

## Endometrial Cancer Risk in Relation to Serum Lipids and Lipoprotein Levels

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### Abstract

**Blood lipids are useful biochemical indicators for assessing the risk of a number of chronic diseases, particularly those associated with obesity. In a multicenter case-control study that included 256 cases and 185 controls less than 75 years old, we studied the risk of endometrial cancer in relation to serum cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and triglycerides. Contrary to expectation, blood lipids were, in general, lower among cases compared with controls. The effects of low blood lipids, specifically cholesterol and low density lipoprotein cholesterol, were limited to older women ( $\geq 55$  years). Risk of the disease in this subgroup of 177 cases and 110 controls was increased 3-4-fold among those with the lowest cholesterol or low density lipoprotein cholesterol values. For example, after adjustment for age, education, smoking status, obesity, and body fat distribution, the relative risks of endometrial cancer across decreasing quartiles of serum cholesterol were 1.0, 2.5, 2.4, and 4.2 ( $P$  for trend  $< 0.01$ ). We examined blood lipid levels by disease stage. The low lipid values of older cases did not appear to be a consequence of the disease. While we cannot rule out the possibility that hypocholesterolemia is a predisposing factor for endometrial cancer, there is no obvious biological explanation for the inverse association.**

### Introduction

Blood lipids are useful biochemical measurements for assessing the risk of developing a number of chronic diseases.

Hypercholesterolemia, for example, is associated with increased risk of coronary artery disease (1). Efforts to reduce serum cholesterol and, perhaps more importantly, to alter cholesterol lipoprotein profiles (e.g., LDL<sup>2</sup> and HDL cholesterol) include advice to avoid obesity, reduce total fat intake, and substitute mono- and polyunsaturates for animal fat (2). While these recommendations are widely endorsed to prevent premature coronary artery disease, a number of epidemiological studies suggest that low serum cholesterol is associated with increased cancer risk (3, 4). Several interpretations of the inverse association have been proposed, including a direct causal link, low cholesterol serving as a marker for the true risk factor(s), or low cholesterol values reflecting disease effects.

The inverse relation of blood cholesterol and cancer risk observed in several cohort studies appears to be most pronounced for cancers of the lung and colon and for hemopoietic cancers (5-7). Most investigations have been restricted to men or included women in such small numbers that gender-specific analyses either were not feasible or were difficult to evaluate. Studies of endometrial cancer may be instructive since a number of risk factors for this disease (e.g., estrogen exposure, obesity, diet) are associated with blood lipids (8, 9). For example, obesity, a major risk factor for endometrial cancer, is positively associated with increased levels of triglycerides and concomitant reductions in HDL cholesterol (9). Several studies suggest that diets rich in total fat and/or animal fat are positively associated with the risk of endometrial cancer (10-13). Consumption of diets rich in saturated fat is associated with increased blood levels of total cholesterol and LDL cholesterol (9).

The relationship of cholesterol to endometrial cancer risk has not been adequately studied and, to our knowledge, the role of various cholesterol lipoproteins has not been evaluated. A large multicenter case-control study provided an opportunity to evaluate risk factors for endometrial cancer (14). The purpose of this report was to assess the risk of endometrial cancer in relationship to serum lipids and cholesterol lipoproteins.

### Materials and Methods

This report is based on data obtained from women who participated in a multicenter case-control study. Cases were accrued during the period June 1, 1987, to May 15, 1990, from seven hospitals in five geographic areas of the United States (Chicago, IL; Hershey, PA; Irvine and Long Beach, CA; Minneapolis, MN; and Winston-Salem, NC). All newly

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<sup>2</sup> The abbreviations used are: LDL, low density lipoprotein; HDL, high density lipoprotein; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol; CI, confidence interval; BMI, body mass index.

diagnosed patients with endometrial cancer who were between the ages of 20 and 74 years, resided in defined catchment areas (usually within 150 miles of the participating medical centers), and had not received previous treatment for their cancer were eligible for the study. A total of 498 incident cases were considered eligible.

For each eligible case, we attempted to select one control matched for age (same 5-year group), race, and location of residence (based on either telephone exchange or zip code). For cases under the age of 65, controls were selected using random digit dialing techniques (15). Of the residential households identified through random digit dialing, an enumeration of female members was obtained for 86%. Older controls were identified by randomly selecting from current Health Care Financing Administration computer tapes a woman of the same age, race, and zip code of residence as each eligible case. A total of 125 of the initially selected random digit dialing controls and 88 of the Health Care Financing Administration controls were eliminated because they reported hysterectomies. These women were replaced with other eligible subjects. A total of 304 random digit dialing and 173 Health Care Financing Administration controls were enlisted.

Interviews were completed with 434 of 498 eligible cases (87.1%) and with 313 of 477 eligible controls (65.6%). The primary reason for nonresponse was refusal (4.8% of cases versus 21.8% of controls). Eligible subjects who were not interviewed were not replaced. All cases were pathologically confirmed with 93% of the interviewed cases having a classification of epithelial cancer. Because of the distinct epidemiological characteristics of sarcomas (16), 29 cases with sarcomas and 16 matched controls were removed from the analysis. Eighty of the interviewed cases and 80 controls refused to provide a blood sample. Blood lipids of 22 cases and 14 controls were not determined due to insufficient sample. Because of the effect of exogenous estrogens on blood lipids and lipoproteins (8, 17), women taking oral contraceptives (2 cases and 0 controls) or menopausal estrogens (44 cases and 16 controls) during the 6-month period prior to the blood collection were removed from the analysis, as were 3 women (1 case and 2 controls) whose use of exogenous hormones could not be determined. This analysis focused on the remaining 256 epithelial cancer cases and 185 controls.

Uniformly trained interviewers administered a standardized questionnaire. The interview included information on demographic factors, pregnancies, menstruation, contraceptive behavior, use of exogenous hormones, family history of cancer, medical conditions, diet, alcohol use, and physical activity. Following the interview a variety of anthropometric measurements were obtained, including waist and thigh circumference to estimate body fat distribution. Detailed descriptions of the methods for diet, alcohol intake, anthropometry, and physical activity assessment are provided elsewhere (13, 18–20).

Participants were asked to provide a fasting blood sample. Nurse interviewers collected samples from cases in the 2-day period prior to surgery. A phlebotomist visited controls in their homes usually within 1 month of the interview. Each field center stored serum samples at  $-70^{\circ}\text{C}$  until the specimens were shipped on dry ice to a central storage facility where they were kept at  $-85^{\circ}\text{C}$ . In mid-1992 the stored samples were sent to a clinical laboratory for chemical analysis. The median time from sample collection to chemical analysis was longer for cases than controls (3.9

versus 2.5 years) because interviewing of controls lagged behind that of cases.

Serum cholesterol, HDLC, and triglycerides were measured enzymatically (21, 22) using an autoanalyzer (Hitachi Model 704/717). Samples for HDLC analysis were pretreated with dextran sulfate to precipitate very low and low density lipoproteins (23). LDLC was calculated by the Friedewald equation (24). The samples were analyzed in batches over a 6-month period. In-house reference samples and blinded quality surveillance samples were inserted into each batch of samples.

Due to skewed distributions, lipid values were log-transformed to evaluate means. Least squares means analysis was used to derive age-adjusted mean values of serum lipids. To estimate the risk of endometrial cancer associated with serum lipids, we calculated odds ratios as approximations of relative risks (25). Unconditional logistic regression was used to adjust for potential confounding variables, deriving maximum likelihood estimates of relative risks and 95% CIs. Tests for trend in the logistic analyses were obtained by categorizing the exposure variable and treating the scored variables as continuous, after eliminating unknown values. To test for trend across stage of disease, we used least-squares regression with stage as the outcome variable and the serum lipid and age as the independent variables. The regression analyses included age as a continuous variable but results were similar when it was entered as a categorical variable (<45, 45–54, 55–64, and  $\geq 65$  years). Education, smoking status, BMI, and body fat distribution were entered into regression analyses as categorical variables. Further adjustment for other potential confounders (*i.e.*, age at menarche, oral contraceptive use, age at menopause, past use of exogenous estrogens, diabetes, alcohol use, physical activity, and intake of total fat and saturated fat) did not materially alter the results.

## Results

The mean age of cases at interview was 58.9 years, compared with 57.1 years among the controls (Table 1). Cases and controls were comparable on race, with 90% of the respondents classifying themselves as non-Hispanic whites. Cases had more years of education and were less likely to be current drinkers or smokers. Early menarche was associated with an increased risk of endometrial cancer but age at natural menopause was not. Cases had fewer births and were less likely to have been oral contraceptive users but they were more likely to have taken menopausal estrogens. Cases, more often than controls, had a history of diabetes, were physically inactive, were obese, tended to accumulate fat on their upper body, and consumed more saturated fat.

Among controls, total cholesterol was highly correlated with LDLC (Spearman  $r = 0.90$ ) and triglycerides ( $r = 0.31$ ). Similarly, LDLC was positively associated with triglycerides ( $r = 0.21$ ). HDLC and triglycerides were inversely associated ( $r = -0.46$ ). With the exception of HDLC, the blood lipids were directly related to age ( $P < 0.01$ ). Spearman correlation coefficients ranged from 0.33 for triglycerides and age to 0.40 for cholesterol and age. Table 2 shows age-adjusted partial correlation coefficients of serum lipids with selected potential confounders. After adjusting for age, neither cholesterol nor LDLC was significantly correlated with education, alcohol intake, smoking, recreational physical activity, BMI, or body fat distribution. HDLC was directly related to education, alco-

**Table 1** Distribution of endometrial cancer cases and controls by other risk factors<sup>a</sup>

	Cases		Controls	
	No.	%	No.	%
Age (yr)				
<45	25	9.8	25	13.5
45–54	54	21.1	50	27.0
54–64	92	35.9	61	33.0
≥65	85	33.2	49	26.5
Education (yr)				
<12	60	23.4	40	21.6
12	76	29.7	55	29.7
13–15	39	15.2	40	21.6
≥16	78	30.5	49	26.5
Alcohol use				
No	116	45.3	62	33.5
Yes	138	53.9	123	66.5
Smoking status				
Never	177	69.1	109	58.9
Former	60	23.4	43	23.2
Current	17	6.6	33	17.8
Age at menarche (yr)				
<13	130	50.8	76	41.1
13	66	25.8	58	31.4
14	38	14.8	27	14.6
≥15	21	8.2	22	11.9
Age at menopause <sup>b</sup> (yr)				
<45	27	14.3	19	15.0
45–49	52	27.5	40	31.5
50–54	82	43.4	49	38.6
≥55	25	13.2	15	11.8
No. of full term births				
0	54	21.1	16	8.7
1	39	15.2	13	7.0
2	51	19.9	61	33.0
3–4	86	33.6	62	33.5
≥5	26	10.2	33	17.8
Oral contraceptive use				
No	210	82.0	119	64.3
Yes	46	18.0	66	35.7
Menopausal estrogen use <sup>b</sup>				
No	163	86.2	119	93.7
Yes	25	13.2	8	6.3
History of diabetes				
No	213	83.2	172	93.0
Yes	41	16.0	13	7.0
Recreational physical activity tertile				
Low	109	42.6	61	33.0
Medium	98	38.3	77	41.6
High	46	18.0	47	25.4
BMI (kg/m <sup>2</sup> ) <sup>c</sup>				
<22.5	49	19.1	41	22.2
22.6–24.9	29	11.3	46	24.9
25.0–28.3	37	14.4	49	26.5
>28.3	139	54.3	44	23.8
Waist-to-thigh circumference ratio <sup>d</sup>				
<1.62	28	10.9	45	24.3
1.62–1.78	49	19.1	49	26.5
1.79–1.99	69	27.0	41	22.2
>1.99	92	36.0	46	24.9
Saturated fat intake (g/day)				
<12	41	16.0	45	24.3
13–18	85	33.2	47	25.4
19–27	60	23.4	46	24.9
>27	67	26.2	46	24.9

<sup>a</sup> For some variables, the number of observations does not equal 441 (256 cases, 185 controls) because of missing values.

<sup>b</sup> Restricted to postmenopausal women.

<sup>c</sup> Body mass index calculated from self-reported weight and height.

<sup>d</sup> Index of body fat distribution.

**Table 2** Age-adjusted Spearman correlation coefficients of serum lipids<sup>a</sup> and potential risk factors for endometrial cancer among 185 control subjects

	Cholesterol	LDLC	HDLC	Triglycerides
Education <sup>b</sup>	0.02	–0.03	0.23 <sup>c</sup>	–0.14
Alcohol <sup>d</sup> intake	–0.05	–0.03	0.32 <sup>c</sup>	–0.25 <sup>c</sup>
Smoking <sup>e</sup>	0.06	0.08	0.12	–0.09
Recreational physical activity <sup>f</sup>	0.01	0.01	0.17 <sup>c</sup>	–0.11
BMI <sup>a</sup>	0.11	0.11	–0.30 <sup>c</sup>	0.30 <sup>c</sup>
Waist-to-thigh circumference ratio <sup>a</sup>	0.08	0.07	–0.17 <sup>c</sup>	0.10

<sup>a</sup> In quartiles.

<sup>b</sup> Education groups defined as <12, 12, 13–15, and ≥16 years.

<sup>c</sup>  $P < 0.05$ .

<sup>d</sup> Alcohol groups defined as 0, <1, 1–4, and >4 drinks/week.

<sup>e</sup> Categories include nonsmokers, former smokers, and current smokers.

<sup>f</sup> Recent physical activity in tertiles.

hol intake, and physical activity and inversely associated with BMI, and upper body fat predominance. Triglycerides were inversely related to alcohol intake but positively associated with BMI. None of the blood lipids were associated with intake of energy, cholesterol, total fat, or saturated fat (data not shown).

Table 3 shows the relationship of endometrial cancer risk to levels of serum lipids and lipoproteins. In general, risk was highest among women with the lowest lipid values. Risk was elevated nearly 2-fold among women in the lowest quartile of serum cholesterol and among women in the lowest quartile of LDL cholesterol. Adjustment for age, education, smoking status, BMI, and body fat distribution did not materially alter these associations. Low levels of HDL cholesterol were also associated with increased risk of the disease (relative risk, 2.7; 95% CI, 1.6–4.6). The relationship, however, was not linear, and the effect of low HDLC was less pronounced (relative risk, 1.7; 95% CI, 0.9–3.2) after adjustment for confounders, particularly BMI. The age-adjusted risk estimates indicated that endometrial cancer risk was reduced about 25% among women with the lowest serum triglycerides compared with women in the highest quartile. After adjustment for BMI and other factors, the direction of the association was reversed; risk was 30% higher (95% CI, 0.7–2.5) among women in the lowest quartile of serum triglyceride compared with women in the highest quartile. There was, however, no response gradient, and no confidence interval excluded unity. No single blood lipid appeared to explain the observed risks. For example, when cholesterol, HDLC, and triglycerides were included in the same regression model the risk estimates for the lowest quartile of the three variables were 1.7 (95% CI, 0.8–3.6) for cholesterol, 1.7 (95% CI, 0.8–3.4) for HDLC, and 1.4 (95% CI, 0.6–2.9) for triglycerides.

The effect of serum lipids across two strata of age are shown in Table 4. Age 55 was selected as the cut point primarily to assess the relationship of HDLC to risk of the disease. Serum HDLC was a potential biochemical marker for alcohol consumption which, in two previous studies (19, 26), was strongly associated with reduced risk of endometrial cancer among women younger than 55 years. While there was no clear response gradient, young women in the lowest quartile of HDLC had 2.7 times the risk of

Table 3 Relative risk of endometrial cancer cases and controls by serum lipoprotein levels (mg/dl)<sup>a</sup>

Variable	Cases	Controls	RR <sup>b</sup>	RR <sup>c</sup>	95% CI
<b>Cholesterol</b>					
>255	52	47	1.0	1.0	
227–255	51	46	1.02	1.12	0.6–2.1
195–226	73	49	1.53	1.72	0.9–3.2
≤194	80	43	2.11	2.06	1.1–4.0
Trend test <i>P</i> value				(0.01)	
<b>LDLC</b>					
>170	52	46	1.0	1.0	
145–170	60	45	1.18	1.28	0.7–2.4
122–144	62	47	1.27	1.36	0.7–2.5
≤121	79	44	1.96	1.93	1.0–3.7
Trend test <i>P</i> value				(0.05)	
<b>HDLC</b>					
>63	49	50	1.0	1.0	
53–63	47	47	1.02	0.98	0.5–1.8
48–52	46	42	1.14	0.81	0.4–1.6
≤47	114	44	2.72	1.74	0.9–3.2
Trend test <i>P</i> value				(0.08)	
<b>Triglycerides</b>					
>146	90	47	1.0	1.0	
100–146	59	47	0.66	0.73	0.4–1.3
73–99	48	47	0.54	0.84	0.4–1.6
≤72	59	44	0.76	1.30	0.7–2.5
Trend test <i>P</i> value				(0.48)	

<sup>a</sup> For some variables, the number of observations does not equal 441 (256 cases, 185 controls) because of missing values.

<sup>b</sup> Age-adjusted relative risk.

<sup>c</sup> Relative risk further adjusted for education, smoking, BMI, and body fat distribution.

women in the highest quartile. Risk associated with low HDLC was reduced to 2.4 (95% CI, 0.8–7.2) after controlling for alcohol intake. Cholesterol and LDLC were not associated with endometrial cancer risk among women under 55 years. Low triglyceride levels were associated with reduced risk of endometrial cancer but there was no response gradient.

Increased risks associated with low serum cholesterol and LDLC were limited to older women (Table 4). Risk of endometrial cancer was increased about 4-fold among women in the lowest quartile of serum cholesterol compared with women in the highest quartile (*P* for trend, 0.002). Risk was increased about 3-fold among women in the lowest quartile of LDLC (*P* for trend, 0.01). HDLC was not associated with endometrial cancer risk among older women after controlling for potential confounders, specifically BMI. Women with the lowest triglyceride values had 2.1 times the risk (95% CI, 0.9–4.8) of those with values above 171 mg/dl but there was no gradient in response.

Because total cholesterol and LDLC were highly correlated we were not able to disentangle the effects of the two variables. Further analyses of older women focused on total cholesterol. To explore the possibility that the relationship of endometrial cancer risk and cholesterol differed among subgroups, we performed a variety of stratum-specific analyses (Table 5). Two categories ( $\geq 240$  and  $< 240$  mg/dl) were created for total cholesterol. The dichotomous cholesterol variable then was cross-classified with two categories (low versus high risk) of BMI (quartiles 1–3 and 4), body fat distribution (quartiles 1–2 and 3–4), physical

Table 4 Relative risk of endometrial cancer by quartiles of serum lipids and lipoproteins (mg/dl) according to age group

Variable	Cases	Controls	RR <sup>a</sup>	95% CI
<b>&lt;55 years</b>				
<b>Cholesterol</b>				
>229	18	18	1.0	
204–229	16	19	0.74	0.2–2.4
180–203	20	18	1.21	0.4–3.8
≤179	25	20	0.91	0.3–2.8
Trend test <i>P</i> value				(0.95)
<b>LDLC</b>				
>150	20	18	1.0	
125–150	14	19	0.85	0.3–2.6
112–124	18	18	0.94	0.3–2.9
≤111	25	19	0.96	0.3–2.8
Trend test <i>P</i> value				(0.98)
<b>HDLC</b>				
>64	12	18	1.0 <sup>b</sup>	
53–64	12	16	1.32	0.4–4.3
48–52	13	19	0.81	0.2–2.6
≤47	42	21	2.36	0.8–7.2
Trend test <i>P</i> value				(0.05)
<b>Triglycerides</b>				
>111	40	18	1.0	
77–111	9	17	0.30	0.1–0.9
60–76	15	20	0.42	0.2–1.2
≤59	15	20	0.38	0.1–1.1
Trend test <i>P</i> value				(0.09)
<b>≥55 years</b>				
<b>Cholesterol</b>				
>274	21	27	1.0	
240–274	41	28	2.47	1.0–6.0
211–239	40	27	2.38	1.0–5.7
≤210	75	28	4.15	1.8–9.7
Trend test <i>P</i> value				(0.002)
<b>LDLC</b>				
>183	26	27	1.0	
155–183	29	27	1.93	0.8–4.5
134–154	44	27	1.85	0.8–4.3
≤133	67	27	3.06	1.3–7.0
Trend test <i>P</i> value				(0.01)
<b>HDLC</b>				
>63	34	24	1.0	
54–63	27	29	0.52	0.2–1.2
47–53	41	28	0.72	0.3–1.6
≤46	75	28	1.03	0.5–2.2
Trend test <i>P</i> value				(0.70)
<b>Triglycerides</b>				
>171	46	25	1.0	
118–171	39	29	0.76	0.3–1.7
90–118	32	27	0.88	0.4–2.0
≤90	60	29	2.10	0.9–4.8
Trend test <i>P</i> value				(0.05)

<sup>a</sup> Adjusted for age, education, smoking, BMI, and body fat distribution.

<sup>b</sup> Further adjusted for alcohol consumption.

activity (moderate-high and low), saturated fat (quartiles 1 and 2–4), alcohol intake (drinker and nondrinker), and smoking status (current smoker and nonsmoker). The lower blood cholesterol level was associated with increased risk among women whose obesity (BMI > 28.3 kg/m<sup>2</sup>) put them at increased risk of endometrial cancer and among women whose BMI was not associated with risk. The effect of

Table 5 Relative risk<sup>a</sup> of endometrial cancer among older women (≥55 years) by two categories of serum cholesterol within strata of potential confounders

Variable and category	Cases	Controls	Serum cholesterol (mg/dl)	
			≥240	<240
BMI (kg/m <sup>2</sup> )				
≤28.3	76	81	1.0	2.40 <sup>b</sup>
>28.3	99	25	6.16 <sup>a</sup>	7.45 <sup>b</sup>
Waist-to-thigh circumference ratio				
<1.79	45	48	1.0	3.02 <sup>b</sup>
≥1.79	117	60	2.88 <sup>b</sup>	4.41 <sup>b</sup>
Physical activity				
Moderate to high	88	71	1.0	1.57
Low	87	39	1.37	3.20 <sup>b</sup>
Saturated fat intake (g/day)				
<19	32	33	1.0	2.00
≥19	142	77	1.81	3.36 <sup>b</sup>
Alcohol intake				
Drinker	88	64	1.0	2.05
Nondrinker	87	46	1.65	2.47 <sup>b</sup>
Smoking status				
Current smoker	50	48	1.0	2.46 <sup>b</sup>
Nonsmoker	125	62	2.74 <sup>b</sup>	4.34 <sup>b</sup>

<sup>a</sup> Adjusted for age and education and further adjusted for smoking, BMI, and body fat distribution as appropriate.

<sup>b</sup> 95% CI excludes unity.

lower blood lipids also was generally consistent across strata of other risk factors including body fat distribution, physical activity, intake of saturated fat, alcohol intake, and smoking.

Finally, to examine the possibility that low levels of cholesterol and other lipids among older cases reflected altered metabolism due to disease, we examined blood levels of cases across disease stages (Table 6). A decrease in blood lipid levels with increasing stage could indicate altered metabolism due to the disease process. On the other hand, blood levels similar for all stages of endometrial cancer but different from control values would suggest that blood levels reflected usual status rather than disease effects. None of the trends in blood levels across disease stage were statistically significant but mean cholesterol and triglyceride values of older women with more advanced disease were lower than those with early stage disease.

## Discussion

To our knowledge this is the first large analytic epidemiological study of endometrial cancer to show that serum cholesterol is inversely associated with risk of the disease. The effect of low cholesterol (and/or LDL) was restricted to women over 55 years but we observed a dose-response relationship in this subgroup, providing further support for the inverse association. Estrogens, both exogenous and endogenous, play a central role in the etiology of endometrial cancer. Menopausal women who use estrogens have increased risk of endometrial cancer (27), and they also experience a reduction in blood cholesterol (8). In the present study, the inverse association of blood cholesterol and endometrial cancer risk could not be attributed to recent use of exogenous estrogens. Furthermore, adjustment for ever use of estrogens did not alter the findings (data not shown). In contrast to exogenous estrogens, relatively little is known

of the relationship of endogenous sex hormones and blood lipids. In one recent study (28), the investigators found no association between endogenous sex steroid hormone concentrations, including estrogens, and serum lipid levels in postmenopausal women.

Concern about low serum lipids, specifically cholesterol, was raised more than 20 years ago following a report of increased cancer risk among men placed on cholesterol-lowering diets (29). However, three subsequent intervention studies did not provide evidence of increased cancer risk among men placed on cholesterol-lowering drugs or diets (30–32). The controversy regarding the relationship of cholesterol and cancer risk has been sustained by conflicting results of prospective epidemiological studies. In two reviews (3, 4) of more than 30 published cohort studies, the authors found ample evidence that serum cholesterol was lower among individuals who subsequently developed cancer. In numerous investigations, the inverse association of serum cholesterol and cancer risk was limited to the first few years of follow-up. This suggested that preexisting but undiagnosed disease at the time of the blood measurement caused the lower cholesterol levels, a phenomenon known as the preclinical disease effect. In some long-term prospective studies (33–35), a preclinical disease effect seemed an unlikely explanation for the low cholesterol values of individuals who developed cancer 10–20 years later.

At the time our study was initiated we thought it unlikely that blood levels of cases would reflect disease effects. We believed that it was appropriate to collect blood samples from women already diagnosed with the disease because endometrial cancer is usually localized and detected in its early stages. Some investigators (36, 37) have reported an increase in LDL receptor activity associated with tumor growth and concomitant decreases in LDL and total cholesterol concentration. When we examined lipid levels by disease stage we found little evidence that the low lipid values of older cases were a consequence of the disease. LDL, for example, was constant across the three disease stages. There was a slight decrease in total cholesterol with progression of the disease. Before completely ruling out disease effects as an explanatory factor for the low cholesterol values of cases, it is worth noting that both cholesterol and triglyceride concentrations were significantly lower at higher disease stage in a recent study of invasive cervical cancer (38).

To our knowledge, only one previous analytic epidemiological study included women in adequate numbers to assess the relationship of serum cholesterol and endometrial cancer risk. Hiatt and Fireman (39) examined the incidence of cancer in California women who had previously provided a blood sample as part of a health examination for a prepaid health plan. The 448 incident cases of endometrial cancer had serum cholesterol levels only slightly lower than those of controls. Other cohort studies with many fewer cases of endometrial cancer have produced conflicting results. In one investigation, the relationship of serum cholesterol to endometrial cancer risk was inverse (33), in one it was direct (40), and in another there was no association (34).

A shortcoming of our study is the low response rate among cases and controls. A significant number of subjects were lost at the interview stage and many of those interviewed refused to provide a blood sample. Unlike those who refused to be interviewed, we could examine characteristics of cases and controls who declined to provide a blood sample. In general, refusers (both cases and controls)

Table 6 Mean values<sup>a</sup> (with 95% CI) of serum lipids and lipoproteins (mg/dl) among controls and cases according to stage of endometrial cancer (analysis restricted to women  $\geq 55$  years)

Group	Number	Cholesterol	LDLC	HDLC	Triglycerides
Controls	110	239 (230–248)	154 (146–162)	52.7 (50.1–55.4)	127 (116–139)
Cases	174 <sup>b</sup>	219 (213–226)	141 (135–146)	49.1 (47.2–51.0)	113 (105–121)
Cases by stage					
I	123	221 (213–229)	141 (134–148)	49.8 (47.5–52.1)	112 (103–122)
II	35	217 (203–232)	138 (126–151)	46.6 (42.7–50.8)	127 (109–149)
III	16	214 (194–236)	142 (124–162)	49.0 (43.0–55.7)	91 (72–115)

<sup>a</sup> Adjusted for age and BMI.

<sup>b</sup> The number of cases does not equal 177 because of missing values for stage or lipid determination.

tended to be older, less educated, smokers, and drinkers. Control women who refused to provide a blood sample tended to be heavier than cases who refused. With the exception of HDLC, this differential would be expected, if anything, to increase rather than decrease the observed case-control differences in blood lipids. The fact that other risk factors for endometrial cancer were similar to those of other studies is also reassuring. We searched for sources of bias which could have resulted in artificially high lipid values among controls and/or low values among cases. We explored the possibility that the control group had unusually high blood lipid levels by comparing the distribution of serum cholesterol values of our control group to those of a reference population. Our quartile cut points for controls were slightly lower than those of women age 55–64 years in the second National Health and Nutrition Examination Survey (41).

We considered the possibility that the inverse association of serum cholesterol and risk of endometrial cancer was secondary to the relationship between cholesterol and some other factor related to the disease. A major strength of our study was the comprehensive assessment of potential risk factors including diet and anthropometry. Others (42, 43) have suggested that the inverse association of cholesterol and cancer risk might be secondary to an association of antioxidants with cancer. We did not measure serum micronutrients but we found no evidence of an inverse association of dietary vitamin C, vitamin A, or carotenoids and cancer risk in this study (13). Kritchevsky (44) observed that the relationship of serum cholesterol and cancer risk among women was dependent on body fat distribution. In our study, low serum cholesterol was associated with increased risk of endometrial cancer regardless of body fat distribution pattern. It is possible that some unknown risk factor (e.g., genetic) for endometrial cancer also predisposes women to low serum lipids.

It is unlikely that the apparent risk associated with low blood cholesterol was due to collection procedures or to an artifact of laboratory analyses. The samples were collected, stored, and analyzed under standardized conditions. Although the time period between collection and analysis was longer for cases than controls, there is no

significant degradation of lipids in serum samples maintained at  $-70^{\circ}\text{C}$ .<sup>3</sup>

We found an inverse association of serum cholesterol and risk of endometrial cancer among older women but it is not clear that low blood cholesterol directly contributes to risk of developing the disease. While we cannot completely rule out bias or confounding as explanatory factors, we did not find clear evidence that lipid levels of the cases were a consequence of the disease. There is, however, evidence in the literature that lipid metabolism is altered by tumors. To fully evaluate the possibility of a preclinical cancer effect for endometrial cancer would require data from a large long-term prospective study, preferably with serial measurements.

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