Cancer Incidence in the National Health and Nutrition Survey I Follow-up Data: Diabetes, Cholesterol, Pulse, and Physical Activity

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Abstract

We examined cancer incidence among 14,407 men and women who were enrolled in the National Health and Nutrition Survey I in the early 1970s and then followed through 1987. We studied 657 male and 593 female cancer cases, using Cox regression. Analyses were conducted for all cancers, lung, colorectal, breast, and prostate cancer. Analyses focused on diabetes, cholesterol, pulse, and physical activity, four risk factors with limited or inconsistent prior evidence. All four risk factors were modestly associated with all cancers for men but not for women. For diabetic men, the rate ratio for all cancers was 1.38 [95% confidence interval (CI) = 1.00–1.91]; the elevated risk was particularly evident for colorectal and prostate cancer. Slight inverse trends of cancer risk with cholesterol were apparent for men but not for women and were diminished compared to prior analyses of these data with less follow-up. Males with the lowest quartile of cholesterol *versus* the highest had a rate ratio of 1.21 (CI = 0.98–1.51) for all cancers. A modest positive trend between pulse and all cancers was seen for males [rate ratio of 1.27 (CI = 1.04–1.57)] for the highest *versus* the lowest quartile). The rate ratio for men with the least amount of nonrecreational physical activity was 1.29 (CI = 0.99–1.69). There is some evidence in these data that findings for cholesterol and nonrecreational physical activity could be artifacts of the early effects of disease because they diminished when cases were restricted to those with longer follow-up.

Introduction

In the early 1970s 14,407 men and women ages 25–74 years were examined in the NHANES1[2] survey (1). Extensive baseline data were collected via exam and questionnaire. Study subjects have been followed through 1987 for mortality and disease incidence via death certificate and hospital discharge data (2).

We have used these data to study the relationship between cancer and four risk factors: diabetes, pulse, cholesterol, and physical activity. Epidemiological evidence of an association with cancer for these risk factors is either limited or inconsistent. In the case of cholesterol and physical activity, we sought to confirm associations observed in earlier follow-ups of these same data.

There have been a number of cohort studies in which diabetics have been shown to have a slight excess risk of all cancer on the order of 10–20% (3–7), sometimes attaining conventional statistical significance. The site most consistently elevated has been the pancreas. Case-control studies have also found a risk of diabetics for pancreatic cancer and have also shown elevations of uterine and liver cancer (8, 9). Two cohort studies of hyperglycemia have reached different results: Levine *et al.* (5) found an increased risk of all cancers for hyperglycemic men, whereas Smith *et al.* (4) did not.

A higher pulse has been found to increase the risk of all cancers in men (10, 11).

Schatzkin *et al.* (12) analyzed these same data with follow-up through 1984 (459 male and 398 female cases) and found an inverse association between cholesterol and all cancers, particularly for men. The inverse trend was most pronounced for lung and all smoking-related cancers. This effect persisted when cases were restricted to those occurring 6 or more years after baseline to exclude the possibility that low cholesterol may have reflected early disease. We have sought to reanalyze this association with follow-up extended through 1987.

There are a number of studies showing that more physical activity protects against cancer, particularly colon cancer [*e.g.*, see Wannamethee *et al.* (11) and Severson *et al.* (13)]. This issue has been studied previously in the NHANES1 data with follow-up ending in 1984. In that analysis, self-reported nonrecreational physical activity was shown to be protective against all cancers (14) for men and women. We have now reexamined this association with follow-up through 1987.

We have examined the role of diabetes, cholesterol, pulse, and nonrecreational physical activity for all cancers, as well as specific cancers for which there were at least 100 cases (colorectal, lung, breast, and prostate).

Materials and Methods

The NHANES1 was conducted from 1971 to 1975 and involved the collection of interview and medical exam data on 23,808 subjects ranging in age from 1 to 74 years (1). Follow-up information for disease incidence was obtained by obtaining hospital records through 1987 for 14,407 participants who were 25–74 years of age when they were examined in NHANES1 (2). Death certificates were also collected for those who died through 1987.

We first eliminated those reporting prevalent or past cancer at baseline, those whose vital status was unknown, and those who were known to be alive but for whom no medical history data during follow-up were available (n = 1353). Cases

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[2] The abbreviations used are: NHANES1, National Health and Nutrition Survey I; CI, confidence interval.

Table 1 Descriptive information on cases and controls

Continuous variables	Cases (n = 1,250) Mean	Noncases (n = 11,804) Mean	Age-adjusted mean for controls (P value[a])
Age at baseline	60	48	ND
Cholesterol (mg/dl)	228	220	231 (0.02)
Pulse	80	80	80 (0.22)
Body mass index (kg/m^2)	26.0	25.6	26.0 (0.52)
Income (in thousands)	$ 5.6	$ 6.5	$ 5.6 (0.49)
Categorical variables	**%**	**%**	**P value[b]**
White	85	85	0.99
Ever diabetes	6	3	0.90
Moderate activity at work	49	46	0.87
Little activity at work	12	10	0.92
Moderate recreational activity	36	38	0.80
Little recreational activity	47	44	0.73
Current smokers	32	30	0.001
Former smokers	23	19	0.59
Missing smoking information	6	7	0.04
Daily/almost daily drinker	17	12	0.001
Weekly/monthly drinker	31	37	0.13
Less than monthly/never	52	51	0.001

[a] P value for a difference between cases and noncases after age adjustment via regression.
[b] NA, not applicable.
[c] P value for a difference between cases and controls, via a Mantel-Haenszel χ^2 after stratification on age at baseline exam (10-year intervals).

Table 2 Distribution of cancers by site and sex

Site	Men	Women	Total
Lung	151	59	210
Colorectal	94	82	176
Breast	0	163	163
Prostate	156	0	156
Other hematopoietic	24	39	63
Bladder	34	22	56
Pancreas	29	25	54
Leukemia	30	14	44
Kidney	28	13	41
Skin, not melanoma	29	12	41
Stomach	21	12	33
Ovary	0	27	27
Liver	13	12	25
Brain	9	12	21
Cervix	0	20	20
Uterus	0	43	43
Esophagus	16	1	17
Larynx	13	2	15
Melanoma	7	3	10
Thyroid	0	5	5
Oral	13	8	21
Other	45	49	94

were defined as: (*a*) any subject with cancer (codes 140–208, International Classification of Disease on a hospital discharge record; or (*b*) for those without cancer on hospital discharge, any subject who had died and had cancer listed anywhere on the death certificate. Those with only nonmalignant skin cancer (n = 31) were not considered cases. In this manner, we identified 657 male and 593 female cases (both cases and controls were about 85% white and 15% black). Eighty-five % of cases were identified from hospital discharge records, whereas the remainder were identified from death certificates only (most of the death certificate cases had cancer listed as the underlying cause). Of all cases, 26 males and 17 females had multiple primary tumors. Cases were followed for an average of 7.7 years.

We used Cox regression for the analysis (15), with matching for race (white, black, and other) and using follow-up time as the variable for time. Separate analyses were conducted for each sex.

Multivariate analyses of the four risk factors of *a priori* interest (diabetes, cholesterol, pulse, and nonrecreational physical activity) were controlled for potential confounders identified from the literature, including age, smoking (current or former *versus* never), alcohol consumption (daily/almost daily or 1–12/month *versus* rarely/never), body mass index, and income. The four risk factors and these confounders were retained in all models. Recreational physical activity was also retained in all models. In addition, a variable for menopause was added to the model for breast cancer.

All variables were taken from the NHANES1 baseline data, with the exception of smoking. Although smoking data were available for only about one-half of the subjects at baseline, most of those missing baseline smoking data had complete smoking histories collected during an interview conducted in 1982–1984. From these data, we ascertained smoking status at baseline. Smoking was categorized into current smoker, former smoker, and never smoker at baseline. A separate category was created for those missing smoking information (6% of cases and controls).

Prevalent diabetes was self-reported at baseline ("has a doctor ever told you that you have the condition"). Physical activity was self-reported (a lot, some, or little) and divided into recreational or nonrecreational activity. Nonrecreational activity was the focus of our analysis because it had been identified as protective against cancer in an analysis of these same data with follow-up through 1984. Cholesterol and pulse were analyzed by quartile (separately for men and women) and, in addition, considered as continuous variables as a test for trend.

Analyses were conducted for all cancers and for some specific sites. Site-specific analyses were limited to four cancers for which there were 100 or more cases to ensure sufficient statistical power. Additional analyses for all cancers were also conducted, considering only cancer cases diagnosed (or deceased) 6 or more years after baseline exam (65% of cases), in order to guard against the possibility that effects of risk factors seen in the overall analysis (especially cholesterol) might have been a product of early and undetected disease.

Although these data were collected by using a multistage cluster sampling procedure so as to be able to make estimates for the United States population, we have ignored design effects in calculating odds ratios and their SEs, treating the data as if it were a simple random sample from a hypothetical general population (a reasonable assumption for the purposes of estimating etiological effects). Other analyses of these data by using unconditional logistic regression indicated that incorporation of design effects did not change estimated regression coefficients and only minimally changed their SEs.

Results

Table 1 gives descriptive information on cases and noncases. Controls are considerably younger than cases, as expected (controls were matched to cases on follow-up time, not on age). Other variables, which are related to age (*e.g.*, prevalent dis-

Table 3 Results for all cancers[a]

Variable	Odds ratio (95% CI)	Test for trend (*P* value)[b]
Males		
Diabetes	1.38 (1.00–1.91)	
Cholesterol (quartiles)		
<190 *vs.* 247+	1.21 (0.98–1.51)	
190–216 *vs.* 247+	1.01 (0.82–1.26)	
217–246 *vs.* 247+	0.98 (0.79–1.21)	0.03
Pulse (quartiles)		
73–79 *vs.* <73	0.87 (0.70–1.09)	
80–87 *vs.* <73	0.99 (0.80–1.24)	
88+ *vs.* <73	1.27 (1.03–1.56)	0.002
Physical activity nonrecreational		
Little *vs.* lots	1.29 (0.99–1.69)	
Some *vs.* lots	1.02 (0.86–1.22)	
Females		
Diabetes	1.14 (0.81–1.62)	
Cholesterol (quartiles)		
<186 *vs.* 252+	0.98 (0.74–1.30)	
186–216 *vs.* 252+	1.12 (0.89–1.41)	
216–251 *vs.* 252+	1.03 (0.84–1.27)	0.44
Pulse (quartiles)		
73–79 *vs.* <73	0.97 (0.76–1.24)	
80–87 *vs.* <73	1.09 (0.86–1.39)	
88+ *vs.* <73	0.97 (0.76–1.22)	0.66
Physical activity, nonrecreational		
Little *vs.* lots	1.20 (0.90–1.61)	
Some *vs.* lots	1.05 (0.87–1.26)	

[a] Adjusted for age, BMI, smoking, alcohol, income, recreational physical activity-see Methods for details
[b] Cholesterol or pulse as continuous variables

Table 4 Results for lung cancer[a]

Variable	Odds ratio (95% CI)	Test for trend(*P* value)[b]
Males		
Diabetes	1.08 (0.50–2.33)	
Cholesterol (quartiles)		
<190 *vs.* 247+	1.48 (0.96–2.29)	
190–216 *vs.* 247+	0.89 (0.55–1.42)	
217–246 *vs.* 247+	0.93 (0.59–1.46)	0.14
Pulse (quartiles)		
73–79 *vs.* <73	0.67 (0.42–1.09)	
80–87 *vs.* <73	0.91 (0.57–1.45)	
88+ *vs.* <73	1.21 (0.79–1.84)	0.44
Physical activity, nonrecreational		
Little *vs.* lots	1.26 (0.71–2.24)	
Some *vs.* lots	1.12 (0.77–1.63)	
Females		
Diabetes	2.19 (0.91–5.23)	
Cholesterol (quartiles)		
<186 *vs.* 252+	1.29 (0.70–2.40)	
186–216 *vs.* 252+	0.50 (0.20–1.30)	
216–251 *vs.* 252+	1.18 (0.51–2.74)	
Pulse (quartiles)		
73–79 *vs.* <73	1.12 (0.51–2.45)	
80–87 *vs.* <73	0.93 (0.41–2.09)	
88+ *vs.* <73	1.13 (0.53–2.40)	
Physical activity, nonrecreational		
Little *vs.* lots	1.41 (0.59–3.35)	
Some *vs.* lots	0.95 (0.52–1.75)	

[a] Adjusted for age, body mass index, smoking, alcohol, income, and recreational physical activity (see "Materials and Methods" for details).
[b] Cholesterol or pulse as continuous variables.

eases), are proportionately higher among cases as a result. Age adjustment eliminates many of these differences. Table 2 gives the distribution of cancer types.

All Cancers. Table 3 gives the results for all cancer cases. Among men, diabetes and low nonrecreational activity were associated with significantly higher risk, and there were significant trends in which lower cholesterol and higher pulse predicted cancer. Analysis by quartiles indicated that elevated risk was apparent only for the lowest quartile of cholesterol and the highest quartile of pulse. There were no significantly elevated rate ratios or trends for women for any of the variables of interest.

After restricting the data to male cases occurring 6 or more years after baseline exam (65% of cases), the negative trend with cholesterol remained significant but, again, was not monotonic (rate ratios 1.22, 1.10, 1.23, and 1.00 by ascending quartile). The odds ratio for diabetes increased from 1.38 to 1.77 (CI = 1.19–2.63), and the increased risk for those with the least amount of nonrecreational physical activity decreased (odds ratio, 1.11). Men continued to exhibit a significant positive trend of increased risk with increased pulse, with the highest quartile again having an odds ratio of 1.30 (CI = 1.00–1.67).

Lung Cancer. Lung cancer results are shown in Table 4. For men diabetes was no longer significantly elevated. The inverse relationship between cholesterol and cancer risk seen for all cancers was observed here as well, with the excess concentrated in those subjects with the lowest cholesterol. Pulse and nonrecreational physical activity showed similar patterns for all cancers. For women, diabetes and nonrecreational physical activity were elevated. Neither cholesterol or pulse showed consistent patterns.

Breast Cancer. Breast cancer results are shown in Table 5. None of the four risk factors of interest was an important predictor. Diabetes was elevated but with a wide CI.

Prostate Cancer. Results are shown in Table 6. Diabetes was elevated, but the CI was wide. Pulse showed a slight elevation, again restricted to the uppermost quartile. Low cholesterol showed no evidence of increased risk. Those most inactive subjects, again, had a slightly increased risk.

Colorectal Cancer. Results for colorectal cancer are shown in Table 7. For men, diabetes was a risk factor (rate ratio, 1.43) but with a wide CI. Lack of physical nonrecreational physical activity caused no increased risk. There was no consistent pattern for cholesterol. Those with a higher pulse were again at increased risk but without a consistent pattern.

For women, diabetes was elevated (rate ratio, 1.40), with a wide CI. All lower quartiles of cholesterol showed decreased risk *versus* the highest. Pulse and physical activity had little consistent pattern.

Discussion

We found an increased of risk of all cancers for diabetics for males only; individual cancers with elevated risks for diabetic males were colorectal and prostate. Women diabetics overall had no excess risk for all cancers; site-specific elevated risks were observed for breast, lung, and colorectal cancer. Findings of other investigators have indicated only a slight 10–20% excess risk for diabetics for all cancers, with excesses concentrated in pancreatic cancer and, to a lesser extent, in liver or uterine cancer. Diabetes is a rare condition in this population (4%). We lacked statistical power to detect much of an effect

Table 5 Breast cancer[a]

	Odds ratios (95% CI)	Test for trend (*P* value)[b]
Diabetes	1.40 (0.70–2.78)	
Cholesterol (quartiles)		
<186 vs *vs.* 252+	0.66 (0.38–1.10)	
186–216 *vs.* 252+	0.92 (0.60–1.40)	
216–251 *vs.* 252+	0.58 (0.38–0.90)	0.33
Pulse (quartiles)		
73–79 *vs.* <73	0.85 (0.54–1.34)	
80–87 *vs.* <73	0.86 (0.55–1.35)	
88+ *vs.* <73	0.81 (0.52–1.26)	0.52
Physical activity, nonrecreational		
Little *vs.* lots	0.86 (0.48–1.55)	
Some *vs.* lots	0.86 (0.61–1.20)	

[a] Adjusted for age, body mass index, smoking, alcohol, income, recreational physical activity, and menopausal status (see "Materials and Methods" for details).
[b] Cholesterol or pulse as continuous variables.

Table 6 Prostate cancer[a]

	Odds ratios (95% CI)	Test for trend (*P* value)[b]
Diabetes	1.45 (0.78–2.71)	
Cholesterol (quartiles)		
<190 *vs.* 247+	0.92 (0.57–1.47)	
190–216 *vs.* 247+	1.13 (0.73–1.73)	
217–246 *vs.* 247+	0.99 (0.65–1.52)	0.43
Pulse (quartiles)		
73–79 *vs.* <73	0.93 (0.59–1.45)	
80–87 *vs.* <73	1.20 (0.77–1.87)	
88+ *vs.* <73	1.28 (0.83–1.97)	0.22
Physical activity, nonrecreational		
Little *vs.* lots	1.31 (0.76–2.26)	
Some *vs.* lots	1.02 (0.70–1.48)	

[a] Adjusted for age, body mass index, smoking, alcohol, income, and recreational physical activity (see "Materials and Methods" for details).
[b] Cholesterol or pulse as continuous variables.

Table 7 Colorectal cancer[a]

Variable	Odds ratio (95% CI)	Test for trend (*P* value)[b]
Males		
Diabetes	1.43 (0.61–3.31)	
Cholesterol (quartiles)		
<190 *vs.* 247+	0.78 (0.44–1.36)	
190–216 *vs.* 247+	0.66 (0.38–1.15)	
217–246 *vs.* 247+	0.61 (0.35–1.06)	0.34
Pulse (quartiles)		
73–79 *vs.* <73	1.34 (0.76–2.34)	
80–87 *vs.* <73	1.08 (0.59–1.98)	
88+ *vs.* <73	1.33 (0.75–2.37)	0.61
Physical activity, nonrecreational		
Little *vs.* lots	1.02 (0.48–2.15)	
Some *vs.* lots	0.96 (0.60–1.53)	
Females		
Diabetes	1.40 (0.64–3.10)	
Cholesterol (quartiles)		
<186 *vs.* 252+	0.71 (0.29–1.80)	
186–216 *vs.* 252+	1.10 (0.58–2.08)	
216–251 *vs.* 252+	0.99 (0.80–2.22)	0.90
Pulse (quartiles)		
73–79 *vs.* <73	1.34 (0.70–2.59)	
80–87 *vs.* <73	1.39 (0.72–2.67)	
88+ *vs.* <73	0.99 (0.50–1.94)	0.88
Physical activity, nonrecreational		
Little *vs.* lots	0.94 (0.40–2.21)	
Some *vs.* lots	1.36 (0.80–2.32)	

[a] Adjusted for age, body mass index, smoking, alcohol, income, and recreational physical activity (see "Materials and Methods" for details).
[b] Cholesterol or pulse as continuous variables.

for diabetics for the rarer cancers of *a priori* interest (pancreatic, liver, or endometrium). Simple inspection of the data did not, however, indicate an excess for any of these cancers.

Hypotheses put forward to explain a relationship between diabetes and cancer include; (*a*) increased cancer detection due to increased medical surveillance of diabetics; (*b*) malignancy causing an increase in severity of subclinical diabetes; (*c*) both diseases increased in obese subjects or in people sharing genetic risk factors common to both diseases (*e.g.*, mediated via hormones); and (*d*) a true etiological relationship, the mechanism of which is unknown (7). Factors (*a*) and (*b*) would seem to be unlikely given our prospective design and our observation that the odds ratio for diabetes increased when cases were restricted to those with at least 6-years follow-up. Obesity was controlled in the analysis. Our data are surprising in that the excess for all cancers is greater than that seen in other studies and is apparent for different cancers that have been observed elsewhere, although CI are wide. A weakness of our design is a reliance on self-reports to define diabetes at baseline interview. However, it would seem unlikely that people with incipient cancer would have tended to over-report diabetes.

We found pulse to be a significant risk factor for all cancers in men; the highest quartile showed a 27% increased risk. This results confirms findings by Persky *et al.* (10) and Wannamethee *et al.* (11). The same modest elevated risk persisted when male cases were restricted to those occurring 6 or more years after baseline exam. A similar, slight elevated risk for the highest quartile was seen for men for lung, prostate, and colorectal cancer. Little consistent trend with pulse was observed for women.

The studies by Persky *et al.* (10) and Wannamethee *et al.* (11) were restricted to men. Wannamethee *et al.* (11) suggested two mechanisms by which heart rate might increase risk of cancer: (*a*) it might be a marker for reduced physical activity, which has been shown in several studies to be a risk factor for cancer; (*b*) that it might reflect adrenergic activity, which is in turn related to stress, which may in turn increases the risk of cancer.

Numerous studies have indicated a protective effect of physical activity against cancer, particularly colon cancer, although studies are not entirely consistent. There have been no strong hypotheses about possible mechanisms, other than the notion that the metabolic products of muscular activity may somehow protect epithelial cells against mutation. Several studies have shown that physical activity is protective independently of its role in preventing obesity, which may be a risk factor for several cancers. Albanes *et al.* (14) have studied self-reported recreational and nonrecreational physical activity in the NHANES1 follow-up data through 1984. These authors studied 460 male and 399 female cases (compared to our 657 male and 593 female cases). They found a significantly increased risk for those with the least amount of nonrecreational physical activity (rate ratio for men, 1.8 and for women, 1.4) for all cancers. Our own findings for this same risk factor were less elevated, with rate ratios of 1.29 and 1.20 for men and women, respectively. These modest elevations decreased when cases were restricted to those with at least 6 years follow-up.

Albanes *et al.* (14) found the effect of little nonrecreational

activity most pronounced for colorectal cancer and lung cancer among men (rate ratio for both 1.6) and postmenopausal breast cancer and cervix cancer among women (rate ratios, 1.7 and 5.2, respectively). We found a higher rate ratio for men for lung (rate ratio, 1.26) but not for colon cancer (rate ratio, 1.03). For women, we found an elevation for lung cancer (rate ratio, 1.41), no excess for breast cancer overall, and a rate ratio of 1.50 (CI = 1.08–2.08) for postmenopausal women.

The primary explanation put forward to explain findings of an inverse relationship between cancer and cholesterol has been that early cancer causes a decrease in cholesterol levels. On the other hand, in analyses of these same NHANES1 data with earlier follow-up (through 1984; 459 male cancers and 398 female cancers), Schatzkin *et al.* (12) found an inverse trend in risk of all cancers, which did not diminish when cancers were restricted to those occurring 6 or more years after baseline. This inverse trend was especially evident for males and for smoking-related cancers or lung cancer (12).

We conducted additional analyses to mimic the analyses by Schatzkin *et al.* (Ref. 12; by using quintiles rather than quartiles of cholesterol and by using the identical cutpoints). For men for all cancers, Schatzkin *et al.* (12) found rate ratios of 1.8, 1.5, 1.0, 1.3, and 1.0 from the lowest quintile of cholesterol to the highest, whereas we found corresponding rate ratios of 1.20, 1.08, 0.97, and 0.89. For women, Schatzkin *et al.* (12) found odds ratios of 1.2, 1.0, 0.8, 0.9, and 1.0, whereas we found corresponding odds ratios of 1.08, 0.98, 1.01, and 0.95. The modest negative trend with cholesterol for men persisted in our data for all cancers when cases were limited to those occurring 6 or more years after baseline (rate ratios of 1.23, 1.08. 1.12, 0.94, and 1.00).

Schatzkin *et al.* (12) found their most striking inverse relationship between cholesterol and cancer for a grouping of smoking-related cancers (lung, mouth, esophageal, larynx, pancreatic, bladder, leukemia, and cervical), with rate ratios for men of 2.1, 1.6, 1.1, 1.4, and 1.0 by ascending quintile of cholesterol. We repeated this analysis and found similar, although somewhat diminished, findings for men (rate ratios for men of 1.71, 1.39, 1.12, 1.18, and 1.00; test for trend, p = 0.007). For women, Schatzkin *et al.* (12) found corresponding rate ratios of 3.3, 1.7, 0.7, 1.1, and 1.0, whereas our parallel findings also indicated a similar, although less dramatic, trend (rate ratios 1.52, 1.08, 1.21, 1.16, and 1.00; test for trend, $P = 0.33$). When smoking-related cases were limited to those occurring 6 or more years after baseline, our data for men showed rate ratios of 1.24, 1.09, 1.03, 0.92, and 1.00 by quintile of cholesterol, which are not different from the same trend for all cancers 6 or more years after baseline. Female smoking-related cancers 6 or more years after baseline showed no excess risk for low cholesterol (rate ratios by quintile of 0.90, 0.87, 0.97, 0.97, and 1.00).

Overall, our data indicate a modest inverse relationship between cholesterol and all cancers among men and noninverse relationship among women. In men, the inverse relationship for all cancers is largely dependent on the 20% excess risk in those with lowest baseline cholesterol *versus* the highest, and there is no consistent monotonic trend. More pronounced excess risk for those with low cholesterol, for both men and women, is apparent for smoking-related cancers, but these excess risks are much diminished or disappear when cases are restricted to those with at least 6-years follow-up. Our findings suggest that the observed inverse associations may in fact be an artifact of early illness altering cholesterol levels downward, particularly for smoking-related cancers.

An exception to the inverse association of cholesterol and cancer among men was colorectal cancer, in which higher cholesterol increased risk. Reports in the literature for colorectal cancer have been inconsistent. Many have found an inverse relationship [*e.g.*, Kreger *et al.* (16)]. However, others have found significant positive associations between rectal cancer and serum cholesterol (17) and between colorectal adenoma and serum cholesterol (18). Both of these positive findings were stronger in men than women. There is also some animal evidence that rats fed dietary cholesterol may have increased colon cancer (19). The mechanism by which higher cholesterol is associated with colorectal cancer might be as a marker of high fat diets, known to increase risk of colon cancer via several purported mechanisms, such as an increase in bile acids, which are tumor promoters in colons of animals.

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References

1. National Center for Health Statistics. Plan and operation of the National Health and Nutrition Survey. *In:* United States 1971–1973, Vital and Health Statistics Series 1, No. 10a, DHEW Publ. No. 73-1310. Washington, DC: United States Government Printing Offices. 1979.

2. National Center for Health Statistics. Plan and operation of the NHANESI epidemiologic follow-up study, 1982–1984. *In:* Vital and Health Statistics Series 1, No. 22, DHHS Publication No. 87-1324. Washington, DC: United States Government Printing Office, 1987.

3. Adami, H., McLaughlin, J., Ekbom, A., Berne, C., Silverman, D., Hacker, D., and Persson, I. Cancer risk in patients with diabetes mellitus. Cancer Causes & Control, *2:* 307–314, 1991.

4. Smith, G., Egger, M., Shipley, M., and Marmot, M. Post-challenge glucose concentration, impaired glucose tolerance, diabetes, and cancer mortality in men. Am. J. Epidemiol., *136:* 1110–1114, 1992.

5. Levine, W., Dyer, A., Shekelle, R., Schoenberger, J., and Stamler, J. Post-load plasma glucose and cancer mortality in middle-aged men and women. Am. J. Epidemiol., *131:* 254–262, 1990.

6. Moss, S., Klein, R., and Klein, B. Cause-specific mortality in a population-based study of diabetes. Am. J. Public Health, *81:* 1158–1162, 1991.

7. Ragozzino, M., Melton, J., Chu-Pin, C., and Palumbo, P. Subsequent cancer risk in the incidence cohort of Rochester, Minnesota, residents with diabetes mellitus. J. Chron. Dis., *35:* 13–19, 1982.

8. O'Mara, B., Byers, T., and Schoenfeld, E. Diabetes mellitus and cancer risk: a multisite case-control study. J. Chron. Dis., *38:* 435–441, 1985.

9. La Vecchia, C., Negri, E., Franceschi, S., D'Avanzo, B., and Boyle, P. A case-control study of diabetes mellitus and cancer risk. Br. J. Cancer, *70:* 950–953, 1994.

10. Persky, V., Dyer, A., Leonas, J., Stamler, J., Berkson, D., Lindberg, H., Oglesby, P., Shekelle, R., Lepper, M., and Schoenberger, J. Heart rate: a risk factor for cancer? Am. J. Epidemiol., *114:* 477–487, 1981.

11. Wannamethee, G., Shaper, A., Macfarlane, P. Heart rate, physical activity, and mortality from cancer and other noncardiovascular diseases. Am. J. Epidemiol., *137:* 735–748, 1993.

12. Schatzkin, A., Hoover, R., Taylor, P., Ziegler, R., Carter, C., Albanes, D., Larson, D., and Licitra, L. Site-specific analysis of total serum cholesterol and incident cancer in NHANES1 epidemiologic follow-up study. Cancer Res., *48:* 452–458, 1988.

13. Severson, R., Nomur, A., Grove, G., and Stemmerman, G. A prospective analysis of physical activity and cancer. Am. J. Epidemiol., *130:* 522–529, 1989.

14. Albanes, D., Blair, A., and Taylor, P. Physical activity and risk of cancer in the NHANES 1 population. Am. J. Public Health, *79:* 744–749, 1989.

15. SAS. SAS User's Guide: Statistics (Version 6.07). Cary, N C: SAS Institute, 1991.

16. Kreger, B., Anderson, K., Schatzkin, A., and Splansky, G. Serum cholesterol level, body mass index, and the risk of colon cancer, Cancer (Phila.), *70:* 1038–1043, 1992.

17. Tornberg, S., Carstensen, J., and Eklung, G. Risks of cancer of the colon and rectum in relation to serum cholesterol and β-lipoprotein. N. Engl. J. Med., *315:* 1629–1633, 1986.

18. Mannes, G., Maier, A., Thieme, C., Wiebecke, B., and Paumgartner, G. Relation between the frequency of colorectal adenoma and the serum cholesterol level. N. Engl. J. Med., *315:* 1634–1638, 1986.

19. Kendall, C., Janezic, S., Friday, D., and Rao, A. Dietary cholesterol enhances preneoplastic aberrant crypt formation and alters cell proliferation in the murine colon treated with azoxymethane. Nutr. Cancer., *17:* 107–144, 1992.

Cancer incidence in the National Health and Nutrition Survey I. Follow-up data: diabetes, cholesterol, pulse and physical activity.

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