Short Communication

The Association of High-Density Lipoprotein Cholesterol with Cancer Incidence in Type II Diabetes: A Case of Reverse Causality?

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Abstract

Background: Low high-density lipoprotein cholesterol (HDL-C) and type II diabetes are associated with an increased risk for cancer. Patients with type II diabetes typically have low HDL-C; however, the association between HDL-C and cancer has not been examined in this population.

Methods: A total of 11,140 patients with type II diabetes were followed for a median of 5 years. Cox proportional hazard models were used to assess the association between baseline HDL-C and risk of cancer incidence and cancer death, with adjustments made for potential confounders. To explore the possibility of reverse causation, analyses were repeated for the cancers occurring in the first and second halves of follow-up.

Results: Six hundred and ninety-nine patients developed cancer, with 48% occurring within the first half of follow-up. For every 0.4 mmol/L lower baseline HDL-C, there was a 16% higher risk of cancer [HR 1.16; 95% confidence interval (CI), 1.06–1.28; P = 0.0008] and cancer death [HR 1.16; 95% CI, 1.01–1.32; P = 0.03]. After adjustment for confounding, the higher risk remained significant for cancer (adjusted HR 1.10; 95% CI, 1.00–1.22; P = 0.05) but not for cancer death (adjusted HR 1.08; 95% CI, 0.93–1.25; P = 0.31). The association was driven by cancers occurring within the first half of follow-up (adjusted HR 1.22; 95% CI, 1.05–1.41; P = 0.008) as no significant association was found between HDL-C and cancer in the second half of follow-up.

Conclusions: Low HDL-C is associated with cancer risk in patients with type II diabetes. However, this association may be explained by confounding and reverse causation.

Impact: HDL-C is not a risk factor for cancer in type II diabetes. Cancer Epidemiol Biomarkers Prev; 1–6. ©2013 AACR.

Introduction

There is a well-recognized relationship between low total cholesterol levels and higher rates of cancer (1). This has been attributed to reverse causation whereby preclinical cancers lower the cholesterol either through increased metabolism or reduced catabolism (2). Complicating the relationship is the understanding that the respective levels of high- and low-density lipoproteins that comprise total cholesterol level may have vastly different effects on cancer risk, just as they have different effects on the risk of cardiovascular disease. To date, studies examining the relationship between high-density lipoprotein cholesterol (HDL-C) and cancer have suggested an inverse association. Several of these studies have considered the possibility of reverse causation, but have presented limited sex- or cancer-specific data (3–5). Furthermore, the possibility of reverse causality was not or could not be addressed in the majority of studies (6–9).

Compared with healthy controls, patients with type II diabetes are at high risk of cancer (10) and have characteristically low HDL-C levels (11). In this population there are several plausible biologic mechanisms for the observed high risk of cancer including insulin-mediated mitogenesis, hyperglycaemia, and upregulation of inflammatory cytokines (10). However, a role for HDL-C has not previously been examined. In these analyses, we explore the association between baseline HDL-C level and cancer incidence in ADVANCE (12, 13), a large contemporary diabetes population drawn from 20 countries, with special consideration of the possibility of reverse causation.

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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Patients and Methods

Study design and population

The study design of ADVANCE is reported in detail elsewhere (14). In brief, patients with type II diabetes ages at least 55 years at study entry and with at least one other cardiovascular risk factor underwent factorial randomization to the fixed combination of perindopril and indapamide or matching placebo and intensive or standard glucose control. ADVANCE enrolled 11,140 subjects who were followed up for a median of 5.0 years. For these analyses, a total of 11,126 patients with HDL-C measurements at baseline were included. Approval for the study was obtained from each center’s institutional ethics committee, and all participants provided written informed consent. At baseline, blood pressure and body mass index (BMI) were recorded, and venous blood was taken for a fasting lipid profile and HbA1C.

Outcomes

The 2 main outcomes for this analysis were total cancer incidence and cancer death, which were prespecified secondary endpoints of the ADVANCE trial. Secondary outcomes were the incidence of the most common specific cancer types: digestive, lung, breast, and prostate. Cancer events were recorded by the treating physician and fatal cases were adjudicated through a centralized committee. The assumption of proportional hazards was checked graphically using the log cumulative hazard plot for all the variables included in the Cox model. To explore the possibility of reverse causality, we repeated the analysis adjusting for potential confounding baseline covariates, specifically: age (continuous), gender (male/female), ethnicity (Caucasian/Asian/other), treatment groups (standard vs. intensive glucose control and placebo vs. fixed-dose blood pressure lowering treatment), smoking status (current/previous/never), HbA1C (continuous), BMI (continuous), duration of diabetes (continuous), total cholesterol (continuous), and statin use (yes/no). The selection of variables was based on identifying all measured clinical variables of known, or suspected, prognostic importance for the outcomes of interest. Notably, baseline HDL-C was significantly lower in those who developed cancer compared with those who did not (1.21 (SD 0.34) vs. 1.26 (SD 0.35) mmol/L; P = 0.0009), and this difference was more pronounced in those who developed cancer in the first half of the follow-up (1.19 (SD 0.33) vs. 1.26 (SD 0.35) mmol/L; P = 0.0007), compared with those who developed cancer in the second half of the follow-up (1.23 (SD 0.34) vs. 1.26 (SD 0.35) mmol/L; P = 0.2).

For every 0.4 mmol/L (1 SD) lower HDL-C, there was a 16% higher risk of developing any cancer [HR 1.16; 95% confidence interval (CI), 1.06–1.28; P = 0.0008] and of dying from cancer (HR 1.16; 95% CI, 1.01–1.32; P = 0.03; Table 2). After adjustment for potential confounders, there was a reduction in the HRs, but statistical significance remained for cancer incidence (adjusted HR 1.10; 95% CI, 1.00–1.22; P = 0.05) but not for cancer death (adjusted HR 1.08; 95% CI, 0.93–1.25; P = 0.3). Before adjustment, baseline HDL-C was significantly associated with prostate cancer; however, following adjustment, this association was no longer apparent. After adjustment, the point estimates of risk for each other type of specific cancer were similar to total cancers. Figure 1 emphasizes the dose–response nature of the association between HDL-C and the risk of cancer incidence. This summary plot shows that there is a significant inverse

Results

Over 5 years, 6.3% (n = 699) of patients developed cancer, with 48% occurring within the first half of follow-up (2.5 years). Cancer of the digestive system was most frequent (2.0%, n = 221) followed by respiratory cancer (1.0%, n = 115), prostate cancer (0.8%, n = 86), and breast cancer (0.6%, n = 64). Other types of cancer occurred in 1.9% (n = 213). Cancer was recorded as the cause of death in 2.8% (n = 316) of patients.

Baseline characteristics by quarter of HDL

The mean baseline HDL-C level was 1.3 mmol/L (SD 0.4 mmol/L, range 0.1–4.0 mmol/L). Table 1 shows the distribution of baseline variables by quarter of HDL-C level. Compared with the lowest quarter of HDL-C, those subjects in the highest quarter were less likely to be male (42.4% vs. 71.8%) or taking a statin (24.4% vs. 30.8%), and more likely to have lower BMI (27.5 vs. 28.9 kg/m²) and to have never smoked (66.7% vs. 49.9%). Higher HDL-C was also associated with lower triglycerides and higher total cholesterol and low-density lipoprotein cholesterol (LDL-C). Age, diabetes duration, HbA1C, and ethnicity were all statistically significantly different between quarters; however, the absolute differences were small.

Baseline characteristics by subsequent cancer incidence

Those who subsequently developed cancer tended to be older, male, Caucasian, and have a higher BMI compared with those who did not develop cancer (online Supplementary Table S1). Notably, baseline HDL-C was significantly lower in those who developed cancer compared with those who did not (1.21 (SD 0.34) vs. 1.26 (SD 0.35) mmol/L; P = 0.0009), and this difference was more pronounced in those who developed cancer in the first half of the follow-up (1.19 (SD 0.33) vs. 1.26 (SD 0.35) mmol/L; P = 0.0007), compared with those who developed cancer in the second half of the follow-up (1.23 (SD 0.34) vs. 1.26 (SD 0.35) mmol/L; P = 0.2).

For every 0.4 mmol/L (1 SD) lower HDL-C, there was a 16% higher risk of developing any cancer [HR 1.16; 95% confidence interval (CI), 1.06–1.28; P = 0.0008] and of dying from cancer (HR 1.16; 95% CI, 1.01–1.32; P = 0.03; Table 2). After adjustment for potential confounders, there was a reduction in the HRs, but statistical significance remained for cancer incidence (adjusted HR 1.10; 95% CI, 1.00–1.22; P = 0.05) but not for cancer death (adjusted HR 1.08; 95% CI, 0.93–1.25; P = 0.3). Before adjustment, baseline HDL-C was significantly associated with prostate cancer; however, following adjustment, this association was no longer apparent. After adjustment, the point estimates of risk for each other type of specific cancer were similar to total cancers. Figure 1 emphasizes the dose–response nature of the association between HDL-C and the risk of cancer incidence. This summary plot shows that there is a significant inverse
dose–response relationship across the quarters of HDL-C, which is attenuated by adjustment for confounding. There was no significant interaction between HbA1C \( (P = 0.8) \) or glucose treatment \( (P = 0.2) \) and the association between HDL-C and cancer incidence. There was a significant interaction between BMI and the association between HDL-C and cancer incidence \( (P < 0.003) \). Subgroup analysis by median BMI indicated that the effects of HDL-C on cancer incidence at higher BMI \( (> 27.5 \text{ kg/m}^2) \) were augmented \( \text{adjusted HR} 1.18; 95\% \ CI, 1.02–1.35; P = 0.02) \), whereas at lower BMI \( (< 27.5 \text{ kg/m}^2) \) they were no longer present \( \text{adjusted HR} 1.02; 95\% \ CI, 0.89–1.18; P = 0.7) \). This effect modification was particularly noticeable for digestive and prostate cancers rather than for lung and breast cancers.

Within the first half of the follow-up, for every 0.4 mmol/L lower HDL-C, the adjusted risk of developing any cancer was 22% higher \( \text{adjusted HR} 1.22; 95\% \ CI, 1.05–1.41; P = 0.008) \). When cancers occurring within the first 2.5 years were censored, the point estimates approached unity and no significant associations were observed despite this analysis set including more than half of all cancers.

**Discussion**

This study shows that low HDL-C is associated with cancer incidence and death in patients with type II diabetes. For every 0.4 mmol/L lower baseline HDL-C, there was a 16% higher risk of developing cancer or dying from cancer, which fell to 10% for cancer incidence and 9% for cancer death after adjustment for confounders. Cancers occurred evenly throughout the study with just under 50% occurring within the first half of follow-up. We observed that the inverse association between baseline HDL-C and cancer was stronger for cancers detected early, conferring a 22% higher risk for every 0.4 mmol/L decrement. This is in contrast to cancers detected later where no significant association was observed. Our data suggest that the apparent association can be partially attributed to confounding, and also reverse causality, whereby cancer leads to low HDL-C rather than HDL-C being truly causal.

Case–control studies have concluded that the characteristic lipid profile of patients with cancer is one of low HDL and LDL-C(15). LDL receptors have been shown to be expressed on certain types of leukemic cells resulting

### Table 1. Baseline variables by quarter of serum HDL-C

<table>
<thead>
<tr>
<th>HDL-C quarters (mmol/L)</th>
<th>Quarter 1: &lt;1.00</th>
<th>Quarter 2: 1.00–1.20</th>
<th>Quarter 3: 1.21–1.42</th>
<th>Quarter 4: &gt;1.42</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n )</td>
<td>3,063</td>
<td>2,906</td>
<td>2,379</td>
<td>2,778</td>
<td></td>
</tr>
<tr>
<td>Age at baseline, y</td>
<td>65.1 (6.4)</td>
<td>65.8 (6.4)</td>
<td>66.0 (6.4)</td>
<td>66.3 (6.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male, %</td>
<td>71.8 (2,199)</td>
<td>61.0 (1,773)</td>
<td>52.6 (1,251)</td>
<td>42.4 (1,177)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes duration, y</td>
<td>7.7 (6.3)</td>
<td>7.8 (6.3)</td>
<td>8.2 (6.6)</td>
<td>8.1 (6.3)</td>
<td>0.004</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>28.9 (5.3)</td>
<td>28.5 (5.0)</td>
<td>28.4 (5.2)</td>
<td>27.5 (5.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hba1c, %</td>
<td>7.5 (1.50)</td>
<td>7.6 (1.6)</td>
<td>7.5 (1.6)</td>
<td>7.4 (1.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.8 (1.2)</td>
<td>5.1 (1.1)</td>
<td>5.3 (1.1)</td>
<td>5.7 (1.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>2.9 (0.9)</td>
<td>3.1 (1.0)</td>
<td>3.2 (1.0)</td>
<td>3.2 (1.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>0.89 (0.11)</td>
<td>1.13 (0.06)</td>
<td>1.33 (0.06)</td>
<td>1.72 (0.29)</td>
<td></td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>2.3 (1.5)</td>
<td>2.0 (1.2)</td>
<td>1.8 (1.1)</td>
<td>1.6 (1.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Smoking status, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>49.9 (1,529)</td>
<td>54.3 (1,578)</td>
<td>59.9 (1,424)</td>
<td>66.7 (1,853)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Former</td>
<td>32.7 (1,001)</td>
<td>29.8 (867)</td>
<td>25.3 (602)</td>
<td>21.3 (592)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current</td>
<td>17.4 (533)</td>
<td>15.9 (461)</td>
<td>14.8 (353)</td>
<td>12.0 (333)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity,%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian/European</td>
<td>62.4 (1,911)</td>
<td>61.3 (1,782)</td>
<td>60.2 (1,432)</td>
<td>55.8 (1,550)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Asian</td>
<td>35.6 (1,091)</td>
<td>36.6 (1,064)</td>
<td>38.1 (906)</td>
<td>42.4 (1,177)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Other</td>
<td>2.0 (61)</td>
<td>2.1 (60)</td>
<td>1.7 (41)</td>
<td>1.8 (51)</td>
<td></td>
</tr>
<tr>
<td>Statin use, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>69.2 (2,120)</td>
<td>70.3 (2,043)</td>
<td>72.3 (1,719)</td>
<td>75.6 (2,101)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Yes</td>
<td>30.8 (943)</td>
<td>29.7 (863)</td>
<td>27.7 (660)</td>
<td>24.4 (677)</td>
<td></td>
</tr>
<tr>
<td>Glucose treatment, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard</td>
<td>49.6 (1,520)</td>
<td>50.4 (1,465)</td>
<td>49.8 (1,185)</td>
<td>50.1 (1,391)</td>
<td>0.9</td>
</tr>
<tr>
<td>Intensive</td>
<td>50.4 (1,543)</td>
<td>49.6 (1,441)</td>
<td>50.2 (1,194)</td>
<td>49.9 (1,387)</td>
<td></td>
</tr>
<tr>
<td>Blood pressure treatment, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>49.4 (1,513)</td>
<td>49.3 (1,434)</td>
<td>51.3 (1,221)</td>
<td>50.3 (1,398)</td>
<td>0.4</td>
</tr>
<tr>
<td>Perindorpl–indapamide</td>
<td>50.6 (1,550)</td>
<td>50.7 (1,472)</td>
<td>48.7 (1,158)</td>
<td>49.7 (1,380)</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE:** Data are mean (±SD) or % (\( n \)). \( P \) values refer to Student \( t \) test, the Mann–Whitney test, or the \( c^2 \) test, as appropriate.
in increased utilization of LDL-C (16), but the same has not been shown for HDL receptors. Low total cholesterol, and therefore low HDL and LDL, have been shown in a wide range of acute and chronic illnesses. Although poor nutrition plays a role (17), there is an interesting body of work that suggests cytokines exert a major influence through several mechanisms (18). Cytokines have been shown to decrease synthesis of apolipoprotein A-I (the main lipoprotein of HDL-C) in the liver (19) and increase catabolism of HDL-C particles (20). It is biologically plausible that undiagnosed cancer results in low HDL-C (21), and therefore low HDL-C. It was shown to decrease synthesis of apolipoprotein A-I (the main lipoprotein of HDL-C) in the liver (19) and increase catabolism of HDL-C particles (20). It is biologically plausible that undiagnosed cancer results in low HDL-C. In our study, careful ascertainment and adjustment for confounding given the risk estimates were attenuated indicating smoking, ethnicity, and BMI indicated a clear role for confounding may have remained. In a similar fashion, cirrhosis, which often predates liver cancer by many years, has been shown to cause low HDL-C due to decreased synthesis (22). Low HDL-C, therefore, may be a marker of the major risk factors for these 2 types of cancer. In our study, careful ascertainment and adjustment for a range of potential confounding factors including smoking, ethnicity, and BMI indicated a clear role for confounding given the risk estimates were attenuated for cancer incidence and no longer significant for cancer mortality.

Kucharska-Newton and colleagues reported a greater risk of developing breast cancer in women with low HDL-C despite exclusion of events occurring in the first 5 years of follow-up (5). However, this association was only seen in premenopausal women and only when HDL-C was stratified as either low or high (using an arbitrary cutoff of 1.29 mmol/L). Analyses by HDL quarters or as a continuous variable did not show a significant

### Table 2. Association between baseline HDL-C and risk of cancer incidence and cancer death per 0.4 mmol/L (1 SD) lower HDL-C

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Crude model HR (95% CI)</th>
<th>Adjusted model Adjusted HR (95% CI)</th>
<th>Cancer within 2.5 years Adjusted HR (95% CI)</th>
<th>Cancer within 2.5–5.0 years Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancer</td>
<td>1.16 (1.06–1.28)</td>
<td>1.10 (1.00–1.22)</td>
<td>1.22 (1.05–1.41)</td>
<td>1.01 (0.89–1.50)</td>
</tr>
<tr>
<td>Digestive cancer</td>
<td>1.12 (0.95–1.31)</td>
<td>1.04 (0.83–1.33)</td>
<td>1.04 (0.83–1.33)</td>
<td>1.03 (0.81–1.31)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1.13 (0.90–1.43)</td>
<td>1.06 (0.83–1.35)</td>
<td>1.28 (0.88–1.89)</td>
<td>0.91 (0.66–1.25)</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>1.37 (1.04–1.82)</td>
<td>0.99 (0.74–1.33)</td>
<td>1.47 (0.91–2.38)</td>
<td>0.75 (0.53–1.06)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>0.81 (0.64–1.04)</td>
<td>1.08 (0.82–1.44)</td>
<td>1.03 (0.67–1.61)</td>
<td>1.09 (0.75–1.59)</td>
</tr>
<tr>
<td>Cancer death</td>
<td>1.16 (1.01–1.32)</td>
<td>1.08 (0.93–1.25)</td>
<td>1.09 (0.85–1.39)</td>
<td>1.08 (0.89–1.28)</td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>316</td>
<td>316</td>
<td>116</td>
<td>200</td>
</tr>
</tbody>
</table>

NOTE: Bold values indicate \( P < 0.05 \).

\( ^{a} \)HRs adjusted for age, sex, diabetes duration, BMI, HbA1C, total cholesterol, smoking, ethnicity, treatment groups, and statin use.
relationship. In another study by the same author reporting on HDL-C and lung cancer, a sensitivity analysis censoring cancers within the first 5 years of follow-up was found to be similar to the whole cohort; however, the statistical significance was not given (4). Taken in entirety, together with our data, there is a lack of persuasive evidence to support a true causal role for HDL-C in the development of cancer.

The strength of this study is that it derives from a large cohort of ethnically diverse patients with prospectively measured HDL-C who were closely followed for 5 years. However, there are several weaknesses. All patients had type II diabetes so the findings may not extrapolate to the general population. The biologic properties of HDL-C, including its anti-inflammatory and anti-oxidant effects, may have been impaired by apolipoprotein glycation (23), but we were unable to test for the extent of this. Although patients were excluded on the basis of any life-threatening nonvascular disease, prior or current cancer was not specifically recorded at study enrolment, which may have resulted in bias toward the conclusions. Although 699 cancers and 316 cancer deaths were recorded, several individual cancer types were not well represented and this may have resulted in insufficient power to show a true weak association. Furthermore, cancer diagnosis, other than cancer death, was not centrally adjudicated, and histologic confirmation of cancer type was not systematically documented.

In conclusion, we show that low HDL-C is a risk marker for cancer. The data suggest that cancer and its associated risk factors may be the cause, rather than the effect, of low HDL-C.

Disclosure of Potential Conflicts of Interest

J. Chalmers has commercial research grant and honoraria from speakers’ bureau from Servier International, M. Woodward is employed (other than primary affiliation: e.g., consulting) as adjunct professor in Johns Hopkins University and is consultant/advisory board member of Roche. N.R. Poulter has honoraria from speakers’ bureau from MSD and Pfizer. S. Zoungas has honoraria from speakers’ bureau from Servier. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions

Conception and design: J. Morton, M.K.C. Ng, N.R. Poulter, S. Zoungas
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. Morton, J. Chalmers, M. Woodward, N.R. Poulter
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J. Morton, M.K.C. Ng, J. Chalmers, M. Woodward, M. Cooper, S. Zoungas
Writing, review, and/or revision of the manuscript: J. Morton, M.K.C. Ng, J. Chalmers, M. Woodward, G. Mancia, N.R. Poulter, M. Marre, M. Cooper, S. Zoungas
Study supervision: M.K.C. Ng, N.R. Poulter

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