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RESEARCH LETTER

Inflammation-Dependent Association of Lipoprotein (a) with Cardiovascular and Cancer Mortality

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Cardiovascular disease (CVD) and cancer rank as the two leading causes of death worldwide. Emerging evidence has suggested common mechanisms between CVD and cancer,[1] such as oxidative stress and inflammation, which not only mediate the process of atherosclerosis but also promote carcinogenesis and tumor growth.[1] Lipoprotein(a) [Lp(a)], an oxidation-specific biomarker,[2] has been associated with CVD and cancer. Inflammation may amplify the Lp(a)-associated CVD risk.[3] It is likely that inflammation may also enhance Lp(a)-associated cancer risk. If true, it will provide new insights into dual risk of cancer and CVD events, and it may also advance our understanding of collaborative management of CVD and cancer. We therefore sought to examine the association of Lp(a) with CVD and cancer deaths in participants with lower versus higher inflammation levels in a nationally representative cohort.

We performed a secondary analysis by using data from the Third National Health and Nutrition Examination Survey (NHANES III), which was conducted from 1988 to 1994 by the National Center for Health Statistics (NCHS), a part of the Centers for Disease Control and Prevention (CDC). All the data are collected and disseminated by the NCHS staff. Further details about NHANES were introduced in the Supplementary Materials. Each participant, as previously described elsewhere,[4] completed a personal interview and underwent a physical examination at the mobile examination center. Serum C-reactive protein (CRP), Lp(a) and other biomarkers were assessed as previously reported.[4] A link between NHANES personal identifiers and death certificates from the National Death Index was used for assessing participants' vital status until 31 December 2019. Of all 31,311 participants underwent examinations of NHANES III, we excluded individuals with incomplete information on covariates or follow-up (N=15,363), who were not fasting or had triglycerides over 400 mg/dL (N=1259) and who had missing data on Lp(a) (N=7886). The final sample includes 6803 individuals (Supplementary Figure 1). Lp(a) was log-transformed and standardized before modelling. A median value of CRP (ie, 0.21 mg/dL) was used as a cutoff point to define systemic inflammation status. We related Lp(a) levels with CVD and cancer mortality using multivariable-adjusted Cox proportional hazards models adjusted for risk factors including age, sex, race, body mass index, history of CVD, history of cancer, current smoking, hypertension, diabetes mellitus, high-density lipoprotein cholesterol level, total cholesterol level, cholesterol-lowering therapy, hypoglycemic medication, and family income. We used R version 4.2.1 for all analyses and the results were expressed as hazard ratios (HRs) and 95% confidence interval (95% CI).

In this study sample (N = 6803, 56.7% females, mean age 46.3±19.4 years), over a median follow-up of 25.8 years, we documented 908 CVD deaths and 552 cancer deaths. As shown in Table 1, Lp(a) was associated with both CVD mortality (HR, 1.09; 95% CI, 1.02–1.17) and cancer mortality (HR, 1.12; 95% CI, 1.02–1.23). In participants with CRP>0.21 mg/dL, per SD

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Table 1 Association of Lp(a) with Cardiovascular and Cancer Mortality According to CRP Threshold

	Cardiovascular Death		Cancer Death	
	Events / All	HR (95% CI)	Events / All	HR (95% CI)
Overall	908 / 6803	1.09 (1.02, 1.17)	552 / 6803	1.12 (1.02, 1.23)
CRP > 0.21 (mg/dL)	443 / 2551	1.14 (1.03, 1.26)	268 / 2551	1.16 (1.02, 1.32)
CRP ≤ 0.21 (mg/dL)	465 / 4252	1.05 (0.95, 1.15)	284 / 4252	1.08 (0.96, 1.23)

Notes: Association of log-transformed lipoprotein(a) with cardiovascular and cancer mortality was estimated using Cox proportional hazards models adjusted for age, sex, race, body mass index, history of cardiovascular disease, history of cancer, current smoking, hypertension, diabetes mellitus, high-density lipoprotein cholesterol level, total cholesterol level, cholesterol-lowering therapy, hypoglycemic medication, and family income.
Abbreviations: HR, hazard ratio; CI, confidence interval; CRP, C-reactive protein.

increase in log-transformed Lp(a) was associated with 14% (HR, 1.14; 95% CI, 1.03–1.26) and 16% (HR, 1.16; 95% CI, 1.02–1.32) higher hazard of CVD and cancer mortality respectively. In contrast, for those with CRP ≤ 0.21 mg/dL, no evident association between Lp(a) and mortality risk was observed. In restricted cubic splines, we observed similar findings (Figure 1).

In this large nationally representative cohort followed for over two decades, we found that Lp(a) was associated with both CVD and cancer mortality only in individuals with relatively higher CRP levels. Our findings suggested that, inflammation may mediate the effect of Lp(a) on dual risk of CVD and cancer mortality. Recent analyses in MESA[3] (Multi-Ethnic Study of Atherosclerosis) demonstrated that Lp(a) was related to incident CVD only with concomitant systemic inflammation. Our results are partially in accordance with this observation, suggesting that the Lp(a)-related risk of CVD mortality is evident only in participants with systemic inflammation. Meanwhile, with a larger sample size and a longer-term follow-up, our study expanded prior findings by focusing not only on CVD but also on cancer mortality, indicating that concomitant elevation of Lp(a) and inflammation may increase both CVD and cancer mortality risk. This implies that the Lp(a)-related risk may be inflammation-dependent in terms of not only atherosclerotic process, but also carcinogenesis.[5] This finding may provide new insights into the role of inflammation in collaborative prevention and treatment strategies of CVD and cancer. Despite a large representative cohort and long-term follow up, there are limitations. First, although plasma Lp(a) levels remain relatively stable over the life course regardless of lifestyle, Lp(a) and other biomarkers were assessed only at baseline, which may lead to potential bias. In addition, given the observational nature of our study, further experimental and randomized studies are warranted to confirm our findings.

Ethics Approval and Informed Consent

All the participants provided written informed consent. The Research Ethics Review Board of the National Center for Health Statistics approved the NHANES III (https://www.cdc.gov/nchs/nhanes/irba98.htm). Data and materials produced by the US Centers for Disease Control and Prevention (CDC) are in the public domain and can be used without permission.

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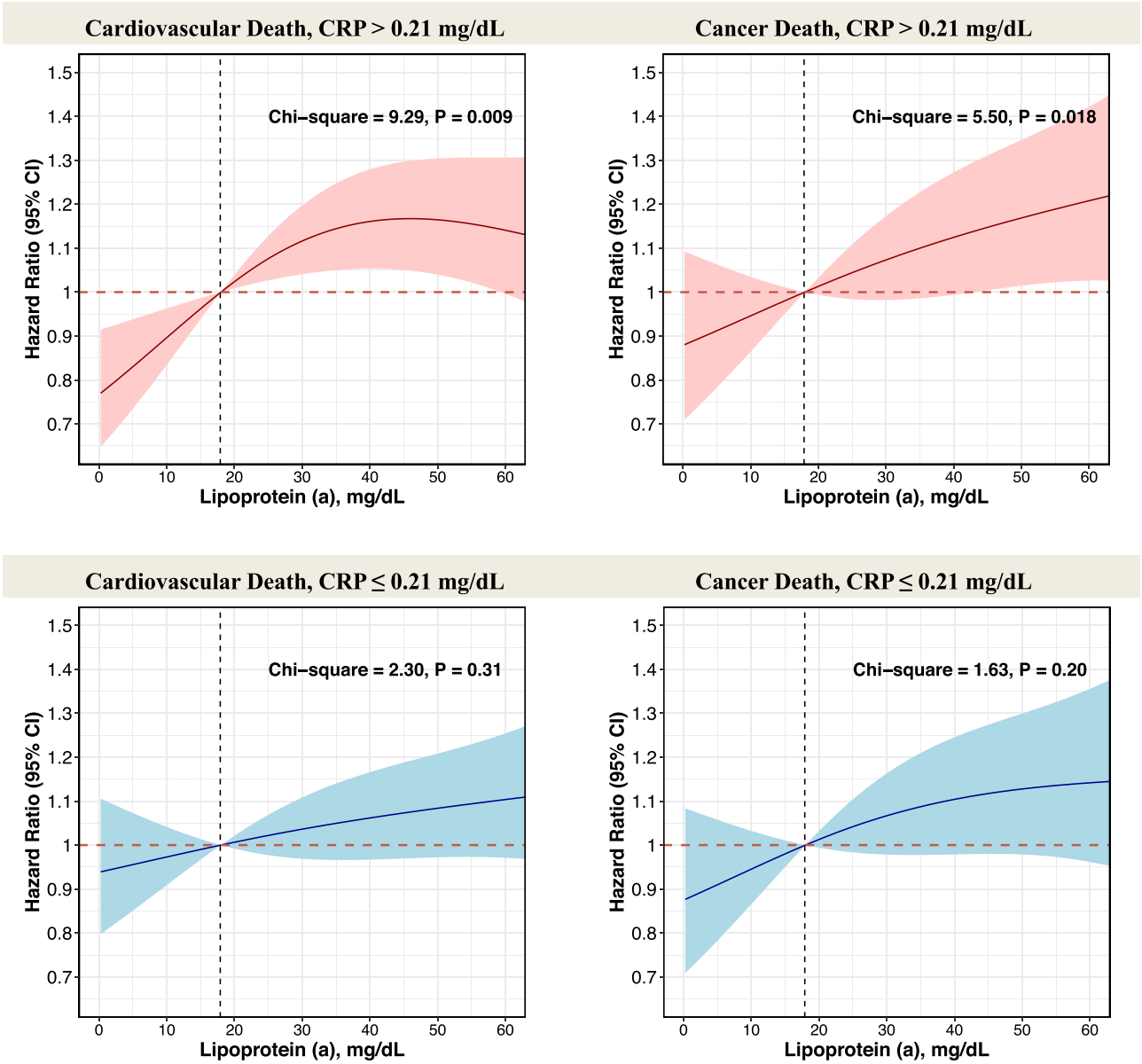

Figure 1 Restricted cubic spline was fitted to capture potential non-linear relationships. Solid lines are multivariable adjusted hazard ratios, with shaded areas showing 95% confidence intervals derived from restricted cubic spline regressions. Reference lines for no association are indicated by the dashed lines at a hazard ratio of 1.0. Analyses were adjusted for age, sex, race, body mass index, history of cardiovascular disease, history of cancer, current smoking, hypertension, diabetes mellitus, high-density lipoprotein cholesterol level, total cholesterol level, cholesterol-lowering therapy, hypoglycemic medication, and family income.

Disclosure

The authors report no conflicts of interest in this work.

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