.02)	135	12 134	0.92 (0.76 to 1.11)	97	11 625	0.86 (0.69 to 1.08)
P_{trend}[c]			.09			.40			.19
$P_{interaction}$[b]			–			.66			–
Age of first use									
Never user	1638	192 659	1 (Referent)	996	110 006	1 (Referent)	642	82 652	1 (Referent)
<60 y	143	16 023	0.92 (0.77 to 1.10)	86	7678	1.01 (0.81 to 1.27)	57	8346	0.86 (0.65 to 1.14)
≥60 y	486	44 236	0.72 (0.64 to 0.81)	287	24 275	0.70 (0.61 to 0.81)	199	19 961	0.75 (0.62 to 0.90)
P_{trend}[c]			<.001			<.001			.002
$P_{interaction}$[b]			–			.98			–
Smoking-related cancers[e]									
Use									
Never user	1092	193 827	1 (Referent)	456	112 153	1 (Referent)	636	81 674	1 (Referent)
Ever user	458	63351	0.98 (0.86 to 1.11)	201	34 681	1.02 (0.84 to 1.23)	257	28 671	0.94 (0.79 to 1.11)
$P_{interaction}$[b]			–			.22			–
Duration of use									
Never user	1092	193 827	1 (Referent)	456	112 153	1 (Referent)	636	81 674	1 (Referent)
<10 y	285	38 911	1.01 (0.87 to 1.18)	124	21 879	0.99 (0.79 to 1.25)	161	17 032	1.01 (0.82 to 1.24)
≥10 y	173	24 440	0.93 (0.79 to 1.10)	77	12 802	1.05 (0.82 to 1.35)	96	11 638	0.85 (0.68 to 1.07)
P_{trend}[c]			.42			.71			.17
$P_{interaction}$[b]			–			.16			–
Age of first use									
Never user	1092	195 639	1 (Referent)	456	112 934	1 (Referent)	636	82 705	1 (Referent)
<60 y	97	16 291	0.92 (0.74 to 1.14)	42	7932	1.09 (0.79 to 1.51)	55	8358	0.83 (0.63 to 1.11)
≥60 y	347	45 906	0.74 (0.65 to 0.85)	150	25 939	0.73 (0.59 to 0.89)	197	19 966	0.74 (0.62 to 0.89)
P_{trend}[c]			<.001			.004			.001
$P_{interaction}$[b]			–			.54			–

[a]All models are adjusted for visit 2 age, sex, joint terms for field center and race (Black from Jackson, Mississippi; Black from any of the other field centers; White from Forsyth County or Washington County [reference is White from Minneapolis]), education level, body mass index, diabetes status (diagnosed diabetes, undiagnosed diabetes, at risk for diabetes [reference is normal]), aspirin use, smoking status and pack-years, drinking status, and family history of any cancer. ARIC = Atherosclerosis Risk in Communities; CI = confidence interval; HR = hazard ratio.

[b]The 2-sided likelihood ratio test was used to test interaction between lipid-lowering drug use and sex (female, male).

[c]The 2-sided Wald test was used to test for trend across categories of lipid-lowering drug use.

[d]Smoking-related cancers include oropharynx cancer, esophagus cancer, lung and bronchus cancer, bladder cancer, liver cancer, pancreatic cancer, stomach cancer, and kidney and other urinary cancer.

[e]Obesity-related cancers include oropharynx cancer, esophagus cancer, lung and bronchus cancer, postmenopausal breast cancer, liver cancer, gallbladder cancer, pancreas cancer, kidney cancer, stomach cancer, colorectal cancer, endometrial cancer, and ovarian cancer.

Table 5. Association of lipid-lowering medication use with total, obesity-associated and smoking-associated cancer incidence by race in ARIC (1990-2015)

	Black			White		
Model[a]	Cases	Person-time	HR (95% CI)	Cases	Person-time	HR (95% CI)
Total cancer						
Use						
Never user	767	48 186	1 (Referent)	2013	133 553	1 (Referent)
Ever user	194	11 334	0.91 (0.75 to 1.09)	895	44 926	1.05 (0.96 to 1.15)
$P_{interaction}$[b]			.09			–
Duration of use						
Never user	767	48 186	1 (Referent)	2013	133 553	1 (Referent)
<10 y	132	7936	0.89 (0.71 to 1.11)	557	26 283	1.18 (1.06 to 1.32)
≥10 y	62	3398	0.94 (0.72 to 1.22)	338	18 643	0.91 (0.81 to 1.03)
P_{trend}[c]			.55			.13
$P_{interaction}$[b]			.25			–
Age of first use						
Never user	767	49 919	1 (Referent)	2013	138 135	1 (Referent)
<60 y	45	2664	1.00 (0.73 to 1.35)	199	12 696	0.92 (0.79 to 1.07)
≥60 y	149	8711	0.64 (0.52 to 0.78)	672	32 139	0.76 (0.69 to 0.84)
P_{trend}[c]			<.001			<.001
$P_{interaction}$[b]			.05			–
Obesity-related cancers[d]						
Use						
Never user	435	50 304	1 (Referent)	1203	138 861	1 (Referent)
Ever user	115	12 412	0.83 (0.65 to 1.05)	531	48 693	1.02 (0.91 to 1.15)
$P_{interaction}$[b]			.26			–
Duration of use						
Never user	435	50 304	1 (Referent)	1203	138 861	1 (Referent)
<10 y	84	8655	0.86 (0.65 to 1.13)	330	28 691	1.13 (0.98 to 1.31)
≥10 y	31	3756	0.77 (0.53 to 1.12)	201	20 003	0.91 (0.78 to 1.06)
P_{trend}[c]			.14			.23
$P_{interaction}$[b]			.26			–
Age of first use						
Never user	435	51 190	1 (Referent)	1203	141 469	1 (Referent)
<60 y	22	2826	0.90 (0.58 to 1.39)	121	13 197	0.93 (0.76 to 1.13)
≥60 y	93	9481	0.62 (0.48 to 0.80)	393	34 755	0.75 (0.66 to 0.85)
P_{trend}[c]			<.001			<.001
$P_{interaction}$[b]			.29			–
Smoking-related cancers[e]						
Use						
Never user	296	51323	1 (Referent)	796	142 504	1 (Referent)
Ever user	78	12 769	0.78 (0.59 to 1.05)	380	50 582	1.03 (0.89 to 1.18)
$P_{interaction}$[b]			.37			–
Duration of use						
Never user	296	51 323	1 (Referent)	796	142 504	1 (Referent)
<10 y	57	8926	0.80 (0.57 to 1.11)	228	29 985	1.08 (0.91 to 1.28)
≥10 y	21	3844	0.76 (0.49 to 1.20)	152	20 597	0.98 (0.81 to 1.17)
P_{trend}[c]			.19			.77
$P_{interaction}$[b]			.36			–
Age of first use						
Never user	296	51761	1 (Referent)	796	143 878	1 (Referent)
<60 y	15	2856	0.88 (0.52 to 1.49)	82	13 435	0.94 (0.74 to 1.19)
≥60 y	63	9760	0.61 (0.44 to 0.83)	284	36 146	0.77 (0.66 to 0.90)
P_{trend}[c]			.002			.001
$P_{interaction}$[b]			.37			–

[a]All models are adjusted for visit 2 age, sex, field center (Black from Jackson, Mississippi; any of the other field center [reference]; and White from Forsyth County and Washington County, Minnesota [reference]), education level, body mass index, diabetes status (diagnosed diabetes, undiagnosed diabetes, at risk for diabetes [reference is normal]), aspirin use, smoking status and pack years, drinking status, and family history of any cancer. ARIC = Atherosclerosis Risk in Communities; CI = confidence interval; HR = hazard ratio.

[b]The 2-sided likelihood ratio test was used to test interaction between lipid-lowering drug use and race (Black, White) in models that included a term for race (Black, White) but not joint terms for race and field center.

[c]The 2-sided Wald test was used to test for trend across categories of lipid-lowering drug use.

[d]Smoking-related cancers include oropharynx cancer, esophagus cancer, lung and bronchus cancer, bladder cancer, liver cancer, pancreatic cancer, stomach cancer, and kidney and other urinary cancer.

[e]Obesity-related cancers include oropharynx cancer, esophagus cancer, lung and bronchus cancer, postmenopausal breast cancer, liver cancer, gallbladder cancer, pancreas cancer, kidney cancer, stomach cancer, colorectal cancer, endometrial cancer, and ovarian cancer.

the need to continue taking aspirin for long periods of time to benefit.

We classified participants according to their age when they first started taking lipid-lowering drugs (younger than 60 years, 60 years and older). This approach was intended to approximate the timing of first use relative to the natural history of cancer development (eg, after adenoma formation, before early invasive colorectal cancer). We used age as the time origin in stratified Cox models based on birth cohort (5-year intervals) described by Korn et al. (13) to account for period effects of lipid-lowering drug use and baseline hazards. This statistical approach helps overcome differences in overall health between participants initiating medication use at younger ages (eg, younger than 60 years) who may have worse overall health compared with participants initiating medication use at older ages (eg, 60 years and older). However, age may not perfectly align with the natural history of cancer development as some cancers may be more aggressive earlier in the natural history, which may occur at any age.

Whereas the null association we observed between ever use of lipid-lowering drugs and cancer incidence is consistent with a meta-analysis of randomized trials of statins and cardiovascular disease outcomes, which found a null association between statins (compared with placebo) with cancer incidence (7), the inverse associations we observed for ever use and cancer mortality and for age of first use at ages 60 years or older and cancer incidence are not consistent with those trials, including those conducted in older adults (14). In these trials, the mean duration of statin use was 4.8 years (7), In our study, inverse associations were more apparent with longer-term use. Although we took into account factors that may confound the association, our study was observational, and we cannot rule out biases that may have been precluded in the trials, albeit cancer was not a primary outcome.

The epidemiologic evidence on statin use and site-specific cancer outcomes has largely focused on incident cancer with little published data on the association with cancer mortality (6,8,15-18). For colorectal cancer mortality, our results are consistent with a registry-based study from Japan (HR = 0.71, 95% CI = 0.46 to 1.08), although that analysis was restricted to individuals with hyperlipidemia (19). The positive association for bladder cancer incidence in men in the current analysis is consistent with findings from a meta-analysis of 5 cohort studies with a suggestive positive association (summary odds ration [OR] = 1.11, 95% CI = 0.91 to 1.35; I^2 = 84%) (18). In a case-control study with a majority of male cases (86%) and controls (84%) with a high proportion of former smokers (cases: 45%; controls: 43%), a positive association with bladder cancer was observed in participants taking statins for 5 years or longer (OR = 1.91, 95% CI = 1.09 to 3.35), and a suggestive positive association was observed among participants aged younger than 60 years at first use of a statin (OR = 1.83, 95% CI = 0.98 to 3.40) (20); our findings are consistent with those for bladder cancer incidence in men. We are not aware of other prospective studies that have addressed statins and bladder cancer mortality in men and women without cancer at baseline.

Excluding prevalent lipid-lowering drug users at visit 2, and with follow-up through 2015, suggestive inverse associations of ever use and duration of use with prostate cancer incidence and mortality observed in the current study remain consistent with our prior ARIC study with follow-up through 2012 that did not exclude prevalent users at visit 2 (9) and with a meta-analysis (8). The inverse association with first use at age 60 years or older and total prostate cancer incidence is a new finding that was not considered in the prior ARIC study (9).

Our findings that lipid-lowering drug use was not associated with lung cancer incidence overall and in men are consistent with a meta-analysis of 7 cohort studies (summary OR = 0.94, 95% CI = 0.82 to 1.07; I^2 = 88%) (17). Ever use and shorter-term use appeared to be associated with higher risk of lung cancer incidence in women, consistent with the findings of a single study included in the meta-analysis restricted to women only (17). We observed a null association between lipid-lowering drug use and breast cancer incidence, consistent with results of a meta-analysis of 11 cohort studies (summary relative risk [RR] = 1.00, 95% CI = 0.96 to 1.05; I^2 = 73%) (15).

We focused on lipid-lowering drugs, not solely statins, because our overarching hypothesis is that cholesterol lowering is the explanatory mechanism. When we considered statins, associations were generally comparable. Although there is compelling biological rationale for the role of lipid-lowering drugs and cancer development and progression, including that altered cholesterol levels affect cell signaling and proliferation, as well as inflammation (3–5), the exact mechanism(s) remains uncertain.

There are several important strengths in our analysis, including the prospective design with over 25 years of follow-up in men and women in the statin era; adjudicated cancer incidence and mortality outcomes; updated information on lipid-lowering drug use, which allowed us to determine duration of use and age of first use; and ability to investigate associations in Black participants. We used time-updated information to control for potential confounders, including diabetes and hyperglycemia in participants without diabetes. We took into account access to and use of health care, including routine physical examination and having a sigmoidoscopy or colonoscopy, and updated measures of total cholesterol to account for potential detection bias.

The main limitation of this study is the overall sample size preventing reporting results for site-specific cancer mortality with less than 6 deaths in any 1 stratum, evaluation of specific types (eg, simvastatin) and classes of statins (lipophilic, hydrophilic), types of nonstatin lipid-lowering drugs, dose, or brief durations of use. We focused on 2 age groups younger than 60 years and 60 years and older for when participants first started taking lipid-lowering drugs, which may not have aligned with the unobserved natural history of cancer development in any given participant. Further, the number of participants first using lipid-lowering drugs before age 60 years was small, resulting in wide confidence intervals and greater uncertainty in the potential benefit with earlier use compared with later use. Although we cannot fully rule out residual confounding, we adjusted for potential confounders including aspirin (often taken by those with the same cardiovascular indications as lipid-lowering drug users) and restricted subanalyses to never smokers and to participants with normal total cholesterol prior to initiating lipid-lowering drug use.

In summary, this study provides additional evidence in support of the inverse association between lipid-lowering drugs and total, obesity- and smoking-associated cancer, especially when starting at age 60 years or older, and in particular, colorectal cancer incidence and mortality, but lipid-lowering drugs may be associated with increased bladder cancer risk in men. These findings require confirmation in other studies. Although our results suggest lipid-lowering drug use at age 60 years and older may contribute to cancer prevention overall, potential benefits for earlier use remains uncertain. Research is needed to evaluate

the potential impact of chemoprevention strategies including lipid-lowering drugs on population-level cancer burden.

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Data Availability

The data underlying this article cannot be shared publicly because of a Maryland law governing sharing of line listed Maryland Cancer Registry Data. ARIC data may be accessed upon request to the ARIC Publications Committee. This may include execution of data use agreements and Maryland Cancer Registry confidentiality forms. Alternatively, ARIC data can be requested via BioLINCC (https://biolincc.nhlbi.nih.gov/studies/aric/), a controlled access database .

References

1. Kantor ED, Rehm CD, Haas JS, Chan AT, Giovannucci EL. Trends in prescription drug use among adults in the United States from 1999-2012. *JAMA*. 2015;314(17):1818–1831.
2. Salami JA, Warraich H, Valero-Elizondo J, et al. National trends in statin use and expenditures in the US adult population from 2002 to 2013: insights from the medical expenditure panel survey. *JAMA Cardiol*. 2017;2(1):56–65.
3. Pisanti S, Picardi P, Ciaglia E, D'Alessandro A, Bifulco M. Novel prospects of statins as therapeutic agents in cancer. *Pharmacol Res*. 2014;88:84–98.
4. Mullen PJ, Yu R, Longo J, Archer MC, Penn LZ. The interplay between cell signalling and the mevalonate pathway in cancer. *Nat Rev Cancer*. 2016;16(11):718–731.
5. Solomon KR, Freeman MR. Do the cholesterol-lowering properties of statins affect cancer risk? *Trends Endocrinol Metab*. 2008;19(4):113–121.
6. Bonovas S. Statins: Do they have a potential role in cancer prevention and modifying cancer-related outcomes? *Drugs*. 2014;74(16):1841–1848.
7. Emberson JR, Kearney PM, Blackwell L, et al. Lack of effect of lowering LDL cholesterol on cancer: meta-analysis of individual data from 175,000 people in 27 randomised trials of statin therapy. *PLoS One*. 2012;7(1):e29849.
8. Bansal D, Undela K, D'Cruz S, Schifano F. Statin use and risk of prostate cancer: a meta-analysis of observational studies. *PLoS One*. 2012;7(10):e46691.
9. Mondul AM, Joshu CE, Barber JR, et al. 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*. 2018;11(12):779–788.
10. Bhaskara S, Whitsel EA, Ballantyne CM, Folsom AR. Validity of self-report of lipid medication use: the Atherosclerosis Risk in Communities (ARIC) study. *Atherosclerosis*. 2015;242(2):625–629.
11. Joshu CE, Barber JR, Coresh J, et al. Enhancing the infrastructure of the Atherosclerosis Risk in Communities (ARIC) Study for Cancer Epidemiology Research: ARIC Cancer. *Cancer Epidemiol Biomarkers Prev*. 2018;27(3):295–305.
12. Chan AT, Giovannucci EL, Meyerhardt JA, Schernhammer ES, Curhan GC, Fuchs CS. Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. *JAMA*. 2005;294(8):914–923.
13. Korn EL, Graubard BI, Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. *Am J Epidemiol*. 1997;145(1):72–80.
14. Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. *Lancet*. 2019;393(10170):407–415.
15. Islam MM, Yang HC, Nguyen PA, et al. Exploring association between statin use and breast cancer risk: an updated meta-analysis. *Arch Gynecol Obstet*. 2017;296(6):1043–1053.
16. Lytras T, Nikolopoulos G, Bonovas S. Statins and the risk of colorectal cancer: an updated systematic review and meta-analysis of 40 studies. *World J Gastroenterol*. 2014;20(7):1858–1870.
17. Tan M, Song X, Zhang G, et al. Statins and the risk of lung cancer: a meta-analysis. *PloS One*. 2013;8(2):e57349.
18. Song M, Zhang X, Wu K, et al. Plasma adiponectin and soluble leptin receptor and risk of colorectal cancer: a prospective study. *Cancer Prev Res (Phila)*. 2013;6(9):875–885.
19. Yokomichi H, Nagai A, Hirata M, et al.; for the BioBank Japan Cooperative Hospital Group. Statin use and all-cause and cancer mortality: BioBank Japan cohort. *J Epidemiol*. 2017;27(3s):S84–s91.
20. Guercio V, Turati F, Bosetti C, et al. Bladder cancer risk in users of selected drugs for cardiovascular disease prevention. *Eur J Cancer Prev*. 2019;28(2):76–80.