

Site-specific Analysis of Total Serum Cholesterol and Incident Cancer in the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study¹

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ABSTRACT

We studied the relation of total serum cholesterol to all cancer and site-specific cancer incidence in a cohort based on a probability sample of the United States population. A total of 5125 men (yielding 459 cancers) and 7363 women (398 cancers) were initially examined in 1971-75 and followed a median of 10 yr. An examination of age-adjusted incidence rates by cholesterol level showed an inverse association between cholesterol and all cancer; lung, colorectal, pancreatic, and bladder cancers; and leukemia. In women a weak inverse relation (reflecting an elevated rate among those only in the lowest cholesterol quintile) was apparent for all cancer; more prominent inverse associations were seen for cancers of the lung, pancreas, bladder, cervix, and for leukemia. A more detailed analysis of cholesterol and colorectal cancer revealed little association in both men and women. For an aggregate group of smoking-related cancers, the inverse relation was especially prominent: the multivariate relative risk estimates for subjects in the lowest cholesterol quintile, compared to those in the highest quintile, were 2.1 (1.1-3.8) and 3.3 (1.4-7.8) for men and women, respectively. The inverse association was present for smoking-related cancers diagnosed 6 or more yr after cholesterol determination in both men and women, suggesting that this association cannot be simply dismissed as a preclinical cancer effect. Further investigation of the cholesterol-cancer question, particularly the relation between cholesterol and smoking-related cancers, may provide useful etiologic leads.

INTRODUCTION

A number of cohort studies have shown in recent years that men with low base-line serum cholesterol levels were at increased risk of cancer (1-16). This inverse association has been particularly observed for cancer of the colon (1, 5-7). The literature on the cancer-cholesterol question, however, has been inconsistent (17-22). Several cohort studies found no relation in men between cholesterol and all cancer as well as colon cancer (23-31). Investigators have generally reported no significant association between serum cholesterol and all cancer in women (9, 12, 13, 15, 24, 30, 31), although a few studies have shown nonsignificant inverse (9, 12, 15) or direct (13) associations. A *positive* association between cholesterol and colorectal cancer recently has been described (32).

This inconsistency extends to one of the leading explanations for the inverse cholesterol-cancer association. Some researchers

have proposed that the inverse relation reflected a "preclinical cancer effect," that is, the metabolic depression of serum cholesterol by undiagnosed malignant neoplasms (2, 17). This hypothesis has been supported by observations that the inverse association between base-line cholesterol and cancer diminished with increasing time from cholesterol determination to diagnosis (2, 3, 13, 14, 16). A few investigators have found, though, that the inverse relation persisted for cancers discovered 2 to more than 15 yr after cholesterol measurement (4, 8, 9, 11, 12).

We have recently had the opportunity to study the association of total base-line serum cholesterol and cancer in a cohort study based on a probability sample of the United States population. In an earlier analysis we found that cholesterol was inversely related to total cancer (both incidence and mortality) in men; in women, the inverse association for incidence was small and nonsignificant, but for mortality this inverse relation was stronger and significant (33). Furthermore, the inverse association in men did not diminish for cases diagnosed several years after cholesterol determination. In this study, we examined the cholesterol-cancer relation for colorectal and other major site-specific cancers.

SUBJECTS AND METHODS

The Cohort. The NHANES I Epidemiologic Follow-up Study was created through a systematic follow-up of subjects examined during the first National Health and Nutrition Examination Survey (34).

The National Center for Health Statistics carried out NHANES³ I from 1971 to 1975 on a probability sample of the civilian noninstitutional population of the United States (35). Persons estimated to be at high risk of malnutrition (children, the elderly, women of child-bearing age, the poor) were oversampled to improve estimates of nutritional status for these groups.

Tracing and reinterview for the NHEFS were conducted between 1981 and 1984. A search for hospital records was triggered primarily by the response of the subject or proxy during the follow-up interview to questions regarding prior hospitalization. In a relatively small number of cases, hospital records were obtained as a result of information provided on the death certificate. Of the adults aged 25-74 who were examined in 1971-75, 14,407 were eligible for inclusion in the NHEFS. Ninety-four % of the 5,811 men and 92% of the 8,596 women examined in NHANES I were successfully traced.

Identification of Cases. Cancer cases at specific sites were identified from the hospital records and/or death certificate by the International Classification of Disease (Eighth Revision) code (36). The category 'all cancer' comprised any ICD code from 140 to 208, excluding nonmelanoma skin cancer (ICD 173). An individual could have had an incident cancer at more than one site. For cases identified through hospital records, the date of first admission for a specific cancer listed in the discharge diagnoses was regarded as the incidence date for that site. The date of death was considered the incidence date for those cancers for which only death certificate data were available.

³ The abbreviations used are: NHANES, National Health and Nutrition Examination Survey; NHEFS, National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study.

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Measurement of Cholesterol and Other Covariates. A base-line non-fasting blood specimen was collected from each Health and Nutrition Examination Survey subject (37). Cholesterol was determined by a semiautomated modified ferric-sulfuric method in the Lipid Standardization Laboratory of the Centers for Disease Control (38).

Data on age, education, poverty index ratio, body mass index, alcohol consumption, and diet were taken from the base-line interview. The dietary data were derived from a 24-h recall interview conducted by a trained nutritionist using 3-dimensional graduated food portion models (39). Standard food composition data were used to calculate nutrient intake (40). Smoking information at base line was collected on only about half of the subjects in the NHANES I. For those persons missing smoking data at base line, we inferred smoking status at base line from the follow-up information. A man without base-line smoking data who reported at follow-up, for example, that he was a current smoker and that he began smoking 20 yr prior to his base-line exam would have been classified as a current smoker at base line with 20 yr duration.

Population for Analysis. Of the eligible men and women 351 and 675, respectively, could not be traced. Subjects were excluded from the incidence analyses as follows: A total of 309 men and 483 women were traced alive but did not have a follow-up interview, either because they refused or could not be contacted. Twenty men and 61 women were missing base-line serum cholesterol information. A total of 10 men and 25 women with prevalent cancer of any site (except nonmelanoma skin cancer) at base line were excluded from analyses of all cancer. A smaller number of prevalent cases were excluded from the site-specific analyses, the precise number varying from site to site. A small number of men and women fell into more than one of these exclusion categories.

The cohort that was analyzed consisted of 5125 men and 7363 women, including 459 cancers in men and 398 cancers in women. The median cohort follow-up time for all analyses was 10 yr. For both men and women, the distributions for cholesterol and several cancer risk factors in the overall NHEFS cohorts were very similar to those in the analyzed cohorts.

Analytical Procedures. Crude incidence rates for quantiles of cholesterol (tertiles for specific cancers, quintiles for all cancer) were calculated by dividing the number of incident cancers occurring among subjects in that quantile by the total number of person-years contributed by the subjects within that quantile. The number of person-years contributed by an individual subject were calculated from base line to the time of cancer incidence, death, or the time of the follow-up interview, whichever came first. All person-years calculations were performed separately for specific sites (or all cancer). A person having two or more incident cancers would thus have had two or more different follow-up times (person-years). For analyses of all cancer, persons with two or more incident cancers were considered to contribute person-years of observation up to the incidence date of the first cancer. Age-adjusted rates were calculated by the direct method (41), with the age-distribution of the analytical cohort as the standard.

We used Cox's proportional hazards regression technique (42) to analyze the simultaneous relation of cholesterol, age, and other variables to all and site-specific cancer incidence and mortality in the cohort. The analyses were performed with the PROC PHGLM procedures available in the SAS statistical package (43).

RESULTS

Men in the study population had a mean age at base line of 52 yr, women a mean age of 48 yr. Of the men and women, 48 and 42%, respectively, had completed less than 12 yr of education at the beginning of the study; 25% of the men and 21% of the women had finished some education past high school. Of the men and women 86 and 84%, respectively, were white. Mean total serum cholesterol (\pm standard deviation) was 221 (\pm 47) for men and 222 (\pm 50) for women.

For men, the ratio of observed cancer cases to expected cases (based on age-, sex-, and race-specific incidence rates from the Connecticut Tumor Registry) was 1.04 (95% confidence inter-

val, 0.95-1.14). The analogous observed:expected ratio for women was 1.01 (0.91-1.11).

Data presented in Table 1 illustrate the relation between total base-line serum cholesterol and a number of factors potentially related to cancer risk. Higher levels of base-line serum cholesterol in both men and women were associated with greater age, poverty index ratio, body mass index, cigarette smoking, alcohol consumption, and lower fiber consumption. There was no material variation across quintiles of serum cholesterol in education and race, and, for women, age at first birth, age at menarche, and parity. Fat intake was unrelated to cholesterol in men, directly related in women.

Age-adjusted cancer incidence rates by level of serum cholesterol for all cancer and several major sites are depicted in Fig. 1. Data are presented for sites with at least 10 cases in both sexes (except for cancers of the prostate, cervix, endometrium, and ovaries, for which 10 cases were required only in the appropriate sex group). For men an inverse relation was evidence for all cancer, lung, colorectal, pancreas, and bladder cancers, and leukemia. There was little association between cholesterol and prostatic cancer or lymphoma. (A very slight inverse relation, not depicted in Fig. 1, was observed in men for a combined group of 26 cases of oral, laryngeal, and esophageal cancers.) Among women there was a slight inverse relation between cholesterol and all cancer (largely confined to the lowest cholesterol quintile), and more prominent inverse asso-

Table 1 Relation of cholesterol to various cancer risk factors

Each number represents the total person-time accumulated by persons within a given cholesterol category who have a specific risk factor status, as a percentage of total person-time accumulated by all subjects within that cholesterol category. For example, 43% of the person-time contributed by men in the lowest cholesterol quintile was characterized by less than 12 yr of education. All percentages, except those for age, have been age adjusted by the direct method (32), according to the distribution of age-specific person-time in the analytic cohort. Poverty index ratio is based on household income adjusted for family size and other demographic characteristics; ratios of 1.0, <1.0, and >1.0 indicate, respectively, "poverty level," "below poverty," and "above poverty." The fiber variable represents total dietary fiber.

	Cholesterol quintiles				
	Q1 (\leq 182)	Q2 (183-205)	Q3 (206-226)	Q4 (227-254)	Q5 (\geq 255)
Men					
Age (\geq 65 yr)	22	28	27	32	34
Education (<12 yr)	43	44	41	44	41
PIR (<1.69) ^{a,b}	26	23	21	25	22
Race (nonwhite)	15	13	13	13	15
BMI (\geq 27) ^c	29	30	34	39	40
Smoking (\geq 27 pack-yr) ^c	25	27	27	26	29
Alcohol (\geq 5 g/day) ^d	22	23	25	25	25
Fat (\geq 41% kcal) ^c	33	33	33	37	32
Fiber (<7.1 g/day) ^b	31	30	31	33	34
Women					
Q1 (\leq 179)	Q2 (180-203)	Q3 (204-229)	Q4 (230-261)	Q5 (\geq 262)	
Age (\geq 65 yr)	7	10	20	31	45
Education (<12 yr)	42	39	41	44	44
PIR (<1.53) ^b	30	28	28	27	24
Race (nonwhite)	17	16	17	17	15
BMI (\geq 27) ^c	28	31	34	37	40
Smoking (\geq 13 pack-yr)	17	17	18	21	22
Alcohol (\geq 5 g/day) ^d	12	15	14	14	15
Fat (\geq 40% kcal) ^c	31	34	35	36	36
Fiber (<5.6 g/day) ^b	29	34	34	36	36
Age at first birth (\geq 25)	21	24	23	21	22
Age at menarche (\leq 11)	15	15	13	16	15
Parity (nulliparity)	16	17	16	17	18

^a PIR, poverty index ratio; BMI, body mass index.

^b Lowest tertile.

^c Highest tertile.

^d Highest tertile among drinkers.

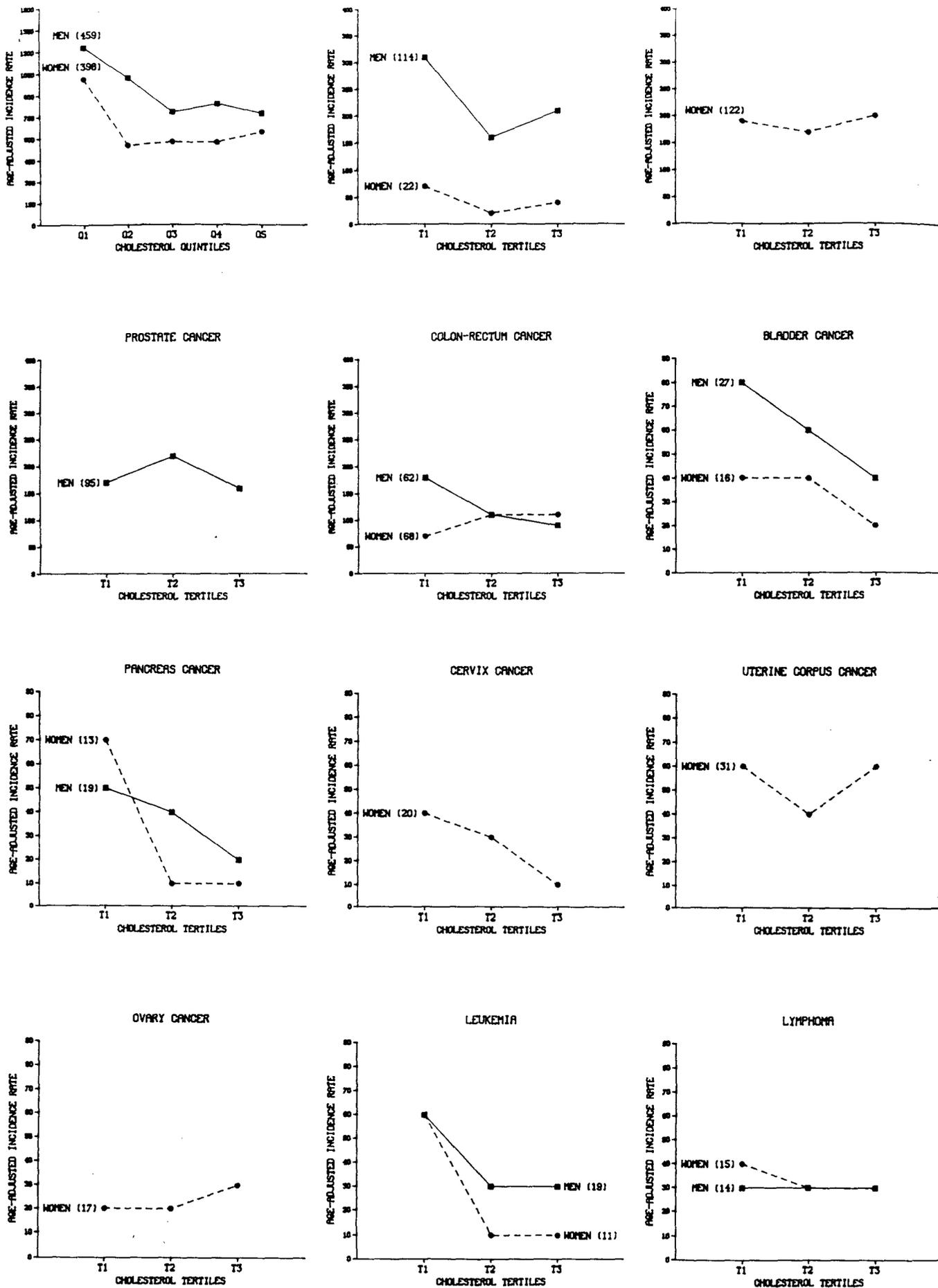


Fig. 1. Age-adjusted, site-specific cancer incidence rates by level of serum cholesterol. Tertiles (T1-T3) of cholesterol (mg/100 ml) are as follows: for men, ≤ 200 , 201-235, ≥ 236 ; for women, ≤ 196 , 197-239, ≥ 240 . Numbers in parentheses, cancer cases for each site.

ciations for cancers of the lung, pancreas, bladder, cervix, and for leukemia. Little relation was apparent in women between cholesterol and breast, colorectal, ovarian, and uterine corpus cancers. It should be noted that the incidence rates for some sites were based on a small number of cases within cholesterol levels.

Data on the association between serum cholesterol and colorectal cancer are presented in greater detail in Table 2. While there was a suggestion of an inverse cholesterol-colorectal cancer relation among men, none of the relative risks was statistically significant. No association was seen in women.

Because the incidence curves and regression results suggested an inverse relation between serum cholesterol and several site-specific cancers known to be related to cigarette smoking, we aggregated sites *a posteriori* to form categories of smoking-related and non-smoking-related cancers. The smoking-related cancers in men were those of the lung, mouth, larynx, esophagus, pancreas, and bladder, and leukemia (44). In women the smoking-related cancers were those of the lung, mouth, larynx, esophagus, pancreas, bladder, and cervix, and leukemia (44, 45). Age-adjusted incidence rates for the smoking-related and non-smoking-related cancers by quintiles of cholesterol are displayed in Fig. 2. An inverse cholesterol-cancer relation similar to that seen for all cancer was found for smoking-related cancers, while only a weak inverse relation was noted for non-smoking-related cancers. In women an inverse relation was also apparent for smoking-related cancers, but not for non-smoking-related cancers.

Age-adjusted and multivariate relative risk estimates from proportional hazards regression models are presented in Table 3 for all cancer, smoking-related cancers, and non-smoking-related cancers. Among men, there was an inverse relation between cholesterol and all cancer, with multivariate relative risks for the first through fourth cholesterol quintiles of 1.8 (1.2-2.7), 1.5 (1.0-2.2), 1.0 (0.7-1.5), and 1.3 (0.9-1.9) (the highest cholesterol quintile was reference). A multivariate test for trend, based on the inclusion of a five-value cholesterol trend variable into the multivariate proportional hazards model described in Table 3, yielded $\chi^2 = 8.83$ ($P = 0.003$).

A clear inverse relation was present for smoking-related cancers in men, with multivariate relative risk estimates of 2.1

(1.1-3.8), 1.6 (0.8-2.9), 1.1 (0.6-2.2), and 1.4 (0.7-2.5) (highest quintile as reference). The multivariate test for trend yielded $\chi^2 = 5.48$ ($P = 0.02$). Since the etiological link between smoking and leukemia is not as well established as that for the other smoking-related sites listed above, we performed separate analyses with leukemia excluded from the smoking-related cancers group. The multivariate risk estimates for smoking-related cancers minus leukemia (101 cases) were 2.1 (1.1-4.0), 1.8 (0.9-3.3), 1.1 (0.6-2.2), and 1.3 (0.7-2.4) (reference was highest cholesterol quintile); the trend test yielded $\chi^2 = 6.29$ ($P = 0.01$). In addition, since the ascertainment of cancer solely by death certificate was arguably less accurate than ascertainment by hospital records, we examined the cholesterol-cancer relation for smoking-related cancers confirmed by hospital records. Relative risk estimates were not materially altered. For the non-smoking-related cancers, there was a weak inverse relation, with $\chi^2 = 3.35$ ($P = 0.07$) for the multivariate trend test.

For women, a small nonsignificant increase in risk was observed among those in the lowest cholesterol quintile (multivariate relative risk estimate was 1.2, 0.8-1.9) (Table 3). The multivariate trend test for all cancer in women yielded $\chi^2 = 0.34$ ($P = 0.5$). The inverse relation was stronger for the smoking-related cancers, with a multivariate relative risk estimate of 3.3 (1.4-7.8) for the lowest compared to the highest quintile. The test for trend for smoking-related cancers yielded $\chi^2 = 12.9$ ($P = 0.02$). The risk estimates for smoking-related cancers minus leukemia (only 45 cases) were 2.2 (0.8-5.7), 1.2 (0.5-3.2), 0.7 (0.3-1.8), 0.9 (0.4-2.0) (highest cholesterol quintile as reference), with a multivariate trend test yielding $\chi^2 = 1.44$ ($P = 0.23$). Relative risk estimates for smoking-related cancers did not differ materially whether based on hospital records alone or on hospital records combined with death certificates. No association was evident between cholesterol and non-smoking-related cancers in women.

We evaluated effect modification in our data by carrying out age-adjusted proportional hazards analyses of cholesterol and cancer within strata of various risk factors, including age, education, poverty index ratio, body mass index, smoking, alcohol consumption, and dietary fat. These stratum-specific analyses were carried out for smoking-related and non-smoking-related cancers. There was no appreciable variation in relative risk estimates for cholesterol across the various risk factor subgroups.

Because of concern for residual confounding by smoking, we paid particular attention to the relation between cholesterol and smoking-related cancers (not exclusively attributable to smoking) among nonsmokers. The inverse relation appeared to hold. For male nonsmokers the relative risk estimates from first to fourth cholesterol quintiles for smoking-related cancers (25 cases) were 4.7 (1.3-17), 2.0 (0.5-8.4), 1.2 (0.2-5.8), and 1.0 (0.2-4.9) (reference was highest cholesterol quintile). The analogous estimates for smoking-related cancers (40 cases) among women nonsmokers were 2.5 (0.8-8.1), 2.2 (0.8-6.3), 2.0 (0.8-5.0), and 1.8 (0.8-4.3).

Finally, to explore the possibility that preclinical cancer was depressing cholesterol levels (the "preclinical cancer effect" hypothesis), we analyzed the cholesterol-cancer relation for the smoking-related cancers within three distinct follow-up periods, 0-1.9, 2-5.9, and ≥ 6 yr from the time of cholesterol measurement to time of cancer diagnosis. As the data in Table 4 demonstrate, the inverse relation between cholesterol and smoking-related cancers persisted in both men and women for cases that were diagnosed more than 6 or 8 yr after cholesterol was measured. Results were essentially unchanged in the anal-

Table 2 Relation of total serum cholesterol to colorectal cancer incidence

Men	Cholesterol quartiles			
	<=189	190-216	217-246	>=246
No. of cases	16	18	10	18
RR ^{a,b}	1.3	1.2	0.6	(1.0) ^c
95% CI	0.6-2.5	0.6-2.4	0.3-1.3	
Multivariate RR ^c	1.7	1.2	0.5	(1.0)
95% CI	0.8-3.7	0.5-2.6	0.2-1.4	
Women	<186	187-217	218-251	>252
No. of cases	6	13	23	26
RR ^{a,b}	0.9	1.1	1.2	(1.0)
95% CI	0.4-2.2	0.6-2.2	0.7-2.2	
Multivariate RR ^d	1.0	0.9	1.3	(1.0)
95% CI	0.3-2.7	0.4-2.1	0.6-2.4	

^a RR, relative risk; CI, confidence interval.

^b Based on proportional hazards models including variables for age and cholesterol.

^c Model includes variables for age, education, body mass index, smoking (pack-yr), alcohol, fat as a percentage of calories, dietary fiber, and cholesterol. Forty-five cases were analyzed in the multivariate model.

^d Model includes variables for age, education, body mass index, smoking (pack-yr), alcohol, fat as a percentage of calories, dietary fiber, age at first birth, age at menarche, parity, and cholesterol. Forty-eight cases were analyzed in the multivariate model.

^e Numbers in parentheses indicate reference groups.

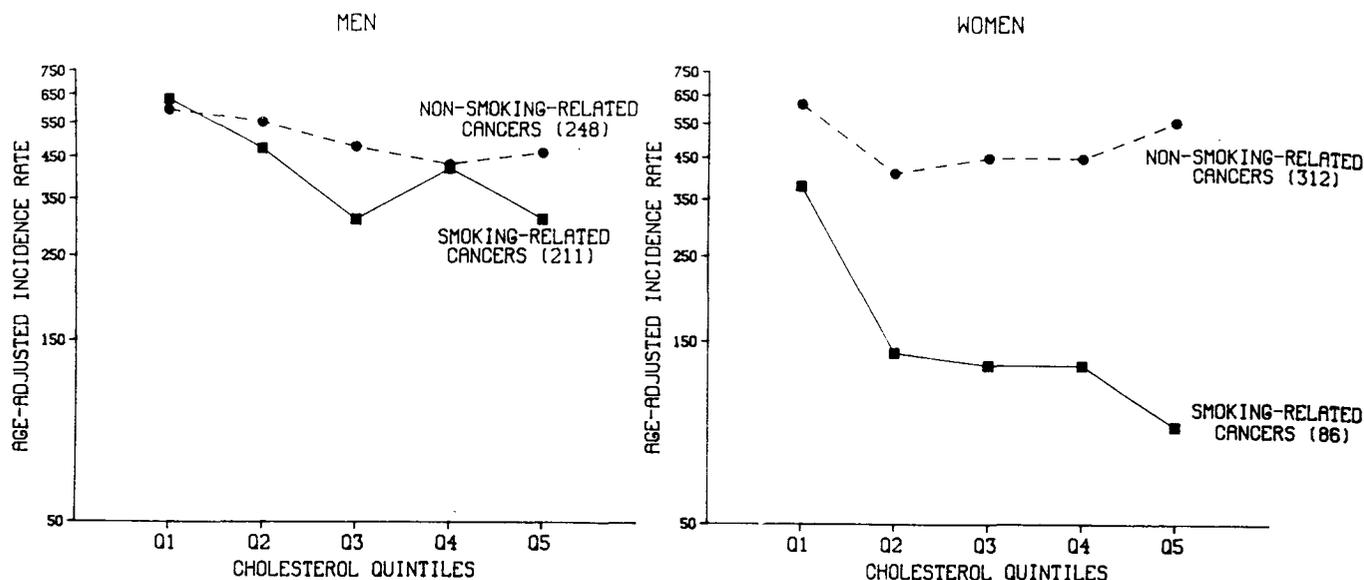


Fig. 2. Age-adjusted incidence rates for smoking- and non-smoking-related cancers by level of serum cholesterol. Quintiles (Q1-Q5) of cholesterol (mg/100 ml) were as follows: for men, ≤ 182 , 183-205, 206-226, 227-254, ≥ 255 ; for women, ≤ 179 , 180-203, 204-229, 230-261, ≥ 262 . Numbers in parentheses, cancer cases for the smoking- and non-smoking-related cancers.

yses of smoking-related cancers confirmed by hospital records, and in multivariate models including variables for cholesterol, age, education or poverty index ratio, race, body mass index, smoking, alcohol consumption, dietary fat intake, dietary fiber intake, and, for women, age at first birth, age at menarche, parity, and menopausal status. For the 41 smoking-related cancers in men diagnosed 8 or more yr after cholesterol measurement, the age-adjusted relative risk estimates for the first through fourth quintiles, relative to the highest quintile, were 5.9 (2.0-18), 1.5 (0.4-5.5), 2.2 (0.7-7.2), 2.2 (0.7-7.2). (There were only 17 such cases in women.)

DISCUSSION

In this cohort study based on a probability sample of the United States population assembled in the early 1970s, we found an inverse relation between base-line total serum cholesterol and total incidence of cancer in men. Men in the lowest quintile of serum cholesterol (≤ 182) had a 60% elevation in risk of all cancer, and the test for trend across levels of cholesterol was statistically significant. Although the number of cases was relatively small, inverse associations were apparent for cancers of the lung, bladder, and pancreas, and for leukemia. There was the suggestion of an inverse relation for colorectal cancer, but relative risk estimates did not achieve statistical significance in more detailed analyses. There was a marginally significant inverse association for all cancer among women in the lowest cholesterol quintile (≤ 179). An inverse association was seen for cancers of the lung, pancreas, bladder, cervix, and for leukemia in women, but not for colorectal cancer.

Based on our observations of increased relative risks for specific sites, we examined the relation of cholesterol to aggregate smoking-related and non-smoking-related cancers. We acknowledge that inferences drawn from a *post hoc* "subgroup" analysis of this type should be viewed with caution. Nevertheless, such an analysis may provide etiological leads for further exploration in other data sets. In this regard, we found that the inverse cholesterol-cancer relation in men was somewhat stronger for smoking-related as opposed to non-smoking-related cancers. A 2-fold excess in cancer risk for the smoking-

related cancers was observed among men in the lowest quintile of cholesterol. This finding persisted for cancers diagnosed several years after cholesterol was measured.

Among women, the weak inverse relation observed for all incident cancer was attributable to the stronger and statistically significant inverse relation for smoking-related cancers in women. There was no association between cholesterol and the non-smoking-related cancers. In an earlier analysis we found a significant inverse association for cancer mortality among women, with point estimates ranging from 2.0 to 2.6 for women in the lowest cholesterol quintile (33). The present findings for smoking-related and non-smoking-related cancers are compatible with the mortality results, in that the mortality experience associated with smoking-related cancers in women tends to be less favorable than that associated with non-smoking-related cancers (like breast and uterine corpus, for example) (46). As with men, the inverse relation for smoking-related cancers in women persisted for several years after base-line cholesterol determination.

The "preclinical cancer effect" hypothesis (2, 17) has received considerable attention as an explanation for the observed inverse association. Malignant neoplasms are known to have protean physiological effects, which might include depression of blood cholesterol. In this regard, leukemic blood and bone marrow cells have been shown recently to have an elevated low density lipoprotein-receptor activity that correlated inversely with plasma cholesterol concentration (47). This elevated low density lipoprotein-receptor activity may account for the hypocholesterolemia noted in leukemic patients (48). However, it is noteworthy that in our data set the inverse relation between cholesterol and leukemia (male and female cases combined) was present after the exclusion of cases diagnosed within the first 2 yr following cholesterol measurement.

In an earlier report we showed that the inverse relation for all cancer among men persisted for all cancers diagnosed 6 or more yr subsequent to cholesterol ascertainment. We have now found that the inverse relation was present for smoking-related cancers diagnosed 6 or more yr after cholesterol determination in both men and women. (In men, the inverse relation was obtained 8 or more yr after base line as well; the number of

Table 3 Relative risk estimates by cholesterol quintiles for all cancers, smoking-related cancers, and non-smoking-related cancers

	Men					All cancer					Smoking-related-cancer					Non-smoking-related cancer				
	<182	183-205	206-226	227-254	≥255	<182	183-205	206-226	227-254	≥255	<182	183-205	206-226	227-254	≥255	<182	183-205	206-226	227-254	≥255
N	1008	1000	1023	1065	1029	1008	1000	1023	1065	1029	1008	1000	1023	1065	1029	1008	1000	1023	1065	1029
No. of cases	94	95	81	97	92	49	44	32	48	38	45	51	49	49	45	51	49	49	54	54
RR ^{a,b}	1.6	1.3	1.0	1.1	(1.0) ^c	2.0	1.4	0.9	1.3	(1.0)	1.3	1.2	1.0	0.9	1.3	1.2	1.0	0.9	0.9	(1.0)
95% CI	1.2-2.1	1.0-1.9	0.7-1.3	0.8-1.4		1.3-3.0	0.9-2.2	0.6-1.5	0.8-2.0		0.8-1.9	0.8-1.7	0.7-1.5	0.7-1.4		0.8-1.9	0.8-1.7	0.7-1.5	0.7-1.4	
Multivariate RR ^c	1.8	1.5	1.0	1.3	(1.0)	2.1	1.6	1.1	1.4	(1.0)	1.6	1.4	0.9	1.2	(1.0)	1.6	1.4	0.9	1.2	(1.0)
95% CI	1.2-2.7	1.0-2.2	0.7-1.5	0.9-1.9		1.1-3.8	0.8-2.9	0.6-2.2	0.7-2.5		0.9-2.7	0.9-2.4	0.5-1.6	0.7-2.0		0.9-2.7	0.9-2.4	0.5-1.6	0.7-2.0	
Women																				
	<179	180-203	204-229	230-261	≥262	<179	180-203	204-229	230-261	≥262	<179	180-203	204-229	230-261	≥262	<179	180-203	204-229	230-261	≥262
N	1409	1502	1489	1484	1479	1409	1502	1489	1484	1479	1409	1502	1489	1484	1479	1409	1502	1489	1484	1479
No. of cases	56	56	75	95	116	19	12	16	21	18	37	44	59	74	98	37	44	59	74	98
RR ^{a,b}	1.4	1.0	1.0	1.0	(1.0)	4.1	1.7	1.5	1.4	(1.0)	1.0	0.9	0.9	0.9	(1.0)	1.0	0.9	0.9	0.9	(1.0)
95% CI	1.0-2.0	0.7-1.4	0.7-1.3	0.8-1.3		2.1-8.0	0.8-3.6	0.8-3.0	0.8-2.8		0.7-1.6	0.6-1.3	0.6-1.2	0.7-1.2		0.7-1.6	0.6-1.3	0.6-1.2	0.7-1.2	
Multivariate RR ^d	1.2	1.0	0.8	0.9	(1.0)	3.3	1.7	0.7	1.1	(1.0)	0.9	0.9	0.8	0.8	(1.0)	0.9	0.9	0.8	0.8	(1.0)
95% CI	0.8-1.9	0.7-1.5	0.6-1.2	0.6-1.2		1.4-7.8	0.7-4.1	0.3-1.9	0.5-2.4		0.6-1.5	0.6-1.3	0.6-1.2	0.5-1.2		0.6-1.5	0.6-1.3	0.6-1.2	0.5-1.2	

^a RR, relative risk; CI, confidence interval.

^b Based on proportional hazards models including variables for age and cholesterol.

^c Model includes variables for age, education, body mass index, smoking (pack-yr), alcohol, fat as a percentage of calories, dietary fiber, and cholesterol. The total number of cases in the multivariate models for all cancer, smoking-related cancers, and non-smoking-related cancers were, respectively, 261, 112, 149. Multivariate trend tests for the relation of cholesterol to all cancer, smoking-related cancers, and non-smoking-related cancers in men yielded, respectively, $\chi^2 = 8.83$ ($P = 0.003$), $\chi^2 = 5.48$ ($P = 0.02$), and $\chi^2 = 3.35$ ($P = 0.07$).

^d Model includes variables for age, education, body mass index, smoking (pack-yr), alcohol, fat as a percentage of calories, dietary fiber, age at first birth, age at menarche, parity, and cholesterol. The total number of cases in the multivariate models for all cancer, smoking-related cancers, and non-smoking-related cancers were, respectively, 268, 52, 216. Multivariate trend tests for the relation of cholesterol to all cancer and smoking-related cancers in women yielded, respectively, $\chi^2 = 0.34$ ($P = 0.5$) and $\chi^2 = 5.42$ ($P = 0.02$).

^e Numbers in parentheses indicate reference groups.

Table 4 Relative risks (95% confidence intervals) for smoking-related cancers in relation to cholesterol by number of yr of follow-up

Relative risks (95% confidence intervals) were derived from proportional hazards models including variables for age and cholesterol. Although the multivariate models were relatively unstable due to the reduced number of cases, estimates were not materially altered in models that included variables for age, cholesterol, education, body mass index, smoking (pack-yr), alcohol, dietary fat as a percentage of total calories, dietary fiber, and, for women, age at first birth, age at menarche, parity.

Men	No. of yr of follow-up (no. of cases)		
	0-1.9 (32)	2-5.9 (90)	≥6 (89)
≤182	1.3 (0.4-4.2)	1.7 (0.9-5.1)	2.5 (1.3-4.9)
183-205	1.9 (0.7-5.5)	1.3 (0.7-2.5)	1.4 (0.7-2.8)
206-226	0.4 (0.1-2.0)	0.9 (0.5-1.9)	1.2 (0.6-2.4)
227-254	1.7 (0.6-4.8)	1.0 (0.5-1.9)	1.5 (0.7-2.9)
≥255	(1.0)	(1.0)	(1.0)
Women			
	0-1.9 (15)	2-5.9 (38)	≥6 (33)
≤179	8.8 (1.5-49)	1.8 (0.6-5.6)	6.2 (2.1-18)
180-203	3.0 (0.4-22)	1.7 (0.6-4.6)	1.3 (0.3-5.3)
204-229	1.8 (0.3-13)	1.1 (0.4-3.0)	2.0 (0.7-6.1)
230-261	3.2 (0.6-17)	1.1 (0.5-2.8)	1.5 (0.5-4.5)
≥262	(1.0)	(1.0)	(1.0)

such cases in women was inadequate for analysis). While it is unlikely that early carcinogenesis could affect cholesterol levels as long as 6 to 8 yr prior to clinical manifestations of disease, this possibility cannot be entirely ruled out. It is worth noting, though, that in the Framingham Heart Study the inverse cholesterol-cancer relation persisted nearly 2 decades after cholesterol measurement (12).

Our finding that cholesterol is inversely associated with smoking-related cancers is intriguing. Several points are noteworthy. First, the inverse association is found among both men and women. Second, although there was a positive association between smoking and serum cholesterol in our data (Table 1), controlling for smoking and other potential confounders did not materially alter the relative risk estimates. Moreover, the inverse relation for smoking-related cancers was present even among nonsmokers, further indicating that residual confound-

ing by smoking was unlikely to account for the findings. Third, the more modest inverse associations seen for all cancer are largely accounted for by the inverse association with the smoking-related cancers. Finally, the inverse relation persisted for smoking-related cancers diagnosed several years after cholesterol measurement.

If smoking-related cancers resulted from biological processes common to those sites most susceptible to the carcinogenic effects of tobacco, and these processes were associated with cholesterol depression, then an inverse relation between cholesterol and smoking-related cancers would be observed. A low level of cholesterol may be a necessary precondition for these processes, or it may be an incidental effect. We note that, in the latter case, the explicit reduction of serum cholesterol (in cardiovascular disease prevention programs, for example) would not in itself increase cancer risk.

It would have been of interest to examine the relation of cholesterol and cancer by histological subtype. Unfortunately a systematic pathological review was not carried out in the NHEFS. Our site-specific findings do suggest that the inverse relation was more prominent for squamous cell carcinomas as compared to adenocarcinomas.

It has been suggested that individuals with relatively elevated cholesterol levels tend to be depleted from a cohort due to "competition" from coronary heart disease mortality. A true lack of association between cholesterol and cancer would be observed as an inverse relation only if the risk for coronary death were substantially higher among those more susceptible to cancer (by reason of environmental exposures and/or genetic factors) than among those less susceptible to cancer. This competing risks explanation remains speculative. A more detailed treatment of the conditions under which competing risks bias might arise, with particular attention directed to the cholesterol-cancer question, is presented elsewhere.⁴

In summary, we found an inverse relation between cholesterol

⁴ A. Schatzkin and E. Slud, unpublished manuscript.

and smoking-related cancers among both men and women that was evident at a considerably later time of follow-up than could be easily explained by the preclinical cancer effect hypothesis. Although we cannot at this time offer more than a schematic pathobiological rationale for these observed relations, we conclude that the findings are strong enough to merit continued epidemiological investigation. In addition, the examination of serial serum cholesterol levels and other metabolic parameters in animal models of tobacco-induced carcinogenesis might be informative.

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