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Baseline and On-Treatment High-Density Lipoprotein Cholesterol and the Risk of Cancer in Randomized Controlled Trials of Lipid-Altering Therapy

Haseeb Jafri, MD,* Alawi A. Alsheikh-Ali, MD, MS,†‡ Richard H. Karas, MD, PhD*

Boston, Massachusetts; and Abu Dhabi, United Arab Emirates

Objectives We sought to examine the relationship between high-density lipoprotein cholesterol (HDL-C) levels and the risk of the development of cancer in large randomized controlled trials (RCTs) of lipid-altering interventions.

Background Epidemiologic data demonstrate an inverse relationship between serum total cholesterol levels and incident cancer. We recently reported that lower levels of low-density lipoprotein cholesterol are associated with a significantly higher risk of incident cancer in a meta-analysis of large RCTs of statin therapy. However, little is known about the relationship between HDL-C levels and cancer risk.

Methods A systematic MEDLINE search identified lipid intervention RCTs with ≥1,000 person-years of follow-up, providing baseline HDL-C levels and rates of incident cancer. Using random-effects meta-regressions, we evaluated the relationship between baseline HDL-C and incident cancer in each RCT arm.

Results A total of 24 eligible RCTs were identified (28 pharmacologic intervention arms and 23 control arms), with 625,477 person-years of follow-up and 8,185 incident cancers. There was a significant inverse association between baseline HDL-C levels and the rate of incident cancer ($p = 0.018$). The inverse association persisted after adjusting for baseline low-density lipoprotein cholesterol, age, body mass index (BMI), diabetes, sex, and smoking status, such that for every 10-mg/dl increment in HDL-C, there was a 36% (95% confidence interval: 24% to 47%) relatively lower rate of the development of cancer ($p < 0.001$).

Conclusions There is a significant inverse association between HDL-C and the risk of incident cancer that is independent of LDL-C, age, BMI, diabetes, sex, and smoking. (J Am Coll Cardiol 2010;55:2846–54) © 2010 by the American College of Cardiology Foundation

The relationship between serum cholesterol levels and the risk of cancer in humans is an area of considerable research and debate, especially in the current era of intensive lipid-modifying therapy and more aggressive cholesterol goals to reduce the risk of cardiovascular disease. To date, the literature on cholesterol and cancer has focused predominantly on total serum cholesterol, demonstrating an inverse relationship between serum cholesterol levels and incident cancer (1). More recently, we reported that serum levels of low-density lipoprotein cholesterol (LDL-C) are significantly and inversely related to the rates of incident cancer in large randomized controlled trials (RCTs) of hydroxymethylglutaryl coenzyme A reductase inhibitors (statins), such that lower levels of LDL-C are associated with higher rates of incident cancer (2).

See page 2855

High-density lipoprotein cholesterol (HDL-C) contributes importantly to cardiovascular disease risk, independent of the effects of LDL-C, with a significant inverse relationship between HDL-C levels and the risk of cardiovascular disease (3–7). However, very little is known about whether there is a relationship between HDL-C levels and cancer risk. Only a small number of studies have explored the association of HDL-C and cancer, and these have produced mixed results (8–11). To date, there is no systematic analysis examining the relationship of HDL-C levels and the risk of incident cancer. In the current study, we took

From the *Molecular Cardiology Research Institute, Department of Medicine, and the †Institute for Clinical Research and Health Policy Studies, Tufts Medical Center and Tufts University School of Medicine, Boston, Massachusetts; and the ‡Institute of Cardiac Sciences, Sheikh Khalifa Medical City, Abu Dhabi, United Arab Emirates. Dr. Alsheikh-Ali is a recipient of a faculty development award from Pfizer/Tufts Medical Center. Dr. Karas has received speaker and consulting fees from Abbott Laboratories and Merck.

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advantage of the numerous large-scale trials of lipid-modifying therapy to examine the relationship between HDL-C levels and the risk of developing cancer.

Methods

Trial inclusion. A MEDLINE search identified lipid intervention RCTs, published up to September 2009 in the English literature, with at least 1,000 person-years of follow-up. To be eligible, trials had to report both baseline HDL-C and rates of incident cancer. The electronic search strategy included the following terms: cancer, neoplasm, HDL-C, fibrate, niacin, hydroxymethylglutaryl coenzyme A reductase inhibitor, statin, lovastatin, pravastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, and rosuvastatin. Citations were limited using the terms "human," "English language," and "randomized controlled trial." Additionally, a manual review of the reference lists of eligible trials was performed to ensure that all appropriate studies were included.

Data extraction. All citations were screened at the abstract level. Full articles of eligible trials were independently reviewed by 2 investigators (H.J. and A.A.A.-A.), and data directly extracted into electronic data tables. For each eligible study, the following variables were extracted from the published article: the intervention used and the dose; the number of patients in the intervention and control arms; duration of follow-up; baseline and on-treatment serum HDL-C, LDL-C, total cholesterol, and triglyceride levels; and the number of patients with newly diagnosed cancer during the follow-up period. In addition, for each trial arm, age, sex, diabetes, smoking status, and body mass index (BMI) were recorded at baseline. Nonmelanoma skin cancers were not consistently recorded in all trials and were therefore not included in the present analysis. Person-years of follow-up for each study arm were calculated by multiplying the reported follow-up in years by the number of subjects in each arm. The number of incident cancers that were included in the analysis was taken from the values reported as defined in each individual study. Cancer rates were expressed as number of incident cancers per 1,000 patient-years of follow-up for the study arm of interest.

Primary and secondary analyses. Our pre-specified primary analysis examined the association between baseline HDL-C levels and incident cancer risk. Each trial arm is considered a separate observation, and intervention and control arms are included together in the analysis. We previously showed in a similar dataset that statin use is not associated with cancer risk (2). The relationship between baseline HDL-C levels and cancer risk was assessed using random-effects meta-regressions (see the Statistical methods section). Secondary analyses were performed examining any association between the rate of incident cancer and the following variables: baseline LDL-C, age, BMI, sex, and the proportion of subjects who smoked or had diabetes. All the variables that showed a significant univariate association with incident cancer were used to adjust the meta-regression of incident cancer risk and baseline-HDL-C in a multivariate model. The above analyses were all repeated using on-treatment HDL-C in place of baseline HDL-C.

Abbreviations and Acronyms

BMI = body mass index
CI = confidence interval
HDL-C = high-density lipoprotein cholesterol
IQR = interquartile range
LDL-C = low-density lipoprotein cholesterol
RCT = randomized controlled trial

Statistical methods. In the main analyses, we assumed that incident cancer rates were normally distributed. We used random-effects meta-regressions to evaluate the association between incident cancer and baseline HDL-C levels or the other variables of interest, as described previously (12). We estimated multivariate associations controlling for each of the predictor variables that showed a significant univariate association with incident cancer. We fitted a single regression line to the pooled data of both intervention and control cohorts indexed by a variable indicating cohort type (intervention vs. control). To determine whether the association of HDL-C with cancer differed between the intervention and control arms, we tested the significance of the interaction term of cohort type with baseline HDL-C level. We repeated this analysis for treatment type (statin, fibrate, other intervention or control) to determine whether the association of HDL-C and cancer was significantly modified by treatment type. Continuous variables were compared using the Student *t* test for independent or paired samples as appropriate. To ensure that our findings were not sensitive to the assumption of a normal distribution of cancer rates, these analyses were repeated, assuming that incident cancer rates follow a Poisson distribution. A p value <0.05 was considered statistically significant. All analyses were performed with STATA version 9.2 (StataCorp, College Station, Texas).

Results

Eligible trials. Our search yielded 2,300 citations that were screened at the abstract level. A total of 2,250 abstracts were excluded (1,458 with follow-up of <1,000 person-years, 295 were not lipid intervention studies, and 497 were not RCTs), resulting in 50 full-text articles retrieved for detailed evaluation. Of these, 26 were eventually excluded (20 had <1,000 person-years of follow-up, 5 did not report cancer incidence [13–17], and 1 did not report baseline HDL-C [18]). Hence, a total of 24 lipid intervention RCTs were included in the main analysis (28 pharmacologic intervention arms and 23 control arms) (Table 1) (19–42). There was a total of 76,265 patients allocated to the lipid intervention arms and 69,478 patients allocated to the control arms. The median duration of follow-up was 5 years (interquartile range [IQR] 2.7 to 5.2 years). The cumulative exposure was 319,062 person-years in the lipid intervention arms and 306,415 person-years in the control arms. A total

Table 1 Characteristics of Large Randomized Controlled Trials Included in the Present Analysis

Study (Ref. #), Year	Arm	Dose*	N	Follow-Up, yrs	Incident Cancer	Baseline HDL-C, mg/dl	Baseline LDL-C, mg/dl	Age, yrs	BMI, kg/m^2	Diabetes, %	Sex, % Male	Smokers, %	Cancer Site (Primary)
LRC-CPPT (19), 1984	Cholestyramine	24 g	1,906	7.4	57	44.4	205	47.6	26.4	0	100	38	NR
	Placebo		1,900		57	44.4	205	47.7	26.2	0	100	37	NR
HHS (20), 1987	Gemfibrozil	600 mg BID	2,051	5	31	47.1	189.2	47	26.6	2.4	100	36.5	NR
	Placebo		2,030		26	47.6	188.2	47	26.6	2.9	100	35.8	NR
POSCH (21), 1990	Ileal bypass	NA	421	9.7	32	40	179	51	NR	0	90.7	35	NR
	Control		417		28	40	179	51	NR	0	90.7	35	NR
EXCEL (22), 1991	Lovastatin	20 mg	1,653	1	18	45	180	56	26	0	60	18	NR
	Lovastatin	40 mg	1,653		20	45	180	56	26	0	58	18	NR
	Lovastatin	20 mg BID	1,653		8	45	180	56	26	0	59	18	NR
	Lovastatin	40 mg BID	1,653		18	45	180	56	26	0	58	18	NR
	Placebo		1,653		12	45	180	56	26	0	58	18	NR
4S (23), 1994	Simvastatin	40 mg	2,221	5.4	90	45.5	188	59	26	5	82	24	GI 12
	Placebo		2,223		96	45.9	188	59	26	4	81	27	GI 14
WOSCOPS (24), 1995	Pravastatin	40 mg	3,302	5.0	116	44	192	55	26	41	100	44	GU 32, GI 31, respiratory 27, other 26
	Placebo		3,293		106	44	192	55	26	35	100	44	GU 26, GI 30, respiratory 28, other 22
CARE (25) 1996	Pravastatin	40 mg	2,081	5.0	172	39	139	59	28	14	86	21	GI 26, breast 12, hematological 8, melanoma 4
	Placebo		2,078		161	39	139	59	28	15	86	21	GI 37, breast 1, hematological 10
Post-CABG (26), 1997	Lovastatin	40–80 mg	676	4.3	48	39.1	155.4	48	NR	2.8	92	62	NR
	Lovastatin	2.5–5 mg	675		42	39.4	155.6	42	NR	2.4	93	61	NR
AFCAPS/TexCAPS (27), 1998	Lovastatin	40 mg	3,304	5.2	252	36.6	150	58	27	6.8	85	13	Prostate 109, colon 25, lung 22, melanoma 14, breast 13, lymphoma 12, bladder 12
	Placebo		3,301		259	36.6	150	58	27	5.4	85	12	Prostate 108, colon 20, lung 17, melanoma 27, breast 9, lymphoma 11, bladder 11
LIPID (28), 1998	Pravastatin	40 mg	4,512	6.1	379	36	150	62	NR	9	83	9	Breast 10, no other sites reported
	Placebo		4,502		399	36	150	62	NR	9	83	10	Breast 10, no other sites reported
VA-HIT (29), 1999	Gemfibrozil	600 mg BID	1,264	5.1	124	32	111	64	29	24	100	22	Prostate 55, GI 18, lung 20, GU 11, hematologic 6, head and neck 5, melanoma 1, other 15
	Placebo		1,267		129	32	112	64	29	25	100	19	Prostate 37, GI 25, lung 24, GU 17, hematologic 11, head and neck 8, melanoma 9, other 8
BIP (30), 2000	Benzafibrate	400 mg	1,542	6.2	85	34.6	149	60	26.7	10	91.2	11.4	NR
	Placebo		1,548		91	34.6	148	60	26.7	10	91.6	12.1	NR
GISSI (31), 2000	Pravastatin	20 mg	2,138	1.9	16	45.7	151.8	60	26	12.9	87	12	NR
	Placebo		2,133		25	45.7	151.5	60	27	14.4	86	11	NR
KLIS (32), 2000	Pravastatin	10–20 mg	2,219	5.0	77	48.9	169	58	24	21.8	100	38	NR
	Conventional therapy		1,634		55	49.7	160	58	24	24.4	100	41	NR
ALLHAT-LLT (33), 2002	Pravastatin	40 mg	5,170	4.8	378	47.6	145.6	66	30	35.9	51	23	Lung 63, colon 46, breast 34
	Placebo		5,185		369	47.4	145.5	66	30	34.4	51	23	Lung 78, colon 38, breast 37

Continued on next page

Table 1 Continued

Study (Ref. #), Year	Arm	Dose*	N	Follow-Up, yrs	Incident Cancer	Baseline HDL-C, mg/dl	Baseline LDL-C, mg/dl	Age, yrs	BMI, kg/m^2	Diabetes, %	Sex, % Male	Smokers, %	Cancer Site (Primary)
HPS (34), 2002	Simvastatin	40 mg	10,269	5.0	814	40.9	131.2	63	NR	19.5	75	14	GU 259, GI 228, respiratory 179, hematologic 64, connective tissue 60, CNS 12, other 6, not specified 38
	Placebo		10,267		803	40.9	131.2	63	NR	19.2	75	14	GU 272, GI 223, respiratory 167, hematologic 52, connective tissue 68, CNS 68, other 2, not specified 49
LIPS (35), 2002	Fluvastatin	80 mg	844	3.9	46	38	131	60	27	14.2	84	25	NR
	Placebo		833		49	37	132	60	26	9.8	83	28	NR
PROSPER (36), 2002	Pravastatin	40 mg	2,891	3.2	245	50.2	146.7	75	27	10.5	48	26	GI 65, GU 58, respiratory 46, breast 18, other 58
	Placebo		2,913		199	50.2	146.7	75	27	11	48	26	GI 45, GU 59, respiratory 42, breast 11, other 42
4D (37), 2005	Atorvastatin	20 mg	619	2.25	44	36	125	65.7	27.6	100	53.8	8.1	NR
	Placebo		636		39	36	127	65.7	27.5	100	54.1	9.1	NR
FIELD (38), 2005	Fenofibrate	20 mg	4,895	5.0	393	42.5	118.5	62	29.8	100	63	9	GI 114, prostate 65, respiratory 45, breast 37, GU 24
	Placebo		4,900		373	42.5	118.5	62	29.8	100	63	9	GI 109, prostate 59, respiratory 41, breast 38, GU 31
MEGA (39), 2006	Pravastatin	20 mg	3,866	5.3	126	57.5	156.3	58	24	21	32	21	GI 58, respiratory 10, breast 10, GU 14, other 30
	Diet		3,966		119	57.5	156.3	58	24	21	31	20	GI 65, respiratory 13, breast 15, GU 10, other 30
CORONA (40), 2007	Rosuvastatin	10 mg	2,497	2.7	156	48	136.9	73	27	30	76	9	NR
	Placebo		2,514		144	47.6	136	73	27	29	76	8	NR
JUPITER (41), 2008	Rosuvastatin	20 mg	8,901	1.9	298	49	108	66	28.3	0	61.5	15.7	NR
	Placebo		8,901		314	49	108	66	28.4	0	62.1	16	NR
AURORA (42), 2009	Rosuvastatin	10 mg	1,389	3.8	107	45	99	64.1	25.4	27.9	61.3	14.5	NR
	Placebo		1,384		118	45	100	64.3	25.4	24.8	63	16.4	NR

*Target dose is in milligrams per day. Year refers to year of publication. All lipid levels are mean or median levels as reported in the trial. Age is the mean or median age for the arm reported in the trial.

AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; AURORA = A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events; BID = twice daily; BIP = Bezafibrate Infarction Prevention Study; BMI = body mass index; CARE = Cholesterol and Recurrent Events trial; CNS = central nervous system; CORONA = Controlled Rosuvastatin in Multinational Trial in Heart Failure; EXCEL = Expanded Clinical Evaluation of Lovastatin; FIELD = Fenofibrate Intervention and Event Lowering in Diabetes; GI = gastrointestinal; GISSI = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; GU = genitourinary; HHS = Helsinki Heart Study; HPS = Heart Protection Study; HDL-C = high-density lipoprotein cholesterol; JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; KLIS = Kyushu Lipid Intervention Study; LDL-C = low-density lipoprotein cholesterol; LIPID = Long-Term Intervention With Pravastatin in Ischemic Disease study; LIPS = Lescol Intervention Prevention Study; LRC-CPPT = Lipid Research Clinics Coronary Primary Prevention Trial; MEGA = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese study; NA = not available; NR = not reported; POSCH = Program on the Surgical Control of the Hyperlipidemias; Post-CABG = Post Coronary Artery Bypass Graft trial; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk; VA-HIT = Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial; WOSCOPS = West of Scotland Coronary Prevention Study; 4S = Scandinavian Simvastatin Survival Study.

of 8,185 patients with incident cancer were included. The incidence of newly diagnosed cancer ranged from 3.0 to 31.6 per 1,000 person-years in the lipid intervention arms and from 2.6 to 27.3 per 1,000 person-years in the control arms.

Among all the eligible RCTs, there was a wide range of baseline and on-treatment lipid parameters, with comparable baseline levels in the intervention versus control arms and favorable on-treatment changes in the intervention arms (Table 1). The median baseline HDL-C for all arms included was 44.4 mg/dl (IQR 39.0 to 47.4 mg/dl). In the lipid-intervention arms, median baseline and on-treatment HDL-C levels were 44.7 mg/dl (IQR 39.0 to 46.7 mg/dl) and 46.4 mg/dl (IQR 42.1 to 49.2 mg/dl), respectively ($p < 0.001$). Baseline and on-treatment HDL-C levels did not differ in the control arms.

Univariate meta-regressions. PRIMARY ANALYSIS. In univariate random-effects meta-regression analysis, there was a significant inverse relationship between baseline HDL-C level and the rate of incident cancer, such that every 10-mg/dl increment in HDL-C was associated with a 28% (95% confidence interval [CI]: 5% to 45%) relatively lower cancer rate ($p = 0.018$) (Fig. 1). The significant inverse association between baseline HDL-C and incident cancer did not differ between the intervention and the control arms ($p = 0.95$) and was not modified by the type of intervention used ($p = 0.726$).

SECONDARY ANALYSIS. When evaluating the other independent variables in the study, there was a significant inverse relationship between baseline LDL-C level and the rate of incident cancer, such that every 10-mg/dl decrement in LDL-C was associated with a 15% (95% CI: 12% to 18%) relatively higher cancer rate ($p < 0.001$) (Fig. 2). In addition, there was a significant and direct relationship between both age and BMI and the rate of incident cancer, such that every 5-year increment in age was associated with a 33% (95% CI: 22% to 45%) relatively higher cancer rate and every 1-kg/m^2 increment in BMI was associated with a 21% (95% CI: 8% to 35%) relatively higher cancer rate ($p < 0.001$ and $p = 0.001$, respectively) (Figs. 3 and 4). Additionally, sex, the proportion of smokers, and the proportion of patients with diabetes mellitus were significantly associated with incident cancer ($p < 0.01$ for all univariate associations).

Multivariate meta-regressions. Multivariate random-effects meta-regression analyses were conducted for baseline HDL-C and incident cancer, controlling for the variables that had significant independent associations with incident cancer in the univariate regression models. After adjusting for baseline LDL-C, age, BMI, diabetes, sex, and smoking status, the significant inverse relationship between baseline HDL-C and rate of incident cancer persisted, such that for every 10-mg/dl increase in HDL-C, there was a 36% (95% CI: 24% to 47%; $p < 0.001$) relatively lower rate of incident cancer. In the multivariate model including all relevant variables in addition to HDL-C, LDL-C and sex (percentage of males) continued to have a significant inverse relationship with the rate of incident cancer ($p = 0.02$ and $p = 0.007$, respectively), and age continued to have a significant direct relationship with rate of incident cancer ($p < 0.001$). In this multivariable model, however, the direct relationship between smoking status and rate of incident cancer approached significance, but failed to achieve it ($p = 0.06$), and the relationships between both

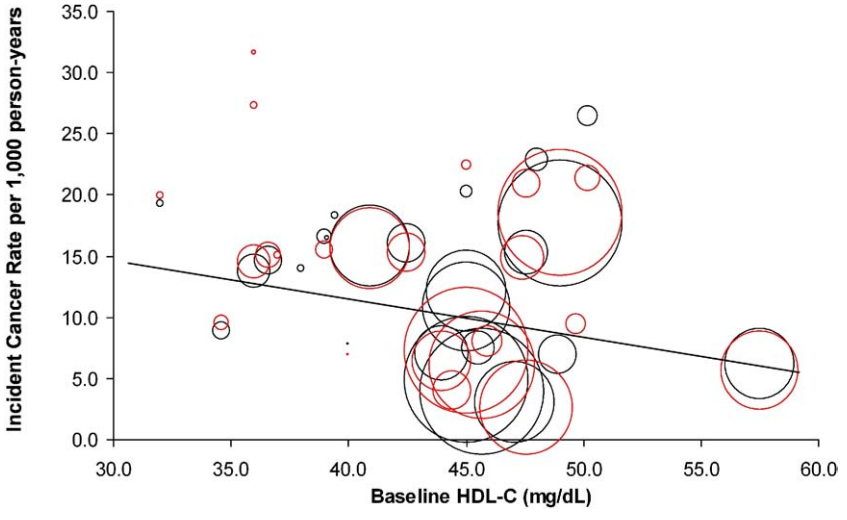

Figure 1 Baseline Levels of HDL-C (mg/dl) and Rate of Incident Cancer per 1,000 Person-Years

The **size of each circle** represents the relative size (i.e., the weight of the arm) of each trial arm for the lipid intervention arm **(black)** and the control arm **(red)**. The **solid black line** is the combined weighted regression line for all trial arms included in the analysis. p = 0.018. HDL-C = high-density lipoprotein cholesterol.

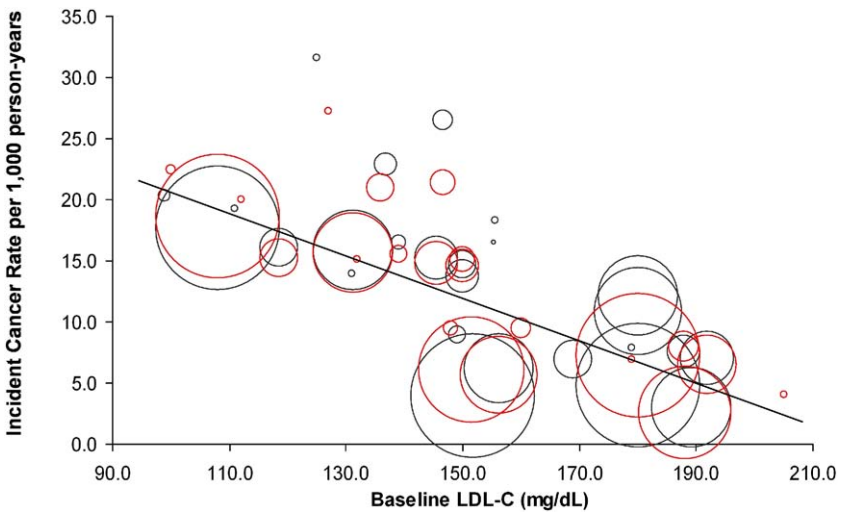

Figure 2 Baseline Levels of LDL-C (mg/dl) and Rate of Incident Cancer per 1,000 Person-Years

The **size of each circle** represents the relative size (i.e., the weight of the arm) of each trial arm for the lipid intervention arm **(black)** and the control arm **(red)**. The **solid black line** is the combined weighted regression line for all trial arms included in the analysis. $p < 0.001$. LDL-C = low-density lipoprotein cholesterol.

BMI and diabetes status with incident cancer rate were no longer statistically significant ($p = 0.71$ and $p = 0.78$, respectively). All findings were unchanged when the analyses were repeated using on-treatment instead of baseline HDL-C levels or with Poisson meta-regressions (data not shown).

Discussion

The current analysis demonstrates a significant inverse association between baseline HDL-C levels and the risk of developing cancer in large RCTs of lipid-altering therapy. Importantly, this relationship persisted after controlling for potentially confounding variables, including baseline levels of LDL-C, age, BMI, and smoking status.

The present study is the most comprehensive assessment of the relationship between HDL-C and risk of cancer to date. This study builds on the few previous nested case-control studies of HDL-C and risk of cancer. Studies from the breast cancer literature provide mixed results. Moorman et al. (8), in an analysis of 95,000 women from the Kaiser

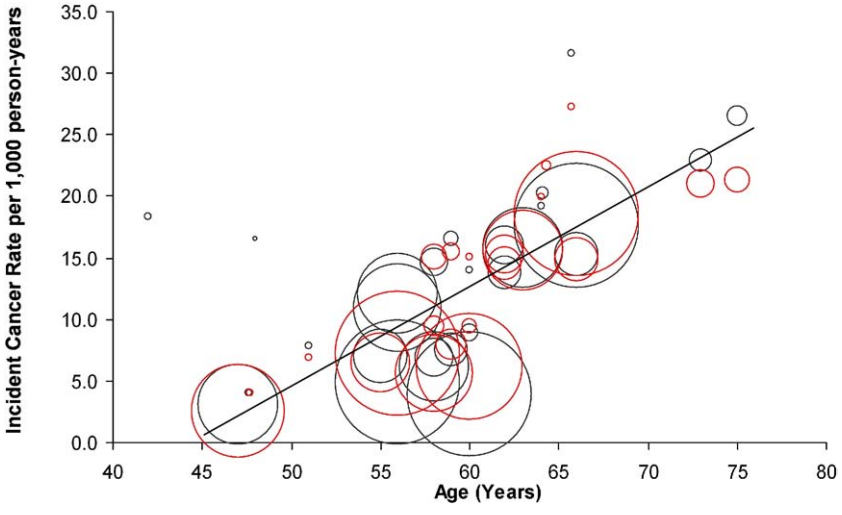

Figure 3 Age (in Years) and Rate of Incident Cancer per 1,000 Person-Years

The **size of each circle** represents the relative size (i.e., the weight of the arm) of each trial arm for the lipid intervention arm **(black)** and the control arm **(red)**. The **solid black line** is the combined weighted regression line for all trial arms included in the analysis. $p < 0.001$.

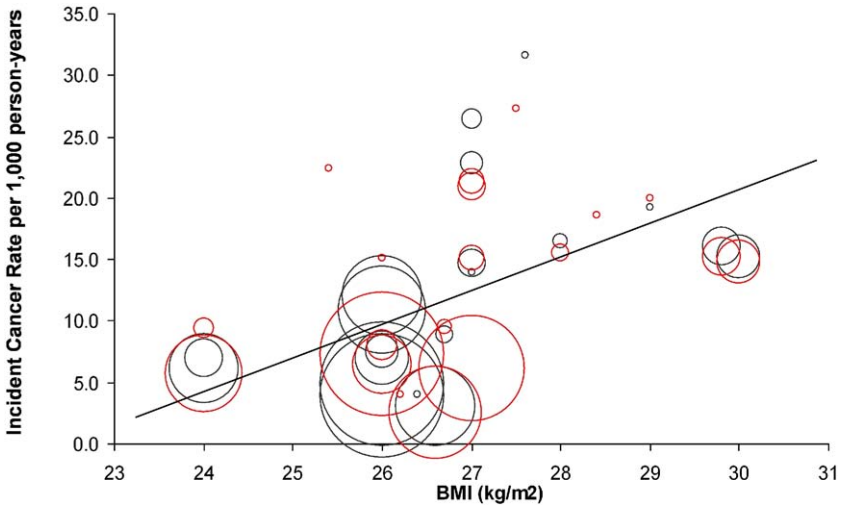

Figure 4 **BMI (kg/m^2) and Rate of Incident Cancer per 1,000 Person-Years**

The **size of each circle** represents the relative size (i.e., the weight of the arm) of each trial arm for the lipid intervention arm **(black)** and the control arm **(red)**. The **solid black line** is the combined weighted regression line for all trial arms included in the analysis. p = 0.001. BMI = body mass index.

Permanente Medical Care Program and Kucharska-Newton et al. (9) in a study of 7,575 women from the ARIC (Atherosclerosis Risk in Communities) study suggested that the relationship of HDL-C and breast cancer varies by menopausal status, where an inverse association between HDL-C and breast cancer exists in pre-menopausal women, but not in post-menopausal women. In contrast, a study of 38,823 Norwegian women by Furberg et al. (10) suggested that low levels of serum HDL-C are independently associated with increased breast cancer risk in post-menopausal females. Additionally, a recent analysis of the ATBC (Alpha-Tocopherol Beta-Carotene Cancer Prevention) study, examining 29,093 Finnish male smokers, identified a significant inverse relationship between HDL-C levels and the risk of incident cancer. They found that this significant inverse association, largely attributed to cancers of the lung, prostate, liver, and hematopoietic system, persisted after exclusion of cases diagnosed during the first 12 years of follow-up (11). These previous analyses are limited by sex or cancer type studied, whereas the current study included a mixed population and reported a broad variety of cancers.

As with all association studies, the present study should not be interpreted as implying a causal relationship between low HDL-C levels and cancer risk. However, it is interesting to consider potential biological mechanisms for the observed inverse association between HDL-C and incident cancer risk. The primary mechanism by which HDL-C exerts its atheroprotective effects is via reverse cholesterol transport, but HDL-C has also been shown to have other beneficial effects via its anti-inflammatory and antioxidant properties (7,43–51). Cancer is well-known to be a proinflammatory state, in which inflammatory cells actively participate in the neoplastic process, allowing tumor cell proliferation, survival, and migration (52–54). Therefore, it is plausible that HDL-C, by mechanisms that are not yet known, may influence some of the proinflammatory mediators involved in carcinogenesis. Further work will need to be done to elucidate these potential mechanisms.

As a secondary analysis, we examined the other potential variables associated with cancer risk in our dataset. We confirmed our previous report that LDL-C levels are inversely associated with the risk of incident cancer in a similar database (2). Additionally, the current analysis further supports the well-established association of age and risk of cancer. Furthermore, we demonstrated that in univariate analyses, there was an association between BMI and cancer; however, this relationship was no longer significant after adjusting for HDL-C. The univariate association between BMI and incident cancer reported here is consistent with a recent meta-analysis of prospective observational studies by Renehan et al. (55), although they did not adjust for HDL-C.

Study limitations. Our findings are limited by the use of trial-level data. It is possible that the relationship of HDL-C and cancer could reflect differences in study design that relate to HDL-C at the population level, thus confounding our observed association between HDL-C levels and cancer. Access to individual patient data would allow a more robust analysis. Furthermore, the process for the identification of cancers was not specifically reported, nor was it uniform across all RCTs, and, thus, an effect of differences in the definitions of cancers could not be excluded. Also, many of the recent, large-scale lipid-lowering RCTs did not report newly diagnosed cancer (13–17), and thus data from these trials could not be

included. Although the possibility of reverse causality could not be addressed in the current analysis because we did not have access to the individual patient data and could not determine the exact time of cancer diagnosis, it seems unlikely that cancer-associated reductions in HDL-C levels in the small subgroup of these cohorts in which cancer actually developed would significantly affect the mean baseline levels for the large cohort overall. Finally, given the median follow-up time of 5 years, we may not have been able to fully appreciate whether the inverse relationship between HDL-C and incident cancer risk is altered over longer periods of follow-up.

Conclusions

Overall, the current epidemiologic data demonstrate an inverse relationship between serum total cholesterol levels and rate of incident cancer. We recently showed in a meta-analysis that there is a strong inverse relationship between LDL-C and the rate of incident cancer. The current study, based on a systematic analysis, is the first to report a strong and significant inverse relationship between baseline HDL-C and the rate of incident cancer. These findings underscore the importance of reporting cancer rates in future lipid intervention trials and further support the importance of basic scientific research to determine potential underlying mechanisms that might mediate these associations.

Reprint requests and correspondence: Dr. Richard H. Karas, Molecular Cardiology Research Institute, Box # 80, Tufts Medical Center, 750 Washington Street, Boston, Massachusetts 02111. E-mail: rkaras@tuftsmedicalcenter.org.

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