Annu. Rev. Nutr. 1992. 12:391–416

SERUM CHOLESTEROL AND CANCER RISK: An Epidemiologic Perspective

Stephen B. Kritchevsky

Department of Biostatistics and Epidemiology, University of Tennessee, Memphis, Tennessee 38163

David Kritchevsky

The Wistar Institute, 3601 Spruce Street, Philadelphia, Pennsylvania 19104-4286

KEY WORDS: HDL cholesterol, LDL cholesterol, epidemiology, randomized clinical trials

CONTENTS

INTRODUCTION

Although the possibility of a relationship between low serum cholesterol levels and the risk of cancer has been raised occasionally, it was not until

0199-9885/92/0715-0391$02.00

Pearce & Dayton reported an excess of cancer cases in a clinical trial of a lipid-lowering diet (75) that much interest was expressed. Their observations led to a review, of the then current work, by Ederer et al (25) who stated that if the findings of Pearce & Dayton were not considered, the remaining data suggested no danger from treatment for hypercholesterolemia; if the Pearce & Dayton data were included, a possible danger could be adduced. They concluded that there was no reason to question or suspend treatment of hypercholesterolemia but that further careful observation was warranted. In 1974, Rose et al (81) published an observational study of colon cancer and serum cholesterol in which, contrary to expectation, they found low serum cholesterol to be statistically associated with increased mortality from colon cancer.

By the early 1980s, the number of investigations reporting a serum cholesterol-cancer link was sufficient to warrant the convening of two meetings by the National Heart Lung and Blood Institute to discuss the association (unpublished). Investigations in this area were fairly evenly split between those finding a link between low serum cholesterol and elevated cancer risk and those not finding an association (28). There was also evidence that cancer prior to its diagnosis could itself lower serum cholesterol levels, so that the direction of causality between low serum cholesterol and cancer was in doubt (82).

Data from clinical trials and epidemiologic studies address two distinct but related questions: (*a*) In a given population, is having a serum cholesterol level in the lower end of the population distribution associated with increased cancer risk? (*b*) Does the reduction of serum cholesterol increase cancer risk? Despite the large number of studies in this area, a definitive evaluation of either of these questions has remained elusive. The great majority of the investigations were designed to study cardiovascular disease; thus methodologic issues relevant to cancer investigations frequently have not been addressed. Several deficiencies are frequently found: the lack of cancer incidence data, the lack of histologic verification of the cancer, the failure to exclude subjects with a history of cancer at baseline, the inadequacy of sample sizes for the detection of meaningful differences in cancer occurrence (especially for individual cancer sites), and the failure to consider potential confounders important to cancer investigations. The subject has raised sufficient concern to stimulate a number of reviews and many attempts to explain the findings. Two of the more thorough reviews have been those by McMichael et al (66, 67), who concluded that preclinical cancer leads to hypocholesterolemia and that low serum cholesterol may pose a risk of cancer, principally colon cancer. In this review, we examine the available literature and offer our perspective on this problem.

GROUND RULES

Part of the difficulty in arriving at a conclusion concerning the relationship between serum cholesterol and cancer is that very few studies in this area have approached the issue in exactly the same way. Though in all studies the measurement of serum cholesterol precedes the diagnosis of cancer, the analyses reflect a variety of assumptions concerning the natural history of cancer and the form of the statistical relationship between serum cholesterol and cancer. To facilitate comparisons across studies, we have made a number of decisions concerning the presentation and inclusion of data. Still, the diversity of approaches should be borne in mind when comparing study results.

Epidemiologic Studies Included

Tables 1–5 summarize the epidemiologic evidence relating to low serum cholesterol and increased cancer risk. In several instances, data from the same cohort at different follow-up times or from subpopulations within a cohort have been reported separately. Since these results are not independent, we have decided to include only one report from each study population. Data from the full cohorts are included in preference to data from subpopulations (18, 79, 102, 113, 118); cancer incidence data are preferred to mortality data (3, 20, 42, 115); and reports with longer follow-up periods are included in preference to those with shorter follow-up periods (4, 41, 76, 77, 83, 102). In three instances, single publications report the experience of multiple cohorts (24, 31, 48). Whenever sufficient information is provided, these cohorts are summarized separately. In one publication, an international collaborative group reported the combined experience of 11 separate cohorts (38). Since results from 7 of the 11 cohorts (accounting for 85% of the combined population) are reported elsewhere in detail and the remaining cohorts were either of modest size or had limited follow-up time, this report was not included in the summary tables. In this review we refer to "serum" cholesterol. It should be noted, however, that a number of studies examined plasma rather than serum cholesterol (3, 18, 39, 79, 82, 97, 100, 113, 118). Reports presenting data only in graphical form are not included in this review (28, 50, 57, 92).

Analysis

The studies presented in Tables 1–5 are shown in roughly descending order of the strength of evidence for an association between low serum cholesterol and cancer. Whenever possible, the comparison reported is the ratio of the risk of cancer development for those in the lowest fraction of the serum cholesterol

Table 1 The relative risk of cancer occurrence associated with low serum cholesterol (males)

Geographic location	Size of study population	Number of cases	Duration of follow-up (years)	Endpoint[a]	Most common site	Relative risk of cancer occurrence	Statistical significance ($p < 0.05$)	Ref.
North America	2,753	79	8.4	M	n.r.[b]	2.27	Yes	18
United States	5,125	459	10	I	Lung	2.2[c]	Yes	86
Honolulu	8,006	750	18	M	Lung	2.12, 1.25[c,d]	Yes, no[d]	102
Rural, Puerto Rico	2,585	52	8	M	n.r.	1.8, 2.2[e,f]	Yes, yes[f]	31
Japan	913	43	15	M	n.r.	2.01	Yes	48
Stockholm	— [g]	65	n.a.[h]	M	n.r.	1.8	No	32
Urban, Puerto Rico	6,208	127	8	M	n.r.	1.1, 1.7[e,f]	No, yes[e]	31
Scotland	7,000	630	12	I	n.r.	1.47[c]	Yes	39
Finland[i]	10,537	301	10	I	Prostate	1.3	No	51
18 US cities	361,662	2,989	8	M	Lung	1.3	No	91
N. Europe	2,322	132	15	M	n.r.	1.27	No	48
S. Europe	5,791	224	15	M	n.r.	1.19	No	48
Sweden	46,140	4,455	20	I	n.r.	1.04, 1.06[e,j]	No	110
N. California	73,671	3,218	9.9	I	Prostate	1.01	No	34
Netherlands	878	203	25	I	n.r.	—[k]	n.a.	56
United States	2,299	78	15	M	n.r.	0.98	No	48
E. Finland	2,745	65	7	I	n.r.	0.83	No	84
London	525[g]	267	n.a.	I	Skin	0.75	No	112

[a] M is total cancer mortality, I is total cancer incidence.
[b] n.r. is not reported.
[c] Compares low to high end of the cholesterol distribution.
[d] First and second entries are for 7–12 and ≥13 years of follow-up, respectively.
[e] Relative risk for a 40 mg/dL decrease in blood cholesterol.
[f] First and second entries are for those aged 45–54 and 55–64 years, respectively.
[g] Case-control study; 197 controls.
[h] n.a. is not applicable.
[i] Nonsmokers only.
[j] Range is for results at time intervals throughout the follow-up period.
[k] Inverted U-shaped relationship.

Table 2 The relative risk of cancer associated with low serum cholesterol in studies not fully accounting for a preclinical cancer effect (males)

Geographic location	Size of study population	Number of cases	Duration of follow-up (years)	Endpoint[a]	Most common site	Relative risk of cancer occurrence	Statistical significance ($p < 0.05$)	Ref.
Denmark	230	n.r.[b]	10	M	n.r.	3.75[c]	Yes	2
Malmö, Sweden	7,725	44	6	M	Stomach	2.67[c]	Yes	76, 77
Framingham	1,946	230	18	I	n.r.	1.66	Yes	115
Stockholm	3,486	156	14	M	Gastro-intest.	1.54	No	6
Evans Co., Ga.	1,250	74	14	I	n.r.	1.46[d]	No	42
Chicago	6,890	116	5	M	Lung	1.27	No	24
Israel	10,059	110	7	M	n.r.	1.25[e]	No	119
Chicago	1,899	78	17	M	Colo-rectal	1.09	No	24
Great Britain	7,690	226	9	M	n.r.	1.04	No	90
Chicago	1,233	99	18	M	Lung	0.72	No	24
Oslo, Norway	3,751	89	10	[redacted]	Stomach	0.64	No	114

[a] See Footnote a in Table 1.
[b] See Footnote b in Table 1.
[c] See Footnote c in Table 1.
[d] Compares below median to above median.
[e] Relative risk for a one standard deviation decrease in blood cholesterol.

Table 3 The relative risk of cancer occurrence associated with low serum cholesterol (females)

Geographic location	Size of study population	Number of cases	Duration of follow-up (years)	Endpoint[a]	Most common site	Relative risk of cancer occurrence	Statistical significance ($p < 0.05$)	Ref.
			Studies accounting for a preclinical cancer effect					
Stockholm	—[b]	35	n.a.[c]	M	n.r.[d]	1.8	No	32
Finland[e]	14,783	549	10	I	Breast	1.2	No	51
N. California	86,464	4,259	10	I	Breast	1.14[f]	Yes	34
Scotland	8,262	554	12	I	n.r.	1.10	No	39
Sweden	46,570	4,580	20	I	n.r.	0.90–1.06[g,h]	No	110
United States	7,363	398	10	I	Breast	1.0[f]	No	86
E. Finland	4,221	78	7	I	n.r.	0.83	No	84
North America	2,476	65	8.4	M	n.r.	0.49	No	18
			Studies not fully accounting for a preclinical cancer effect					
Evans Co., Ga.	1,370	53	14	I	n.r.	1.3[i]	No	42
Framingham	2,317	208	18	I	Breast	1.27	No	115
Stockholm	2,378	74	14	M	Gastro-intest.	0.97[f]	No	6
Chicago	5,750	55	5	M	Colo-rectal	0.40	No	24

[a] See Footnote a in Table 1.
[b] Case-control study; 196 controls.
[c] See Footnote h in Table 1.
[d] See Footnote b in Table 1.
[e] See Footnote i in Table 1.
[f] See Footnote c in Table 1.
[g] See Footnote e in Table 1.
[h] See Footnote j in Table 1.
[i] See Footnote d in Table 2.

Table 4 The relative risk of cancer occurrence associated with low serum cholesterol (combined sexes)

Geographic location	Size of study population	Number of cases	Duration of follow-up (years)	Endpoint[a]	Most common site	Relative risk of cancer occurrence	Statistical significance ($p < 0.05$)	Ref.
Europe[b]	822	18	3.1	M	n.r.[c]	3.9	Yes	99
United States	10,940	286	5	I	Lung	1.5	No	69
New Zealand	630	n.r.	17	M	n.r.	1.4[d]	n.r.	83
China	9,021	263	13	M	Lung	1.07[d]	No	14

[a] See Footnote a in Table 1.
[b] Preclinical period not considered in analysis.
[c] See Footnote b in Table 1.
[d] See Footnote e in Table 1.

Table 5 Site-specific associations between low serum cholesterol and cancer

Site	Sex	Size of study population	Number of cases	Duration of follow-up (years)	Endpoint[a]	Relative risk of cancer occurrence
Brain	Female	22,324	14	18	I	1.05[b]
	Male	17,718	32	18	M	0.68[c]
	Male	26,001	30	18	I	0.74[b]
Breast	Female	24,329	242	14	I	2.0[d]
	Female	46,570	1,182	20	I	1.04, 1.28[c,e]
	Female	14,783	95	10	I	1.14[f]
	Female	95,179	1,035	7.9	I	1.06[b]
Colon	Male	2,753	13	8.4	M	5.2
	Male	1,946	30	18	I	3.5
	Male	361,662	138	8	M	1.27[b]
	Male	8,006	80	12–14	I	Inv., No[g]
	Female	86,464	320	10	I	1.09[b]
	Male	73,671	278	10	I	0.90[b]
	Male	45,987	257	15	I	0.90
	Female	46,911	271	15	I	0.88
Lung	Male	5,791	44	15	M	2.54
	Male	913	5	15	M	2.08
	Male	10,537	34	10	I	1.85[f]
	Male	2,322	50	15	M	1.15
	Male	73,671	162	9.9	I	1.06[b]
	Male	2,299	29	15	M	1.05
	Male	361,662	437	8	M	1.04[b]

[a] See Footnote a in Table 1.
[b] See Footnote c in Table 1.
[c] See Footnote e in Table 1.
[d] For cases occurring under 51 years of age only.
[e] First entry is for all women; second is for women <50 years of age adjusting for beta-lipoprotein levels.
[f] See Footnote i in Table 1.
[g] Inverse relationship during follow-up years 5–9.9; no relationship after 10 years of follow-up.

distribution (usually fourths or fifths) compared to the risk of cancer for those in the rest of the distribution. When necessary, this was calculated from data supplied in the original report. Some reports compare the risk of cancer development for those in the lower end of the serum cholesterol distribution with the risk for those in the higher end. In other reports, statistical modeling was used to describe the risk relationship between serum cholesterol and cancer. In these instances the relative risk of cancer development associated with a 40-mg per deciliter (1.03 mmol per liter) decrement in serum cholesterol is presented. Results adjusted for multiple confounders were used when

available. In some studies, the differences in mean serum cholesterol levels between noncases and cases were reported (1, 10, 53, 81, 82, 105). There is little basis on which to compare results from grouped data with results based on individual risk of cancer. Thus, studies reporting grouped differences are not included in the tables.

The Preclinical Cancer Effect

Substantial empirical evidence indicates that, in males, cancer can reduce low density lipoprotein cholesterol (LDL-C) prior to diagnosis, a process that McMichael et al (67) termed a preclinical cancer effect. Cancer patients, except those with breast cancer, have significantly lower serum cholesterol levels than do matched controls (2a, 73). In many epidemiologic studies, the relationship between serum cholesterol and increased cancer risk is strongest for those individuals whose cancer was diagnosed shortly after their cholesterol baseline measurement (10, 34, 38, 48, 51, 82, 91). The implication is that cancer, present but undiagnosed at baseline, was responsible for the lower serum cholesterol among at least some of those who went on to develop the disease. Finally, five studies have reported serial serum cholesterol measurements in individuals who eventually developed cancer. In each study, a decline in serum cholesterol was observed prior to diagnosis in at least some of those developing cancer (10, 55, 91, 98, 117). The effect appears to be manifest approximately two years prior to the diagnosis of clinical disease and four years prior to death, though these periods may be longer for slower growing tumors (55, 91, 98, 117). The mechanism by which cancer can lower serum cholesterol is unclear. However, Ueyama et al (110a) describe a gallbladder tumor cell line derived from a man whose serum cholesterol dropped prior to diagnosis. The culture medium from this cell line was found to increase LDL receptor activity in skin fibroblasts derived from normal individuals.

To avoid spurious associations between low cholesterol and cancer risk it is necessary to account for a preclinical cancer effect analytically. To do so, investigators commonly exclude from analysis individuals whose cancers developed in the first few years of follow-up (i.e. those cancers that are presumed to have been present but undiagnosed at the time of cholesterol measurement). Table 1 includes those studies of males that account for a preclinical cancer effect of at least two years prior to diagnosis or four years prior to death, and the estimates of the strength of association are from statistical analyses accounting for the effect. Table 2 summarizes studies of males that do not account for a sufficiently long preclinical cancer effect. Table 3 summarizes both types of studies for females. Table 4 describes studies that combined the sexes and includes one study that does not provide for a preclinical cancer effect.

Randomized Trials to Lower Serum Cholesterol

Table 6 presents the cancer experience of randomized trials of cholesterol-lowering interventions, both pharmacologic and dietary. Included are both primary and secondary prevention trials and trials in which cholesterol lowering was only one feature of the intervention. In several instances, both the in-trial and post-trial experience have been reported, and both are included in the table.

IS HAVING LOW SERUM CHOLESTEROL ASSOCIATED WITH INCREASED CANCER RISK?

As can be seen in Tables 1–4, the epidemiologic evidence relating low serum cholesterol and cancer risk is inconsistent: both direct and inverse relationships have been reported, and in one study, males in the middle third of the cholesterol distribution had the highest risk of cancer (56).

Taken as a whole, the literature supports a weak association between low serum cholesterol levels and increased occurrence of all cancers in males (Table 1). Among males, the median association across all studies is consistent with about a 30% increase in cancer risk for those with low serum cholesterol levels. The results range from a 227% increase in risk to a 25% decrease in risk. If there were no relationship at all, one would expect the median of the findings to be consistent with a relative risk of one (i.e. no association). Instead, 13 of the 18 study populations (72%) show a relative risk of cancer greater than 1.0. In those studies not fully accounting for a preclinical cancer effect (Table 2), the range of observed results is somewhat broader but the median finding is also consistent with about a 30% increase in cancer risk for those having low serum cholesterol levels.

In Table 1, a preponderance of the studies finding either little or no association between low serum cholesterol and cancer were studies of cancer incidence rather than cancer mortality. Within some study populations a stronger link is noted with mortality than with incidence. The Lipid Research Clinics Mortality Follow-up study found one of the strongest relationships between plasma cholesterol and cancer mortality (18). However, in two of the program's clinics, little or no relationship was found between plasma cholesterol and cancer incidence (113, 118). Similarly, Kagan et al (41) found a significant inverse relationship between serum cholesterol and cancer mortality through nine years of follow-up, but Stemmermann et al (103) found a relationship between serum cholesterol and cancer incidence only for cancer of the colon. On the other hand, Isles et al (39) found the association between plasma cholesterol levels and cancer mortality was weaker than that between plasma cholesterol and cancer incidence. Kark et al (42) found a relative risk of cancer incidence of 1.46 comparing those below and above the

median of the serum cholesterol distribution. Looking at the same population, Davis et al (20) found a distinctly U-shaped relationship between cholesterol and mortality, with those in the middle tertile of the serum cholesterol distribution having a lower mortality rate than those in either the high or low tertile.

In females, the evidence for a low serum cholesterol-cancer association is weaker than in males (Table 3). In 11 of the 12 studies that included both males and females, the strength of the association between cancer and low serum cholesterol in females was weaker than or equal to the association seen in males. In one study (18), low plasma cholesterol was related to decreased cancer mortality among women but increased mortality among men. Only 1 of the 12 study populations found a statistically significant association in women (34). The median of the distribution of findings is consistent with a 5–10% increase in cancer risk for females with low serum cholesterol.

The difference in the strength of association by sex suggests an underlying role of hormonal or metabolic factors. To investigate this question, Kritchevsky (54) examined the role of body fat distribution in the association. Men tend to have more central fat than women both on an absolute and relative basis (59). Increased central adiposity has been associated with lower sex hormone-binding globulin levels in both sexes and with increased free testosterone in premenopausal women (26, 27, 101). In males participating in the National Health and Nutrition Survey Epidemiologic Follow-up Study (NHEFS) low serum cholesterol was associated with increased cancer incidence regardless of body fat distribution. In the females, however, low serum cholesterol was associated with increased cancer risk only among those with central adiposity. In females with peripheral adiposity, low serum cholesterol was associated with decreased cancer risk.

Though few studies have examined lipoprotein subfractions, the low serum cholesterol-cancer association appears to be attributable primarily to LDL-C (18, 100). The relationship between triglyceride levels and cancer has been inconsistent; several studies have reported very weak inverse or null associations (10, 18, 31, 76, 79, 100, 113). In general, no relationship between high density lipoprotein cholesterol (HDL-C) and cancer occurrence has been observed (18, 79, 116, 119). However, Keys (47) found increased HDL-C to be associated with increased cancer mortality.

It is noteworthy that, in males, all of the studies demonstrating a statistically significant association between low serum cholesterol and cancer examined populations that were either entirely or in part community based (2, 6, 18, 31, 48, 86, 102, 115). Cohorts consisting of employed males generally show little or no association. This finding suggests that factors associated with socioeconomic status play some role in the association. Indeed, the association between low serum cholesterol and cancer in Evans County white males was

Table 6 Cancer occurrence in trials of cholesterol reduction

Trial type	Cholesterol lowering intervention	Control	Treatment N	Control N	Treatment cases	Control cases	I/M[a]	Study duration (years)	Post-trial follow-up (years)	Ref.
Primary	Clofibrate	Olive oil	5331	5296	42	25	M	5.3	—	17
Primary[b]	Clofibrate	Olive oil	5331	5296	206	197	M	5.3	7.9	17
Primary	Diet[c]	None	604	628	5	8	M	5.0	—	36
Primary	Diet[d]	Usual care	6428	6438	81	69	M	6–8	—	71
Primary[b]	Diet[d]	Usual care	6428	6438	140	149	M	6–8	3.8	72
Primary	Cholestyramine and diet	Placebo and diet	1906	1900	16(57)	15(57)	M(I)	7.4	—	62
Primary	Diet, probucol, and clofibrate[e]	None	612	610	0	3	M	5.0	—	104
Primary[b]	Diet, probucol, and clofibrate[e]	None	612	610	13	21	M	5.0	10	104
Primary	Gemfibrozil and diet	Placebo and diet	2051	2030	11(31)	11(26)	M(I)	5.0	—	30
Mixed	Diet	Placebo	424	422	31(60)[c]	17(38)[f]	M(I)	8.3	—	75
Mixed[b]	Diet	Placebo	424	422	65	48	I	8.3	2	75
Mixed	Colestipol HCL	Placebo	548	546	2	2	M	1–3	—	23

Mixed	Diet	None	2197	2196	16	12	M	4.5	—	29
Mixed[g]	Diet	None	2344	2320	7	8	M	4.5	—	29
Secondary	Diet	None	229	229	4	4	I	5.0	—	60
Secondary[b]	Diet	None	206	206	7	5	M	5.0	6	61
Secondary	Niacin	Lactose	1119	2789	14	27	M	6.2	—	11
Secondary[b]	Niacin	Lactose	1119	2789	45	124	M	6.2	8.8	11
Secondary	Clofibrate	Lactose	1103	2789[h]	11	27	M	6.2	—	11
Secondary[b]	Clofibrate	Lactose	1103	2789	37	124	M	6.2	8.8	11
Secondary	Colestipol HCl, niacin, and diet	Placebo and diet	94	94	2	[redacted]		2.0	—	5
Secondary	Clofibrate, nicotinic acid, and diet	Diet	279	276	10	6	n.r.[i]	5.0	—	12

[a] Endpoint; I is cancer incidence, M is cancer mortality.
[b] Same study population as preceding entry.
[c] Treatment group also advised to quit smoking.
[d] Treatment also included blood pressure control through diet and drugs and a cigarette smoking intervention program.
[e] Probucol was used to treat type IIA hyperlipidemia and clofibrate was used to treat type IIB. Treatment also included drug treatment for blood pressure control and interventions design to encourage increased physical activity and smoking cessation.
[f] Deaths are from carcinomas only.
[g] Women only.
[h] Same control group as preceding entry.
[i] See Footnote b in Table 1.

much more pronounced in those of lower socioeconomic status than in those of higher socioeconomic status (42).

Site-Specific Relationships

Table 5 presents findings from investigations of several specific cancer sites. No indication of statistical significance is given because, in light of the small number of cases, lack of significance could be misinterpreted as a null result. In several studies of males, the strongest site-specific relationships have been found for colon cancer (18, 81, 103, 115). Generally, no relationship has been seen in females. In the Honolulu Heart Study, the relationship was particularly strong for men over age 55 at baseline (103). Several studies, however, have found no relationship (34, 37, 91), and Törnberg et al (109) found that males and females with both high serum cholesterol and high beta-lipoprotein levels were at elevated risk of colon cancer.

The location of the tumor in the bowel may be important. Stemmermann et al (103) found a relationship with low serum cholesterol levels primarily for tumors of the cecum and ascending colon. However, Sidney et al (94) found no association no matter which part of the bowel was examined.

The idea that low serum cholesterol is directly related to colon cancer risk is inconsistent with findings from studies of individuals with adenomatous polyps, the hypothesized colon cancer precursor lesion. In a case-control study, Mannes et al (64) found that subjects with high cholesterol levels were twice as likely to have polyps as those with low cholesterol levels. Two other case-control studies found no association between polyps and cholesterol levels (21, 73). Among other sites of the gastrointestinal tract, stomach cancer has been linked to low cholesterol levels while rectal cancer has been linked with elevated levels (107, 109).

Despite the attention focused on colon cancer, other sites have been linked more consistently with low serum cholesterol levels. Lung cancer has consistently, albeit weakly, been related to low cholesterol levels in males but not females. The strongest relationship was observed among three Southern European cohorts participating in the Seven Countries Study: those in the lowest quintile of the distribution were more than 2.5 times more likely to die from lung cancer (48). In the extended follow-up of the Honolulu Heart program, Stemmermann et al (102) reported that the mean baseline cholesterol level for subjects dying of lung cancer more than 12 years after the initial examination was 212.7 mg per deciliter (5.50 mmol per liter) compared to 218.4 mg per deciliter (5.64 mmol per liter) for the survivors.

Malignancies of the hematopoietic system have also been associated frequently with low cholesterol levels. In a study of over 360,000 males, participants in the lowest quintile were at over 80% increased risk (91). Knekt et al (51) found that among nonsmokers, males in the lowest quintile were

five times more likely to develop either leukemia or lymphoma than were males with higher cholesterol levels. Nonsmoking women with low cholesterol were 1.7 times more likely to develop either leukemia or lymphoma than were nonsmoking women with higher cholesterol levels.

Among females, cervical cancer has been consistently related to low serum cholesterol levels. In a study of cancer incidence among health plan enrollees (34), the cervix was the only site for which a statistically significant relationship with low serum cholesterol was noted after excluding cases diagnosed during the first two years of follow-up. Schatzkin et al (87) also reported a strong association between cervical cancer and low serum cholesterol in the NHEFS. In an Australian case-control study, women with low plasma cholesterol levels (<154.4 mg per deciliter; <3.99 mmol per liter) were more than two times as likely to have *in situ* cervical cancer than were women with high cholesterol levels (≥231.6 mg per deciliter; 5.98 mmol per liter) (8).

In two studies of breast cancer, tumors diagnosed in women below about 50 years of age were linked to low cholesterol levels, but cancer diagnosed at later ages was not (108, 111). Törnberg et al (108) found that in younger women, both higher serum beta-lipoprotein and lower serum cholesterol levels were associated with increased risk of breast cancer. This finding implies that low HDL-C was associated with increased cancer risk. As reviewed by Boyd & McGuire (7), a number of studies have reported depressed HDL-C levels in women with breast cancer. Several other studies have not found a relationship between total serum cholesterol and breast cancer, but none of the analyses were stratified by age of disease onset (35, 39, 51, 87).

Schatzkin et al (87) reported a strong relationship between low serum cholesterol and increased incidence of smoking-related cancers (sites: lung, mouth, larynx, esophagus, pancreas, bladder, cervix, and leukemia). The relationship was seen in both men and women and persisted throughout the follow-up period. The relationship was slightly stronger for nonsmokers than for smokers, a finding similar to that of Knekt et al (51) for all cancers. In males, Cowan et al (18) found that low total plasma cholesterol and LDL-C levels were only slightly more strongly related to mortality from smoking-related cancers (sites: larynx, lung, and bladder) than to mortality for all cancers. They found that females with low plasma LDL-C levels had elevated mortality from smoking-related tumors, contrary to the relationship seen for all cancers.

Distinct from many other sites, brain cancer has been linked to elevated cholesterol levels (see Table 5). Three studies have found higher cholesterol to be associated with increased occurrence of brain cancer, at least in males (1, 52, 97). Abramson & Kark (1) found that patients with primary brain tumors had serum cholesterol levels 22 mg per deciliter (0.57 mmol per liter)

higher than controls. Two other studies have found high cholesterol to be associated with increased occurrence of malignant tumors of the nervous system (91, 112).

Explanations and Hypotheses

Several mechanisms have been offered to explain why low cholesterol levels might be associated with increased cancer risk.

1. CHOLESTEROL AND THE PHYSICAL CHEMISTRY OF THE CELL MEMBRANE Researchers have speculated (74) that increased cell membrane fluidity, which might be associated with low serum cholesterol levels, may increase the likelihood of neoplastic transformation. However, Marenah et al (65) found that HDL-C and LDL-C levels were unrelated to cell membrane fluidity in monocytes from individuals with a wide range of serum cholesterol levels (124–387 mg per deciliter; 3.20–10.0 mmol per liter).

2. MEMBRANE CHOLESTEROL AS AN INFLUENCE ON TUMOR ANTIGENICITY Another suggestion is that the loss of membrane cholesterol may render tumor cells less antigenic (93), thereby allowing transformed cells to escape immune system surveillance. A link between low serum cholesterol and reduced tumor immunogenicity would explain why low serum cholesterol may be more strongly linked with cancer mortality than with cancer incidence. However, as a rule, solid tumors tend to contain more, not less, cholesterol than normal tissues (13).

3. ANTIMITOGENIC EFFECTS OF VERY LOW AND LOW DENSITY LIPOPROTEINS The presence of LDL can inhibit the activation of lymphocytes after exposure to a variety of mitogens and antigens (15, 19, 70), and the major apoproteins that constitute LDL (apo B and apo E) can inhibit lymphocyte activation in their purified forms (63). Ito et al (40) have also shown that LDL can inhibit cell proliferation in a number of cultured cell lines. Possibly, low levels of circulating lipoproteins are permissive of mitogenesis, or, conversely, high levels may exert an antipromoting effect.

4. LOW DENSITY LIPOPROTEINS AS INHIBITORS OF VIRALLY INDUCED CELL TRANSFORMATION Chisari et al (16) found that physiologic concentrations of both LDL and VLDL suppress Epstein-Barr virus-induced immortalization of adult human B lymphocytes. Their findings suggest the possibility that hypocholesterolemia may play a role in other virally linked malignancies. Epidemiologic evidence points strongly to a viral etiology for cervical cancer (33). Cervical cancer is one of the cancers most strongly linked to low serum cholesterol levels in females.

5. GENETIC APOPROTEIN VARIANTS MAY BE LINKED TO INCREASED CANCER SUSCEPTIBILITY Katan (45) has suggested that the apolipoprotein E (apo E) E-2 allele may explain the low serum cholesterol-cancer association. Apo E-2 is associated with lower total cholesterol levels in a number of populations, but it is not known whether the E-2 phenotype is associated with increased cancer risk. If there were a genetic explanation, one would expect to see an excess of cancer in families of probands with low cholesterol levels. Two studies have found that low levels of cholesterol were associated with increased cancer occurrence in mothers of probands (22, 120). Schrott et al (88) found that cancer was more commonly reported at death among the relatives of children with low serum cholesterol levels than among the relatives of children with high cholesterol levels. Contrary to these findings, Reed et al (80) found lower cancer family history scores in participants with low total cholesterol levels, but an excess of cancer mortality in the parents of males with higher HDL-C levels.

6. DIETARY DETERMINANTS OF SERUM CHOLESTEROL AND CANCER If diet underlay the low cholesterol-cancer association, one would expect either increased polyunsaturated fat intake or lower saturated fat and dietary cholesterol intake among those developing cancer. In the NHEFS, despite having lower serum cholesterol levels, males developing cancer ingested a more hyper-cholesterolemic diet than those not developing cancer (54). The difference primarily reflected increased saturated fat and cholesterol intake; there was no difference in linoleic acid intake. Interestingly, Laskarzewski et al (58) found that the LDL-C level of progeny whose mothers had died of cancer was lower with increasing dietary cholesterol consumption than the level of those whose mothers had not died of cancer.

7. LEVELS OF FAT-SOLUBLE ANTIOXIDANTS OR VITAMINS AND CANCER Vitamin E and several carotenoids are transported in the LDL particle, and their circulating levels are correlated with serum cholesterol (44, 96, 106). Low cholesterol levels, therefore, could also mean low levels of these substances—especially in populations already at marginal levels. Low levels of beta-carotene have been linked fairly consistently to elevated risk of lung cancer, but the relationship between other carotenoids and cancer has not been well studied (68). Low levels of vitamin E have also been linked to increased risk of lung cancer, though less consistently than levels of beta-carotene (68). It may be, therefore, that the observed relationship between low serum cholesterol and cancer could, in fact, be due to a relationship between low levels of circulating vitamin E and/or carotenoids and not to any direct effect of serum cholesterol. Whether or not the association between low serum cholesterol and cancer is confounded by lipid-soluble vitamins and anti-

oxidants and cancer has not been determined. Kark et al (43) found that the low cholesterol-cancer association in the Evans County study was diminished after accounting for serum retinol levels. Subsequent study, however, has not supported an association between low serum vitamin A levels and increased cancer risk (68).

8. LOW SERUM CHOLESTEROL MIGHT REFLECT HIGHER BILE ACID FLUXES IN THE BOWEL Subjects who eliminate dietary cholesterol more efficiently or those on drugs that enhance cholesterol excretion via the bile would have an increased flux of bile acids through the colon. Bile acids and their salts have been shown to be promoters of colon cancer in experimental animals. This explanation might be plausible for colon cancer, but low serum cholesterol levels are associated with other sites as well. The data have recently been reviewed by Broitman (9).

None of these explanations can explain why males should be preferentially affected. None of the explanations offered are mutually exclusive. The difficulty in understanding this relationship may be that the relationship between cholesterol and cancer depends on a number of different pathways for different tumor types.

DOES REDUCING SERUM CHOLESTEROL INCREASE CANCER RISK?

The epidemiologic evidence does not address the question of whether or not reducing serum cholesterol—as opposed to having low serum cholesterol—leads to an increase in cancer occurrence. The most direct evidence derives from randomized clinical trials of lipid-lowering interventions (see Table 6). Thirteen reports, including 14 experimental cholesterol-lowering interventions, have also provided data on cancer occurrence. With the exception of one investigation (29), the majority of study participants have been male.

A modest excess of cancer occurrence has been reported in trials of lipid-towering interventions. In all, 252 cancers deaths (this number includes 6 incident cases from trials not reporting mortality) have been reported among 25,269 individuals randomized to the experimental interventions, and 208 cancer deaths (this number includes 5 incident cases) have been reported among the 25,774 individuals randomized to various control groups, for a 24% excess in the occurrence of cancer in the intervention groups ($p < 0.05$). The excess of cancer in treatment groups is seen to a greater or lesser extent in both dietary and pharmacologic interventions (23% and 26%, respectively) and in primary, secondary, and mixed prevention trials (18%, 20%, and 43%, respectively). Three trials provided both incidence and mortality data, but

there is insufficient evidence to judge if patterns of incidence and mortality differ (30, 62, 75).

In four studies of pharmacologic interventions, both the placebo and treatment groups received dietary counseling for cholesterol reduction (5, 12, 30, 62). In other words, there was no real control group since serum cholesterol reduction was a feature of both treatment arms. When these four studies are dropped from consideration, a 26% excess in cancer occurrence is noted among the treatment groups.

The trials reviewed are of short duration relative to the carcinogenic process. Risk increases due to exposure to tumor initiators such as cigarette smoke are typically evident only after at least ten years from first exposure. If the lowering of serum cholesterol has an effect, it is on a later stage in the carcinogenic process, either promotion or progression. An important clue concerning the biologic process involved comes from the post-trial cancer experience of these trials.

The post-trial cancer experience has tended to be very different from the in-trial experience. During the WHO clofibrate trial, the annual cancer mortality rate was 1.9 per thousand in the clofibrate group and 1.2 per thousand in the placebo group. In the post-trial follow-up the rates were 2.61 and 2.78 per thousand, respectively (17). In a dietary intervention trial, Pearce & Dayton (75) reported an excess of 14 carcinoma deaths in the intervention group during the trial period and an excess of 3 deaths within one year of the end of the trial, but a deficit of 6 deaths in the second year after the trial. In both the Coronary Drug Project and the Multiple Risk Factor Intervention Trial, modest increases in cancer mortality in the experimental groups during the studies were followed by deficits in cancer mortality after the conclusion of the trials (11, 72).

The combination of an excess of cancers during the intervention period followed by a post-trial deficit suggests that serum cholesterol lowering provides an environment that somehow promotes tumor outgrowth. The reduction of circulating lipoprotein levels may lessen whatever antiproliferative effect they might exert. Alternatively, serum cholesterol lowering might accelerate the growth of tumors already established. Thus, after the trial stops and the pool of initiated tumors in the experimental group is depleted, the group experiences a lower post-trial rate of cancer occurrence than that of the control group.

Cholesterol is synthesized from acetate in a well-characterized pathway in which acetate is converted to beta-hydroxymethylglutarate (HMG), which under the influence of HGM-CoA reductase is converted to mevalonic acid. Mevalonic acid is metabolized to isoprenyl pyrophosphate. From this point, the pathway involves the combination of 2 isoprenoid units to give a geranyl

derivative (10 carbon atoms), and then a farnesyl derivative (15 carbon atoms). Two farnesyl units combine to form squalene ($C_{30}H_{50}$), which is cyclyzed to lanosterol, which is eventually converted to cholesterol.

Until recently investigators thought that beyond HMG-CoA the synthetic process was committed to cholesterol, dolichol, and ubiquinone. It is now apparent that other vital metabolic pathways depend on products of cholesterol biosynthesis and may be affected if synthesis is affected. Siperstein et al (95) have shown that the inhibition of HMG-CoA activity blocks cellular DNA synthesis, which carries forward when exogenous mevalonate is provided. The $p21^{ras}$ growth protein is farnesylated as a posttranslational modification. Without this modification, the protein is inactive and cell growth is blocked (32a). Furthermore, some evidence suggests that the induction of *de novo* cholesterol synthesis may enhance cell growth. Kazanecki et al (46) found that reducing serum LDL by dietary manipulation stimulated cell proliferation in a number of tissues in weanling rats. In the context of carcinogenesis, Rao et al (78a) found that serum cholesterol reduction through either a high polyunsaturated fat diet or cholestyramine promoted 7,12-dimethylbenz[*a*]anthracene-induced mammary tumors in female rats.

It could be that by stimulating *de novo* cholesterol synthesis, lipid-lowering interventions cause an increase in the pool of substrate necessary to carry forward cell division. While this process may not affect tightly regulated normal cell populations, it may allow accelerated proliferation in transformed populations. Based on this model, clinical trials of HMG-CoA inhibitors would be expected to show a reduction of cancer occurrence in the treatment groups, since the amount of mevalonate and its metabolites would be reduced.

SUMMARY AND CONCLUSIONS

This review has examined the evidence surrounding two questions: (*a*) Is having low serum cholesterol associated with increased risk of cancer? (*b*) Does reducing serum cholesterol increase the occurrence of cancer? Some elevated risk of cancer for males with low serum cholesterol levels has been noted: the median of the studies examined is consistent with a 30% increased risk. The answer for females is less clear. The median of the studies examined suggests no more than a 5–10% increased risk associated with having low serum cholesterol. However, the risk seems to depend strongly on whether females have a central or peripheral body fat pattern (54). The cancers most consistently associated with low serum cholesterol levels are those of the colon and lung in males, the cervix and breast (but only for females under 50 years of age) in females, and leukemia in both sexes. In contrast, high cholesterol levels have been linked with an increase in brain cancer.

While immunologic, genetic, and dietary explanations have been offered to

explain the association, it is difficult to support the idea that low serum cholesterol causes cancer in any direct manner. First, the findings themselves tend to be generally weak and somewhat inconsistent. Second, the strong influence of fat distribution in women suggests that a metabolic/hormonal basis underlies the association. One would not expect the results to differ by body fat pattern if the relationship were a causal one. Finally, if there were a direct causal role, one would expect populations with low serum cholesterol levels to have higher cancer rates. In China, counties with the lowest average plasma cholesterol levels have the lowest cancer rates (78). While this observation is open to a number of interpretations, it does not support the idea that low serum cholesterol is a tumor initiator.

In aggregate, the trials of lipid-lowering interventions reviewed here show an increase in cancer occurrence (primarily mortality) of approximately 24% in the cholesterol-lowered groups. However, the post-trial experience has shown a comparative deficit of cancer occurrence in the experimental groups. Recent evidence indicates that products in the cholesterol biosynthetic pathway affect DNA replication and cell proliferation. These findings suggests a mechanism by which cholesterol lowering might accelerate the development of tumors already initiated. The data that have been reviewed in no way suggest that treatment of hypercholesterolemia should not be pursued. They do suggest the presence of a relatively small subpopulation in whom reduction of plasma cholesterol may lead to increased occurrence of cancer. Vigorous efforts should be made to identify the susceptible population.

ACKNOWLEDGMENTS

The authors thank Diane Becton for her assistance with the tables and Nannette C. Gover for her editorial advice.

Literature Cited

1. Abramson, Z. H., Kark, J. D. 1985. Serum cholesterol and primary brain tumors: a case-control study. *Br. J. Cancer* 52:93–98
2. Agner, E., Hansen, P. F. 1983. Fasting serum cholesterol and triglycerides in a ten-year prospective study in old age. *Acta Med. Scand.* 214:33–41
2a. Alexopoulos, C. G., Blatsios, B., Avgerinos, A. 1987. Serum lipids and lipoprotein disorders in cancer patients. *Cancer* 60:3065–70
3. Anderson, K. M., Castelli, W. P., Levy, D. 1987. Cholesterol and mortality: 30 years of follow-up from the Framingham Study. *J. Am. Med. Assoc.* 257:2176–80
4. Beaglehole, R., Foulkes, M. A., Prior, I. A. M., Eyles, E. F. 1980. Cholesterol and mortality in New Zealand Maoris. *Br. Med. J.* 280:285–87
5. Blankenhorn, D. H., Nessim, S. A., Johnson, R. L., Sanmarco, M. E., Azen, S. P., et al. 1987. Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. *J. Am. Med. Assoc.* 257:3233–40
6. Böttiger, L. E., Carlson, L. A. 1982. Risk factors for death for males and females. *Acta Med. Scand.* 211:437–42
7. Boyd, N. F., McGuire, V. 1990. Evidence of association between plasma high-density lipoprotein cholesterol and risk factors for breast cancer. *J. Natl. Cancer Inst.* 82:460–68

8. Brock, K. E., Hoover, R. N., Hensley, W. J. 1989. Plasma cholesterol and *in situ* cervical cancer: an Australian case-control study. *J. Clin. Epidemiol.* 42:87–89
9. Broitman, S. A. 1986. Cholesterol conundrums: The relationship between dietary and serum cholesterol in colon cancer. In *Dietary Fat and Cancer*, ed. C. Ip, D. F. Birt, A. E. Rogers, C. Mettlin, pp. 435–59. New York: Liss
10. Cambien, F., Ducimetiere, P., Richard, J. 1980. Total serum cholesterol and cancer mortality in a middle-aged male population. *Am. J. Epidemiol.* 112:388–94
11. Canner, P. L., Berge, K. G., Wenger, N. K., Stamler, J., Friedman, L., et al. 1986. Fifteen year mortality in Coronary Drug Project patients: Long-term benefit with niacin. *J. Am. Coll. Cardiol.* 8:1245–55
12. Carlson, L. A., Rosenhamer, G. 1988. Reduction of mortality in the Stockholm Ischaemic Heart Disease Secondary Prevention Study by combined treatment with clofibrate and nicotinic acid. *Acta Med. Scand.* 223:405–18
13. Chen, H. W., Kandutsch, A. A., Heiniger, H. J. 1978. The role of cholesterol in malignancy. *Prog. Exp. Tumor Res.* 22:275–316
14. Chen, Z., Peto, R., Collins, R., MacMahon, S., Lu, J., et al. 1991. Serum cholesterol concentration and coronary heart disease in population with low cholesterol concentrations. *Br. Med. J.* 303:278–82
15. Chisari, F. V. 1977. Immunoregulatory properties of human plasma in very low density lipoproteins. *J. Immunol.* 119: 2129–36
16. Chisari, F. V., Curtiss, L. K., Jensen, F. C. 1981. Physiologic concentrations of normal human plasma lipoproteins inhibit the immortalization of peripheral B lymphocytes by the Epstein-Barr virus. *J. Clin. Invest.* 68:329–36
17. Committee of the Principal Investigators. 1984. WHO cooperative trial on primary prevention of ischaemic heart disease with clofibrate to lower serum cholesterol: final mortality follow-up. *Lancet* 2:600-4
18. Cowan, L. D., O'Connell, D. L., Criqui, M. H., Barrett-Connor, E., Bush, T. L., et al. 1990. Cancer mortality and lipid and lipoprotein levels: the Lipid Research Clinics Program Mortality Follow-up Study. *Am. J. Epidemiol.* 131:468–82
19. Curtiss, L. K., Edgington, T. S. 1976. Regulatory serum lipoproteins: regulation of lymphocyte stimulation by a species of low density lipoprotein. *J. Immunol.* 116:1452–58
20. Davis, C. E., Knowles, M., Kark, J., Heyden, S., Hames, C. G., et al. 1983. Serum cholesterol levels and cancer mortality: Evans County twenty-year follow-up study. In *Dietary Fats and Health*, ed. E. G. Perkins, W. J. Visek, pp. 892–900. Champaign, Ill: Am. Oil Chem. Soc.
21. Demers, R. Y., Neale, A. V., Demers, P., Deighton, K., Scott, R. O., et al. 1988. Serum cholesterol and colorectal polyps. *J. Clin. Epidemiol.* 41:9–13
22. Deutscher, S. 1971. Levels of serum cholesterol among offspring of parents who died of cancer: a comparison with coronary heart disease. *J. Natl. Cancer Inst.* 46:217–24
23. Dorr, A. E., Gundersen, K., Schneider, J. C. Jr., Spencer, T. W., Martin, W. B. 1978. Colestipol hydrochloride in hypercholesterolemic patients—effect on serum cholesterol and mortality. *J. Chronic Dis.* 31:5–14
24. Dyer, A. R., Stamler, J., Paul, O., Shekelle, R. B., Shoenberger, J. A., et al. 1981. Serum cholesterol and risk of death from cancer and other causes in three Chicago epidemiological studies. *J. Chronic Dis.* 34:249–60
25. Ederer, F., Leren, P., Turpeinen, O., Frantz, I. D. Jr. 1971. Cancer among men on cholesterol-lowering diets: experience from five clinical trials. *Lancet* 2:203–6
26. Evans, D. J., Barth, J. H., Burke, C. W. 1988. Body fat topography in women with androgen excess. *Int. J. Obesity* 12:157–62
27. Evans, D. J., Hoffmann, R. G., Kalkhoff, R. K., Kissebah, A. H. 1983. Relationship of androgenic activity to body fat topography, fat cell morphology and metabolic aberrations in premenopausal women. *J. Clin. Endocrinol. Metab.* 57:304–10
28. Feinleib, M. 1982. Summary of a workshop on cholesterol and noncardiovascular disease mortality. *Prev. Med.* 11:360–67
29. Frantz, I. D. Jr., Dawson, E. A., Ashman, P. L., Gatewood, L. C., Bartsch, G. E., et al. 1989. Test of effect of lipid lowering by diet on cardiovascular risk: the Minnesota Coronary Survey. *Arteriosclerosis* 9:129–35
30. Frick, M. H., Elo, O., Haapa, K., Heinonen, O. P., Heinsalmi, P., et al. 1987. Helsinki Heart Study: primary-

prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *New Engl. J. Med.* 317:1237–45
31. Garcia-Palmieri, M. R., Sorlie, P. D., Costas, R. Jr., Havlik, R. J. 1981. An apparent inverse relationship between serum cholesterol and cancer mortality in Puerto Rico. *Am. J. Epidemiol.* 114:29–40
32. Gerhardsson, M., Rosenqvist, U., Ahlbom, A., Carlson, L. A. 1986. Serum cholesterol and cancer: a retrospective case-control study. *Int. J. Epidemiol.* 15:155–59
32a. Goldstein, J. L., Brown, M. S. 1990. Regulation of the mevalonate pathway. *Nature* 343:425–30
33. Gusberg, S. B., Runowicz, C. D. 1991. Gynecologic cancers. In *Clinical Oncology,* ed. A. I. Holleb, D. J. Fink, G. P. Murphy, pp. 498–97. Atlanta, Ga: Am. Cancer Soc.
34. Hiatt, R. A., Fireman, B. H. 1986. Serum cholesterol and the incidence of cancer in a large cohort. *J. Chronic Dis.* 39:861–70
35. Hiatt, R. A., Friedman, G. D., Bawol, R. D., Ury, H. K. 1982. Breast cancer and serum cholesterol. *J. Natl. Cancer Inst.* 68:885–89
36. Hjermann, I., Byre, K. V., Holme, I., Leren, P. 1981. Effect of diet and smoking intervention on the incidence of coronary heart disease: report from the Oslo study group of a randomised trial in healthy men. *Lancet* 2:1303–13
37. Holtzman, E. J., Yaari, S., Goldbourt, U. 1987. Serum cholesterol and the risk of colorectal cancer. *New Engl. J. Med.* 317:114
38. International Collaborative Group. 1982. Circulating cholesterol levels and risk of death from cancer in men aged 40 to 69 years: experience of an International Collaborative Group. *J. Am. Med. Assoc.* 248:2853–59
39. Isles, C. G., Hole, D. J., Gillis, C. R., Hawthorne, V. N., Lever, A. F. 1989. Plasma cholesterol, coronary heart disease, and cancer in the Renfrew and Paisley survey. *Br. Med. J.* 298:920–24
40. Ito, F., Takii, Y., Suzuki, J., Masamune, Y. 1982. Reversible inhibition by human serum lipoproteins of cell proliferation. *J. Cell Physiol.* 113:1–7
41. Kagan, A., McGee, D. L., Yano, K., Rhoads, G. G., Nomura, A. 1981. Serum cholesterol and mortality in a Japanese-American population: the Honolulu Heart Program. *Am. J. Epidemiol.* 114:11–20
42. Kark, J. D., Smith, A. H., Hames, C. G. 1980. The relationship of serum cholesterol to the incidence of cancer in Evans County, Georgia. *J. Chronic Dis.* 33:311–22
43. Kark, J. D., Smith, A. H., Hames, C. G. 1982. Serum retinol and the inverse relationship between serum cholesterol and cancer. *Br. Med. J.* 284:152–54
44. Kark, J. D., Smith, A. H., Switzer, B. R., Hames, C. G. 1981. Retinol, carotene, and the cancer/cholesterol association. *Lancet* 1:1371
45. Katan, M. B. 1986. Apolipoprotein E isoforms, serum cholesterol, and cancer. *Lancet* 1:507–8
46. Kazanecki, M. E., Melhem, M. F., Spichty, K. J., Kelly, R. H., Rao, K. N. 1989. Diet-induced reduction in serum lipoproteins stimulates cell proliferation in weanling rats. *Pharmacol. Res.* 21:533–47
47. Keys, A. 1980. Alpha lipoprotein (HDL) cholesterol in the serum and the risk of coronary heart disease and death. *Lancet* 2:603–6
48. Keys, A., Aravanis, C., Blackburn, H., Buzina, R., Dontas, A. S., et al. 1985. Serum cholesterol and cancer mortality in the Seven Countries Study. *Am. J. Epidemiol.* 121:870–83
49. Deleted in proof.
50. Klimov, A. N., Shestov, D. B. 1986. Ischemic heart disease in a Leningrad subpopulation: prevalence and follow-up studies. In *Atherosclerosis VII,* ed. N. H. Fidge, P. J. Nestel, pp. 45–49. New York: Elsevier Sci.
51. Knekt, P., Reunanen, A., Aromaa, A., Heliövaara, M., Hakulinen, T., et al. 1988. Serum cholesterol and risk of cancer in a cohort of 39,000 men and women. *J. Clin. Epidemiol.* 41:519–30
52. Knekt, P., Reunanen, A., Teppo, L. 1991. Serum cholesterol concentration and risk of primary brain tumours. *Br. Med. J.* 302:90
53. Kozarevic, D., McGee, D., Vojvodic, N., Gordon, T., Racic, Z., et al. 1981. Serum cholesterol and mortality: the Yugoslavia Cardiovascular Disease Study. *Am. J. Epidemiol.* 114:21–28
54. Kritchevsky, S. B. 1992. Dietary lipids and the low blood cholesterol-cancer association. *Am. J. Epidemiol.* In press
55. Kritchevsky, S. B., Wilcosky, T. C., Morris, D. L., Truong, K. N., Tyroler, H. A. 1991. Changes in plasma lipid and lipoprotein cholesterol and weight prior to the diagnosis of cancer. *Cancer Res.* 51:3198–3203
56. Kromhout, D., Bosschieter, E. B., Drijver, M., Coulander, C. 1988. Serum

cholesterol and 25-year incidence of and mortality from myocardial infarction and cancer: the Zutphen Study. *Arch. Intern. Med.* 148:1051–55

57. Lannerstad, O., Isacsson, S.-O., Lindell, S. 1979. Risk factors for premature death in men 56–60 years old. *Scand. J. Soc. Med.* 7:41–47
58. Laskarzewski, P., Khoury, P., Morrison, J. A., Kelly, K., Mellies, M., et al. 1982. Cancer, cholesterol and lipoprotein cholesterols. *Prev. Med.* 11:253–68
59. Leibel, R. L., Edens, N. K., Fried, S. K. 1989. Physiologic basis for the control of body fat distribution in humans. *Annu. Rev. Nutr.* 9:417–43
60. Leren, P. 1966. The effect of plasma cholesterol lowering diet in male survivors of myocardial infarction. *Acta Med. Scand. Suppl.* 466:1–92
61. Leren, P. 1970. The Oslo Diet-Heart Study: eleven year report. *Circulation* 42:935–42
62. Lipid Research Clinics Program. 1984. The Lipid Research Clinics Coronary Primary Prevention Trial Results: I. reduction in incidence of coronary heart disease. *J. Am. Med. Assoc.* 251:351–64
63. Macy, M., Okano, Y., Cardin, A. D., Avila, E. M., Harmony, J. A. K. 1983. Suppression of lymphocyte activation by plasma lipoproteins. *Cancer J. Res.* 43:2496s–2502s
64. Mannes, G. A., Maier, A., Thieme, C., Wiebecke, B., Paumgartner, G. 1986. Relation between the frequency of colorectal adenoma and the serum cholesterol level. *New Engl. J. Med.* 315:1634–38
65. Marenah, C. B., Lewis, B., Hassall, D., La Ville, A., Cortese, C., et al. 1983. Hypocholesterolaemia and noncardiovascular disease: metabolic studies on subjects with low plasma cholesterol concentrations. *Br. Med. J.* 286:1603–6
66. McMichael, A. J. 1991. Serum cholesterol and human cancer. In *Cancer and Nutrition*, ed. R. B. Alfin-Slater, D. Kritchevsky, pp. 141–58. New York: Plenum
67. McMichael, A. J., Jensen, O. M., Parkin, D. M., Zaridze, D. G. 1984. Dietary and endogenous cholesterol and human cancer. *Epidemiol. Rev.* 6:192–216
68. Merrill, A. H. Jr., Foltz, A. T., McCormick, D. B. 1991. Vitamins and cancer. See Ref. 66, pp. 261–320
69. Morris, D. L., Borhani, N. O., Fitzsimons, E., Hardy, R. J., Hawkins, C. M., et al. 1983. Serum cholesterol and cancer in the Hypertension Detection and Follow-up Program. *Cancer* 52:1754–59
70. Morse, J. H., Witte, L. D., Goodman, D. S. 1977. Inhibition of lymphocyte proliferation stimulated by lectins and allogeneic cells by normal plasma lipoproteins. *J. Exp. Med* 146:1791–1803
71. Multiple Risk Factor Intervention Trial Research Group. 1982. Multiple Risk Factor Intervention Trial: risk factor changes and mortality results. *J. Am. Med. Assoc.* 248:1465–77
72. Multiple Risk Factor Intervention Trial Research Group. 1990. Mortality rates after 10.5 years for participants in the Multiple Risk Factor Intervention Trial: findings related to a priori hypotheses of the trial. *J. Am. Med. Assoc.* 263:1795–1801
73. Neugut, A. I., Johnsen, C. M., Fink, D. J. 1986. Serum cholesterol levels in adenomatous polyps and cancer of the colon: a case-control study. *J. Am. Med. Assoc.* 255:365–67
74. Oliver, M. F. 1981. Serum cholesterol—The knave of hearts or the joker. *Lancet* 2:1090–95
75. Pearce, M. L., Dayton, S. 1971. Incidence of cancer in men on a diet high in polyunsaturated fat. *Lancet* 1:464–67
76. Peterson, B., Trell, E. 1983. Premature mortality in middle-aged men: serum cholesterol as risk factor. *Klin. Wochenschr.* 63:795–801
77. Peterson, B., Trell, E., Sternby, N. H. 1981. Low cholesterol level as risk factor for noncoronary death in middle-aged men. *J. Am. Med. Assoc.* 245: 2056–57
78. Peto, R., Borenham, J., Chen, J., Li, J., Campbell, T. C., et al. 1989. Plasma cholesterol, coronary heart disease, and cancer. *Br. Med. J.* 298:1249

78a. Rao, K. N., Melhem, M. F., Gabriel, H. F., Eskander, E. D., Kazenecki, M. E., et al. 1988. Lipid composition and de novo cholesterolgenesis in normal and neoplastic rat mammary tissues. *J. Natl. Cancer Inst.* 80:1248–53

79. Reed, D., Yano, K., Kagan, A. 1986. Lipids and lipoproteins as predictors of coronary heart disease, stroke and cancer in the Honolulu Heart Program. *Am. J. Med.* 80:871–78
80. Reed, T., Wagener, D. K., Donahue, R. P., Kuller, L. H. 1986. Family history of cancer related to cholesterol level in young adults. *Gen. Epidemiol.* 3:63–71
81. Rose, G., Blackburn, H., Keys, A., Taylor, H. L., Kannel, W. B., et al.

1974. Colon cancer and blood-cholesterol. *Lancet* 1:181–83
82. Rose, G., Shipley, M. J. 1980. Plasma lipids and mortality: a source of error. *Lancet* 1:523–26
83. Salmond, C. E., Beaglehole, R., Prior, I. A. M. 1985. Are low cholesterol values associated with excess mortality? *Br. Med. J.* 290:422–24
84. Salonen, J. T. 1982. Risk of cancer and death in relation to serum cholesterol: a longitudinal study in an Eastern Finnish population with high overall cholesterol level. *Am. J. Epidemiol.* 116:622–30
85. Deleted in proof
86. Schatzkin, A., Hoover, R. N., Taylor, P. R., Ziegler, R. G., Carter, C. L., et al. 1987. Serum cholesterol and cancer in the NHANES I Epidemiologic Followup Study. *Lancet* 2:298–301
87. Schatzkin, A., Hoover, R. N., Taylor, P. R., Ziegler, R. G., Carter, C. L., et al. 1988. Site-specific analysis of total serum cholesterol and incident cancer in the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. *Cancer Res.* 48:452–58
88. Schrott, H. G., Clarke, W. R., Wiebe, D. A., Connor, W. E., Lauer, R. M. 1979. Increased coronary mortality in relatives of hypercholesterolemic school children: the Muscatine study. *Circulation* 59:320–26
89. Deleted in proof
90. Shaper, A. G., Phillips, A. N., Pocock, S. J. 1989. Plasma cholesterol, coronary heart disease, and cancer. *Br. Med. J.* 298:1381
91. Sherwin, R. W., Wentworth, D. N., Cutler, J. A., Hulley, S. B., Kuller, L. H., et al. 1987. Serum cholesterol levels and cancer mortality in 361 662 men screened for the Multiple Risk Factor Intervention Trial. *J. Am. Med. Assoc.* 257:943–48
92. Shestov, D. 1981. Results of four years of follow-up of USSR populations. In *USA-USSR 1st Lipoprotein Symp., Leningrad, May 26–27*, pp. 391–407. Bethesda, Md: Natl. Inst. Health
93. Shinitzky, M. 1984. Membrane fluidity in malignancy: adversative and recuperative. *Biochim. Biophys. Acta* 738:251–61
94. Sidney, S., Friedman, G. D., Hiatt, R. A. 1986. Serum cholesterol and large bowel cancer. *Am. J. Epidemiol.* 124: 33–38
95. Siperstein, M. D., DoVale, H., Silber, J. R. 1987. Relationship of cholesterol to DNA synthesis in normal and cancerous cells. In *Drugs Affecting Lipid Metabolism*, ed. R. Paoletti, D. Kritchevsky, W. L. Holmes, pp. 1–8. Berlin: Springer-Verlag
96. Smith, A. H., Hoggard, B. M. 1981. Retinol, carotene, and the cancer/cholesterol association. *Lancet* 1:1371–72
97. Smith, G. D., Shipley, M. J. 1989. Plasma cholesterol concentration and primary brain tumours. *Br. Med. J.* 299:26–27
98. Sorlie, P. D., Feinleib, M. 1982. The serum cholesterol-cancer relationship: an analysis of time trends in the Framingham Study. *J. Natl. Cancer Inst.* 69:989–96
99. Staessen, J., Amery, A., Birkenhäger, W., Bulpitt, C., Clement, D., et al. 1990. Is a high serum cholesterol level associated with longer survival in elderly hypertensives? *J. Hypertens.* 8:755–61
100. Stähelin, H. B., Rösel, F., Buess, E., Brubacher, G. 1984. Cancer, vitamins and plasma lipids: prospective Basel Study. *J. Natl. Cancer Inst.* 73:1463–68
101. Stefanick, M. L., Williams, P. T., Krauss, R. M., Terry, R. B., Vranizan, K. M., et al. 1987. Relationships of plasma estradiol, testosterone, and sex hormone-binding globulin with lipoproteins, apolipoproteins, and high density lipoprotein subfractions in men. *J. Clin. Endocrinol. Metab.* 64:723–43
102. Stemmermann, G. N., Chyou, P., Kagan, A., Nomura, A. M. Y., Yano, K. 1991. Serum cholesterol and mortality among Japanese-American men: the Honolulu (Hawaii) Heart Program. *Arch. Intern. Med.* 151:969–72
103. Stemmermann, G. N., Nomura, A. M. Y., Heilbrun, L. K., Pollack, E. S., Kagan, A. 1981. Serum cholesterol and colon cancer incidence in Hawaiian Japanese Men. *J. Natl. Cancer Inst.* 67:1179–82
104. Strandberg, T. E., Salomaa, V. V., Naukkarinen, V. A., Vanhanen, H. T., Sarna, S. J., et al. 1991. Long-term mortality after 5-year multifactorial primary prevention of cardiovascular diseases in middle-aged men. *J. Am. Med. Assoc.* 266:1225–29
105. Thomas, C. B., Duszynski, K. R., Shaffer, J. W. 1982. Cholesterol levels in young adulthood and subsequent cancer: a preliminary note. *Johns Hopkins Med. J.* 150:89–94
106. Thurnham, D. I. 1989. Lutein, cholesterol and risk of cancer. *Lancet* 2:441–42
107. Törnberg, S. A., Carstensen, J. M., Holm, L.-E. 1988. Risk of stomach can-

cer in association with serum cholesterol and beta-lipoprotein. *Acta Oncol.* 27:39–42

108. Törnberg, S. A., Holm, L.-E., Carstensen, J. M. 1988. Breast cancer risk in relation to serum cholesterol, serum beta-lipoprotein, height, weight, and blood pressure. *Acta Oncol.* 27:31–37
109. Törnberg, S. A., Holm, L.-E., Carstensen, J. M., Eklund, G.. A. 1986. Risks of cancer of the colon and rectum in relation to serum cholesterol and beta-lipoprotein. *New Engl. J. Med.* 315:1629–33
110. Törnberg, S. A., Holm, L.-E., Carstensen, J. M., Eklund, G. A. 1989. Cancer incidence and cancer mortality in relation to serum cholesterol. *J. Natl. Cancer Inst.* 81:1917–21

110a. Ueyama, Y., Matsuzawa, Y., Yamashita, S., Funahashi, T., Sakai, N., et al. 1990. Hypocholesterolaemic factor from gallbladder cancer cells. *Lancet* 336:707–9

111. Vatten, L. J., Foss, O. P. 1990. Total serum cholesterol and triglycerides and risk of breast cancer: a prospective study of 24,329 Norwegian women. *Cancer Res.* 50:2341–46
112. Wald, N. J., Thompson, S. G., Law, M. R., Densem, J. W., Bailey, A. 1989. Serum cholesterol and subsequent risk of cancer: results from the BUPA study. *Br. J. Cancer.* 59:936–38
113. Wallace, R. B., Rost, C., Burmeister, L. F., Pomrehn, P. R. 1982. Cancer incidence in humans: relationship to plasma lipids and relative weight. *J. Natl. Cancer Inst.* 68:915–18
114. Westlund, K., Nicolaysen, R. 1972. Ten-year mortality and morbidity related to serum cholesterol. *Scand. J. Clin. Lab. Invest.* 30(Suppl. 127):1–24
115. Williams, R. R., Sorlie, P. D., Feinleib, M., McNamara, P. M., Kannel, W. B., et al. 1981. Cancer incidence by levels of cholesterol. *J. Am. Med. Assoc.* 245:247–52
116. Wilson, P. W., Abbott, R. D., Castelli, W. P. 1988. High density lipoprotein cholesterol and mortality: The Framingham Heart Study. *Arteriosclerosis* 6:737–41
117. Winawer, S. J., Flehinger, B. J., Buchalter, J., Herbert, E., Shike, M. 1990. Declining serum cholesterol levels prior to diagnosis of colon cancer: a time-trend, case-control study. *J. Am. Med. Assoc.* 263:2083–85
118. Wingard, D. L., Criqui, M. H., Holdbrook, M. J., Barrett-Connor, E. 1984. Plasma cholesterol and cancer morbidity and mortality in an adult community. *J. Chronic Dis.* 37:401–6
119. Yaari, S., Goldbourt, U., Even-Zohar, S., Neufeld, H. N. 1981. Associations of serum high density lipoprotein and total cholesterol with total, cardiovascular, and cancer mortality in a 7-year prospective study of 10,000 men. *Lancet* 1:1011–15
120. Yamaguchi, N., Yamamura, J., Takahashi, K., Nakamura, R., Okubo, T. 1990. Familial history of cancer and dietary pattern, serum cholesterol, serum protein and blood hemoglobin. *Gan No Rinsho Japan.* n.v.:377–81. (In Japanese; from Medline abstr.)