Changes in Plasma Lipid and Lipoprotein Cholesterol and Weight prior to the Diagnosis of Cancer

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ABSTRACT

Changes in lipoprotein cholesterol, total plasma cholesterol, and weight prior to the diagnosis of cancer were examined in 103 men who developed cancer in a cohort of 3805 type IIA hyperlipidemic men aged 35–59 enrolled in the Lipid Research Clinics Coronary Primary Prevention Trial. Study measurements were made bimonthly. After adjusting for the effects of the trial intervention and other determinants of lipid levels, the cholesterol levels of the cases diagnosed with nonlocalized cancer dropped below the expected level approaching diagnosis when compared to the entire study population. The decrease averaged 9.3 mg/dl and began about 2 years prior to diagnosis. Weight levels dropped an average of 1.2 kg over the same period. Weight and cholesterol were significantly lower than expected within 8 months of diagnosis ($P < 0.05$). No decrease was seen for those diagnosed with localized malignancies. Patterns for low-density lipoprotein cholesterol reflected those of total cholesterol level. There was no clear relationship between cancer diagnosis and patterns of change for triglycerides and high-density lipoprotein cholesterol. In the future, investigations of any relationship between a host physiological state and cancer occurrence should account for the metabolic effects of preclinical disease demonstrated here. To protect against spurious conclusions, incident cases occurring within 2 years of measurement should be analyzed separately. In studies of cancer mortality, deaths occurring within 3.5 years of the base-line measurement should be analyzed separately.

INTRODUCTION

The report in 1974 by Rose et al. (1) of an inverse association between blood cholesterol level and the risk of cancer sparked a large body of epidemiological research. However, the likelihood that the relationship between low blood cholesterol and cancer risk is a causal one is difficult to evaluate given the general population (7). Several epidemiological investigations have found that the relationship between low blood cholesterol and cancer is strongest in the first 2 years following the base-line examination lowered blood cholesterol levels, a process that McMichael et al. (15) have termed a preclinical cancer effect.

Not every epidemiological investigation has found a preclinical cancer effect, and in at least two reports, the inverse association between cholesterol and cancer has strengthened with increasing time from the base-line measurement (16, 17). Until the nature of the effect of cancer on cholesterol levels is better understood, other questions surrounding the cancer-cholesterol relationship cannot be validly addressed.

In the absence of repeated measurements of cholesterol preceding the diagnosis of cancer, evidence for the preclinical cancer effect is only circumstantial. Three studies have reported direct evidence for a reduction of blood cholesterol preceding cancer diagnosis: the Paris Prospective Study, the Multiple Risk Factor Intervention Trial, and the Framingham Study (8, 13, 18). In the first two studies, the cholesterol decreases were measured from the time before death from cancer rather than before diagnosis, so the possible cholesterol-lowering effect of cancer treatment cannot be separated from the effects of the cancer itself. The Framingham data are for cancer incidence rather than for cancer mortality. However, the interval between measurements was 2 years, so the data cannot address changes over shorter durations. In none of the studies were measurements of lipoprotein cholesterol subfractions available.

This paper examines the preclinical cancer effect in a study population with both cancer incidence data and frequent cholesterol measurement (every 2 months), the Lipid Research Clinics Coronary Primary Prevention Trial. The CPPT was a multicentered, double-blinded, placebo-controlled trial of the bile acid sequestrant cholestyramine among type IIA hypercholesterolemic men, i.e., men with elevated total serum cholesterol due to low-density lipoprotein cholesterol. The trial tested the hypothesis that long-term reduction of serum cholesterol leads to a lowered incidence of coronary heart disease. In addition to total plasma cholesterol, high-density lipoprotein cholesterol, triglyceride, and weight were also measured bimonthly.

MATERIALS AND METHODS

Study Population. The study population, the design, and the results of the CPPT have been described in detail elsewhere (19–22). Briefly, between November 1973 and July 1976, 3806 men aged 35–59 with type IIA hyperlipidemia were randomized into two groups: one received the resin cholestyramine and the other an inert placebo. Type IIA hyperlipoproteinemia was defined as a total cholesterol level in excess of 265 mg/dl, a low-density lipoprotein cholesterol in excess of 190 mg/dl, and a fasting triglyceride level of less than 300 mg/dl. For this analysis, the study follow-up period ended April 30, 1983. The median follow-up time from randomization to the end of the study period was 7.6 years.

Among the exclusion criteria were the presence of conditions predisposing to coronary heart disease (e.g., moderate to severe hypertension, obesity, or diabetes mellitus), secondary hyperlipoproteinemia, or any potentially life-shortening disease. Enrollees were free of clinically apparent cancer. Moreover, as part of the exclusion concerning life-shortening disease, a history of any cancer, except for basal cell carcinoma of the skin, was grounds for exclusion. One randomized partici...
The data from the study was analyzed to determine if there was a preclinical cancer effect. The authors fitted two linear models, one for each treatment group, to predict each individual's total cholesterol, HDL-C, triglyceride, and weight levels. The models were fitted using a linear model and then averaged over time intervals preceding the diagnosis of cancer. The deviations from predicted cholesterol levels were used to identify cases that might have been missed due to preclinical cancer effects.

The statistical methods used included selecting independent variables to increase the precision of the prediction. The variables included in the models were age, the mean of the six previous measurements of lipid or weight, the base-line level, and the dose of drug taken. The models also included factors such as smoking or drinking status during the previous year, any change in smoking or drinking habits, and the average number of cigarettes smoked per day.

The results showed that there was a decrease in cholesterol levels prior to the diagnosis of cancer, indicating a preclinical cancer effect. However, the decrease was not as pronounced as expected, and the mean of the previous six measurements of lipid or weight was not as low as predicted. The authors suggested that a drop in cholesterol levels could be a sign of advanced, undiagnosed disease, but this conclusion was not definitive.

The study was limited by the small number of participants, and the results should be interpreted with caution. The findings suggest that there may be a preclinical cancer effect, but further research is needed to confirm this.

Table 1: Variables included in models used to predict lipid or weight levels

<table>
<thead>
<tr>
<th>Year into trial</th>
<th>Variablea</th>
<th>0-1</th>
<th>2-7</th>
<th>8+</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>C</td>
<td>P</td>
<td>C</td>
<td>P</td>
</tr>
<tr>
<td>1.</td>
<td>Age</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Mean of previous 6 lipid or weight levels</td>
<td>0 0 0 0 0 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Base-line lipid or weight level</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-6.</td>
<td>Year of randomization</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7-17.</td>
<td>Clinic of randomization</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.</td>
<td>Change in smoking status</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19.</td>
<td>Change in average amount drunk</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20.</td>
<td>Average amount smoked</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21.</td>
<td>Drinking status</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22-32.</td>
<td>Month of measurement</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>33.</td>
<td>Mean of previous 6 body mass indices</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>34.</td>
<td>Dose of drug taken</td>
<td>x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35.</td>
<td>Dose-smoking interaction</td>
<td>0 x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36.</td>
<td>Dose-drinking interaction</td>
<td>0 x x x x x x</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Variables 4-19 and 21-32 are indicator variables; all others are continuous variables.

P indicates placebo group; C indicates cholestyramine group; x indicates variable included in model; and 0 indicates variable not included in model.
elevated. In addition, three men had triglyceride measurements set to missing because of levels above 1000 mg/dl. Since LDL-C estimates often depended on the triglyceride measurement, the corresponding LDL-C levels were also set to missing.

RESULTS

Table 2 presents the characteristics of the study population and of those diagnosed with cancer during the trial. Cases and noncases were similar at base line, although cases tended to be older. Surprisingly, cases were neither more likely to have been smokers nor to have consumed more alcohol than the noncases.

Pathological confirmation was available for 71% of the 106 primary malignant neoplasms documented during the trial, excluding nonmelanoma skin cancer. Three of the cases attended no visits after randomization and will not be considered further (sites: bladder, kidney, and larynx). Table 3 lists the site distribution of the 103 cases used in this analysis.

In Fig. 1, which presents the mean deviations from predicted cholesterol level by prediagnostic interval for the cancer cases, each point on the graph represents the mean difference between the observed and predicted cholesterol level in consecutive 4-month intervals preceding the diagnosis of cancer. The date of diagnosis was taken to be the date of a positive biopsy. In the absence of a pathology report, it was the date that some documentation first referred to the cancer as malignant. The rightmost point along the abscissa is the mean deviation from predicted for measurements within 4 months of diagnosis. The point to its left is the mean deviation from expected for measurements more than 4 but less than 8 months prior to diagnosis, and so forth. The 95% confidence bands were derived by constructing 95% confidence intervals around each point and then connecting the upper and lower bounds of the intervals. The confidence intervals should be interpreted primarily as indicators of measurement precision. They should be interpreted as hypothesis tests only cautiously, given the large number of comparisons reported. Points were not plotted if fewer than 10 cases contributed information to the interval.

In general, there is no clear association between cholesterol level and the diagnosis of cancer (see Fig. 1). The largest mean change was for the interval just after 6 years prior to diagnosis, when the cases were 6.8 mg/dl lower than expected. There is no strong evidence of a reduction in cholesterol level approaching the diagnosis of cancer. Fig. 2 shows the mean deviation from expected cholesterol level for those diagnosed with extensive disease. Here there is evidence of a decrease in cholesterol level associated with the diagnosis of cancer, with a 9.3 mg/dl decrease from the 16- to 20-month interval to the first interval prior to diagnosis. Just prior to diagnosis, the cases' plasma cholesterol averaged 6.4 mg/dl below predicted (95% confidence interval, 0.2, 12.9).

The mean deviations from predicted cholesterol levels for those diagnosed with local disease are shown in Fig. 3. There is no evidence for a decrease in cholesterol levels approaching diagnosis. There are, however, two occasions of significantly lower than expected cholesterol levels, in the 72- to 74-month and in the 28- to 32-month prediagnostic intervals.

The patterns of LDL-C are similar to those for total cholesterol (data not shown). Among the extensive disease group,
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Fig. 2. Mean deviations from predicted plasma cholesterol level for cases diagnosed with extensive disease by time preceding diagnosis (with 95% confidence bands).

Fig. 3. Mean deviations from predicted plasma cholesterol level for cases diagnosed with no evidence of extensive disease by time preceding diagnosis (with 95% confidence bands).

There is evidence for a decrease in LDL-C within 20 months of diagnosis as there was for total cholesterol. There was not a clear pattern for either HDL-C or triglyceride (data not shown). For HDL-C, the mean deviation was never more than 1.3 mg/dl from predicted. The deviations from predicted triglyceride level were erratic and conformed to no obvious pattern.

The mean deviations from predicted weight for those with extensive disease are shown in Fig. 4. The patterns of weight deviations are very similar to those for total cholesterol. The cases' weights were below predicted between 6 and 7 years prior to diagnosis. Within 4 months of diagnosis, their weight was 1.2 kg lower than predicted, while between 16 and 20 months of diagnosis, their weight was 0.1 kg lower than predicted.

DISCUSSION

The results indicate that there is a decrease in plasma cholesterol levels associated with cancer apparent within 20 months of diagnosis in patients diagnosed with nonlocalized disease. No decrease approaching diagnosis is seen in those diagnosed with localized disease. Of the lipoprotein fractions, LDL-C most clearly reflects the decrease in total cholesterol. The role of HDL-C and triglyceride in explaining the overall pattern of total cholesterol change is less clear.

A loss in body weight is also seen prior to diagnosis. Its pattern closely resembles that of the decrease in plasma cholesterol levels. Whether the lipid decrease is secondary to the loss of weight or whether the lipid and weight decrease are manifestations of the same underlying metabolic process was not addressed with these data.

There are two reasons to believe that the decrease in weight and cholesterol are related to progressing disease. (a) Extensive disease is associated with the observed effect while nonextensive disease is not, so the presence of a tumor is not sufficient to cause the effect; (b) studies of cholesterol and cancer using cancer mortality as an end point, and studies of cholesterol levels after cancer diagnosis, tend to show even lower cholesterol levels, suggesting a process that is continuing over time (13, 31, 32).

The physiological reasons for the decrease are a matter requiring further investigation. Studies have found increased LDL-C catabolism in patients with prostate cancer, and some malignant cells have been shown to have increased LDL receptor activity (33–35). A host response to a progressing tumor mediated by a substance such as tumor necrosis factor may be involved (36, 37). Physiological responses to tumor necrosis factor include anorexia, cachexia, and disturbances in lipid metabolism (36). Two serum growth factors, human mononuclear colony-stimulating factor and human granulocyte-macrophage colony-stimulating factor, have both been shown to lower blood cholesterol (38, 39). It is not known whether these substances are found at elevated levels in those with extensive disease but not localized disease. Recently, Ueyama et al. (40) have shown that cells from a patient's gallbladder cancer tumor secrete in culture a substance that stimulates LDL receptor activity in normal fibroblasts from other individuals.

The decreases in total cholesterol levels prior to cancer diagnosis seen in the CPPT participants with extensive disease are similar to decreases observed by Sorlie and Feinleib (18) using data from the Framingham cohort and Sherwin et al. (13) using MRFIT data. Fig. 5 compares the adjusted cholesterol decreases of the CPPT cases with extensive disease with male cases from the other two studies. The data from MRFIT were...
for cholesterol measurements prior to death rather than diagnosis. The published data were adjusted in a way conceptually similar to the analysis of the CPPT data. For those who died of cancer during the CPPT, the mean time between cancer diagnosis and death was about 1.5 years. The MRFIT data are plotted assuming an average time of 1.5 years between diagnosis and death. The data from the Framingham Study are adjusted for trends in cholesterol levels over time but not for base-line differences between cases and noncases. Although not reported in the published data, by inspection of Fig. 5, the base-line difference between cases and noncases is about 5.5 mg/dl. Both the unadjusted data and the data adjusted for differences at base line are shown in the figure. The data from these three studies are remarkably similar, especially in the amplitude of change within 2 years of diagnosis. Despite the differences in analytic techniques, the CPPT and the MRFIT curves are almost coincident. The data from Framingham indicate an average decrease of about 6.6 mg/dl beginning sometime between 2 and 4 years prior to diagnosis. The data from these three epidemiological studies are consistent with studies of cholesterol levels in those diagnosed with cancer (31, 32, 41).

The Framingham data are for all incident cases, and so the changes in those in the cohort diagnosed with extensive disease may be considerably larger. Both the MRFIT and CPPT populations were selected, in part, because of high blood cholesterol levels. The changes found in these two studies may be damped compared to decreases found in less selected populations. If, for instance, part of the explanation for the high cholesterol levels in these studies is the presence of a defective LDL receptor gene (as in familial heterozygous hypercholesterolemia), and tumors lower cholesterol by inducing LDL receptors in non-tumor cells, then those with an LDL receptor defect would be expected to show only one-half the response of those with both genes intact. Hence, cancer would lower serum cholesterol less in groups selected because of high cholesterol levels.

The total cholesterol level from 6 to 7 years prior to diagnosis is lower than expected in both extensive and nonextensive disease groups and in both treatment arms (data not shown) (4). There are similarly timed reductions in LDL-C, weight, and triglyceride. The significance of these reductions is unclear. Many of the measurements in these prediagnostic intervals are from the first year of the trial. Both randomization groups experienced an increase in triglyceride levels and a decrease in LDL-C and total cholesterol levels in the first year of the trial (22). The decrease in LDL-C in the placebo group is probably attributable to a combination of a regression to the mean effect and the effect of a cholesterol-lowering diet prescribed to all trial participants. In addition to these effects, the active treatment group took cholestyramine. The diet was one high in polyunsaturated fat designed to lower cholesterol levels 3 to 4% (19). It could be that “overresponders,” detected by having a greater than average drop in cholesterol in the early trial period, were at greater risk of developing cancer. This hypothesis can be tested by examining cases detected after the conclusion of the trial, since they should also show this exaggerated lipid decrease early in the trial.

The question of greatest health concern is whether or not lowering blood cholesterol levels will increase the risk of cancer. The most direct evidence to address this question comes from clinical trials of cholesterol-lowering interventions. The present analysis was not designed to address this issue, but a report of the long-term health consequences of trial participation is in preparation. For several reasons, cardiovascular disease trials have a limited ability to answer the question: most were not designed to examine cancer end points, or were too small to have enough power to convincingly answer the question, or did not follow study subjects long enough to accommodate a reasonable disease latency period in the data analysis. As recently reviewed by Lackner et al. (42), the clinical trial evidence, despite its deficiencies, does not support the hypothesis that lowering cholesterol will increase cancer risk.

In epidemiological studies that account for a preclinical cancer effect in the analysis, the evidence for a relationship between low cholesterol and cancer is inconsistent (4). In most epidemiological studies, when an increase in cancer risk is observed with decreasing cholesterol levels, the relationship is usually seen only below about 195 mg/dl (43). The epidemiological data suggest, therefore, that reducing high cholesterol to this level would not be expected to increase the risk of developing cancer.

The absence of a consistent relationship makes a direct causal role for low cholesterol in the etiology of cancer difficult to support. Several authors have suggested that the low cholesterol-cancer association may be secondary to an inverse relationship between fat-soluble antioxidants or vitamins and cancer (44–48). Blood levels of many of these fat-soluble substances are strongly correlated with levels of blood cholesterol (44, 48–50). This hypothesis remains to be satisfactorily tested.

The results of the study indicate that from about 2 years prior to cancer diagnosis, lipid metabolism is affected for those who are eventually diagnosed with extensive disease. Researchers attempting to relate physiological measurements with the occurrence of cancer need to be mindful of the possible effects of preclinical disease. To protect against spurious conclusions, incident cases occurring with 2 years of measurement should be analyzed separately. In studies of cancer mortality, deaths occurring within 3.5 years of the base-line measurement should be analyzed separately.

REFERENCES

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