Total Cholesterol and Body Mass Index in Relation to 40-Year Cancer Mortality (The Corfu Cohort of the Seven Countries Study)

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Abstract

Purpose: **We evaluated risk factors of cancer mortality based on a 40-year follow-up of the Corfu cohort (Seven Countries Study).**

Material and Methods: **The population studied in this analysis consisted of 529 rural men (49 ± 6 years old) enrolled in 1961. Since then, periodic visits every 5 years were made to define the causes of death of the participants. Cox proportional hazards models evaluated various risk factors in relation to cancer mortality.**

Results: **The death rate at the end of the follow-up was 87.1% (i.e., 461 deaths in 529 participants). Of those deaths, 118 (25.6%) were because of cancer (30 deaths were due to cancer of trachea, bronchus, and lung, and the rest were due to other malignant neoplasms). Cancer was the second cause of death in this cohort, after coronary heart disease. Age (hazard ratio, 1.05 per year; $P < 0.05$), smoking (hazard ratio, 1.97; $P < 0.01$), total serum cholesterol levels (hazard ratio, 0.95 per 10 mg/dL; $P < 0.05$), and body mass index (hazard ratio, 0.93 per 1 kg/m^2; $P < 0.05$) showed a significant association with cancer deaths after controlling for physical activity status and anthropometric indices. It should be noted that the protective effect of total cholesterol on cancer mortality was observed only between 183 and 218 mg/dL baseline levels.**

Conclusion: **Cancer was one of the leading causes of death in this cohort. Smoking was associated with increased risk of cancer, whereas moderate total serum cholesterol and increased body and mass index seemed to have a protective effect on 40-year cancer mortality.** (Cancer Epidemiol Biomarkers Prev 2005;14(7):1797–801)

Introduction

According to the National Cancer Institute of the Unites States, cancer mortality is one of the leading causes of death in America, as well as in other parts of the world (1, 2). In 2000, cancer accounted for over 7 million deaths (13% of total mortality) and there were more than 10 million new cancer cases worldwide. Furthermore, WHO reports that by the year 2020 there will be 15 million new cases each year (3). The causal pathway of various types of cancer has been extensively investigated in many observational, clinical, and experimental studies. It is well known that tobacco use is one of the main, preventable, causes of cancer and it is associated with 80% to 90% of all lung cancer deaths, including deaths from cancer of the oral cavity, larynx, esophagus, and stomach (3). Some, but not all, investigators suggest that low serum cholesterol has been associated with an increased risk of cancer mortality (4–6); however, this has led to uncertainty about the benefit of lower blood cholesterol on human health. Finally, regular physical activity and the maintenance of a healthy body weight, along with a healthy diet, have been suggested as measures that could considerably reduce cancer risk (7–9).

Despite the large amount of evidences about the prognostic markers of cancer mortality, long-term predictors have rarely been reported in the literature. In the context of an international project conducted from 1960 to 2000 in Europe, United States, and Japan (the Seven Countries Study), we aim to evaluate the 40-year incidence of cancer mortality among middle-aged men that consisted one of the cohorts of the study (the Corfu cohort in Greece). We also sought to investigate the associations between several factors [e.g., age, smoking habits, total serum cholesterol, body mass index (BMI), and physical activity] and cancer mortality, and to compare these results with the findings reported in previous analyses about coronary heart disease and stroke mortality.

Materials and Methods

The Seven Countries Study (10) enrolled 12,763 men, 40 to 59 years old, from 16 cohorts of the seven participating countries (United States, Italy, Japan, the Netherlands, Greece, former Yugoslavia, and Finland). The population studied in this work was the Corfu cohort. From September to October 1961, 529 men from six rural villages (San Marcus, Scriperon, Sokraki, Doucades, Gardelades, and Korakiana) were examined and consisted the Corfu cohort (11, 12). This cohort was made up of almost all the men who lived in the above area (95.3%) and were 40 to 59 years old in the early fall of 1961. These were mainly small-scale, nonmechanized farmers (55%). Since 1961, several periodic visits—every 5 years—were made by the Seven Countries Study investigators in the Corfu Island to define the vital status of the participants (the compliance varied from 98% to 100%). Unfortunately, no clinical or any other information was available through the periodic visits. The causes of death were obtained during the periodic visits from the study research group, using information from local registers and hospital or necroscopy records (when it was available). In two cases, the causes of death were ascertained

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by the information provided by their family members. On July 2001, collection of data on vital status and causes of death was complete for 40 years and no subject was lost to follow-up (12). A single reviewer following defined criteria, employing the 8th Revision of the WHO-International Classification of Diseases, determined causes of death. In the presence of multiple causes, a hierarchical preference was adopted with violence, cancer in advanced stages, coronary heart disease, and stroke, in that order. WHO-International Classification of Diseases codes were then transformed into a more compact classification called Laboratory of Physiological Hygiene. The end point of this analysis was mortality due to cancer of trachea, bronchus, and lung (Laboratory of Physiological Hygiene code 751 or WHO-International Classification of Diseases code 162), as well as other malignant neoplasms (Laboratory of Physiological Hygiene code 752 or WHO-International Classification of Diseases codes 140-208), occurred in subjects free from any chronic disease at entry examination (10, 11).

In the present analysis, the following entry information have been considered: age in years, physical activity status, supine resting systolic and diastolic blood pressures, self-reported cigarette smoking, total serum cholesterol in milligrams per deciliter measured in a casual blood sample by the method of Abell-Kendall, modified by Anderson and Keys (13), BMI (kilogram of weight divided by square meter of height), triceps and subscapular skinfold thickness (measured to the nearest 0.5 mm on the unclothed chest just below the tip of the right scapula), unclothed right arm circumference in millimeter, after cleaning from the contribution of skin and s.c. fat by subtracting these components by the use of the triceps skinfold [formula: clean circumference = crude circumference − (triceps skinfold × 3.14)], vital capacity during a minute (in deciliters per meter of height), and forced expiratory volume in 0.75 second (in deciliters per meter of height). Physical activity classification was based on the responses to questions about occupation and usual leisure time activities, including part-time jobs and other nonoccupational exercise (11). A list of almost 100 occupations was used for final classification and has been published by Keys et al. (10). Thus, all men were classified at entry into three classes: class 1, men who were sedentary or engaging in little exercise; class 2, men who were moderately active during a substantial part of the day; and class 3, men who did hard physical work much of the time. A rough estimate of energy expenditure corresponding to these three physical activity classes was made on the basis of ergonometric procedures carried out by the investigators of the study. Thus, for class 1 the energy expenditure was <2,400 kcal/d; for class 2 it was between 2,400 and 3,000 kcal/d; and for class 3 it was more than 3,000 kcal/d (10). Further details about the protocol and procedures applied in the Seven Countries Study have been presented in detail elsewhere (10–13).

Statistical Analysis. We have calculated that the number of enrolled participants (n = 529) and the 40 years of follow-up provide us with 82% statistical power for assessing 10% two-sided differences on death rates between various groups of study (i.e., smokers versus nonsmokers, etc.) at $P = 0.05$.

Continuous variables are presented as mean ± SD and categorical variables are presented as absolute and relative frequencies. Death rates were calculated using the observed person-time in years. The proportion of surviving persons has been recorded every 6 months. Survival analysis was done using the Cox proportional hazards model with cancer as end point and the aforementioned risk factors as predictors. The continuous factors (blood pressures, anthropometric indices, and total serum cholesterol) were entered linearly, whereas age was exponentially tested in the survival model. The assumption of linearity was graphically tested, plotting −log[Survival function (t)] versus time. The associations between the investigated factors and the fatal events are presented as exponentials (hazard ratios) of the estimated coefficients. The goodness-of-fit test was based on the comparison of the observed and expected survival probabilities under the assumption of proportional hazards. The assumption of proportionality was graphically assessed through the plots of weighted deviance residuals versus time. $P < 0.05$ was considered as statistically significant. SPSS (SPSS, Inc., Chicago, IL) version 10.1 software was used for all the statistical calculations.

Results

Table 1 presents the baseline information about the investigated factors. It is of interest that about 75% of men reported smoking habits at entry examination, whereas roughly one of three reported heavy physical activities (80% of them due to occupational activities).

At the 40-year follow-up, 461 of 529 (87%) enrolled middle-aged men were dead. One-hundred eighteen (25.6%) of these deaths were due to cancer. Of these, 30 (25%) deaths were due to cancer of trachea, bronchus, or lung, and the rest were due to other malignant neoplasms. Cancer was the second cause of death closely after coronary heart disease (120 deaths). Figure 1 presents the survival curve for cancer, coronary heart disease, and stroke during the 40-year period. The cumulative survival shows a smooth decrease over the first 10 to 20 years of follow-up, and it becomes steeper after the third decade of observation. No significant differences were observed between the mortality rates of cancer, coronary heart disease, and stroke (log-rank = 0.24, $P = 0.88$; Fig. 1).

Table 2 shows the solutions from the applied survival model. The first part of the table illustrates the effect of all variables entered in the initial model on cancer mortality, whereas the second part presents the variables that remained statistically significant after the multivariate evaluation (final model). Based on these findings, the most significant age-adjusted predictors of cancer mortality were smoking (adverse), total serum cholesterol, and BMI (protective).

Overall, smoking was associated with 2-fold higher risk of cancer death (Table 2). Forty-nine percent of these deaths were attributed to cigarette smoking. Moreover, smoking of more than 10 cigarettes per day was associated with 3-fold [hazard ratio, 2.89; 95% confidence interval (95% CI), 1.71-4.79] higher risk of cancer death, whereas heavy smoking (>30 cigarettes/d) was associated with 8-fold higher risk (hazard ratio, 7.84; 95% CI, 3.48-17.62) of cancer deaths. Stopping smoking before entering into the study was associated with 70% lower risk (hazard ratio, 0.30; 95% CI, 0.13-0.69) of cancer death as compared with active smokers. No significant interaction was

Table 1. Characteristics of 529 men in the Corfu cohort at entry (1961)

Age at entry (y)	50 ± 6
Serum total cholesterol (mg/dL)	205 ± 46
Smoking (≥1 cigarettes/d)	393 (74.3%)
Heavy smoking (>30 cigarettes/d)	112 (21%)
Cigarettes among smokers (n/d)	11.1 ± 10.7
Physical activity status	
Class 1 (sedentary)	167 (32%)
Class 2 (moderate)	197 (37%)
Class 3 (heavy)	165 (31%)
Systolic blood pressure (mm Hg)	137 ± 20
Diastolic blood pressure (mm Hg)	83 ± 12
BMI (kg/m^2)	25 ± 4
Triceps skinfold thickness (mm)	7.1 ± 3.2
Subscapular skinfold thickness (mm)	10.6 ± 5.7
Right arm circumference (mm)	274 ± 28
Vital capacity (dL/m)	36.9 ± 6.7
Forced expiratory volume (dL/m)	26.1 ± 5.7

NOTE: Values are expressed as mean ± SD or absolute (relative frequency).

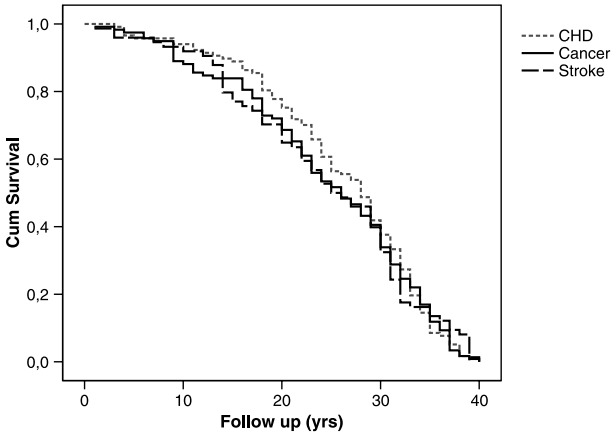

Figure 1. Cumulative survival curves for cancer (*continuous line*), coronary heart disease (*CHD*, *dotted line*), and stroke for the Corfu cohort during the 40-year period (1961-2001).

observed between smoking habits and physical activity status on the investigated outcome.

An inverse association was found between increased total serum cholesterol levels and cancer mortality (Table 2). We observed that a 10 mg/dL increase in baseline total cholesterol levels was associated with 5% lower risk of death due to cancer (hazard ratio, 0.95; 95% CI, 0.89-0.98). However, when we categorized total cholesterol levels into tertiles (<183, 183-218, and >218 mg/dL), we observed that only men in the middle tertile had lower risk of cancer death compared with the lowest tertile (Table 2).

Finally, BMI was inversely associated with risk of cancer, independently from physical activity status and fitness levels. We found that a 1 kg/m^2 increase in BMI baseline levels was associated with 7% lower risk of cancer, after controlling for age and other potential confounders (Table 2).

The inverse associations reported above for total serum cholesterol, BMI, and cancer mortality were also confined to lung cancers [hazard ratio for total cholesterol, 0.93 ($P < 0.001$); hazard ratio for BMI, 0.94 ($P < 0.001$)], as well as to early observed cancer deaths [i.e., within the first 20 years of follow-up; hazard ratio for total cholesterol, 0.95 ($P < 0.001$); hazard ratio for BMI, 0.97 ($P < 0.001$)].

Finally, arterial blood pressures, other anthropometric indices, physical activity, and fitness markers were not associated with risk of cancer in these middle-aged men (Table 2).

Discussion

In this work, we presented cancer mortality data based on the 40-year follow-up of the Corfu cohort from the Seven Countries Study. To the best of our knowledge, this is one of the longest follow-up studies on cancer mortality. We observed that, during the follow-up period, the proportion of cancer deaths was at the second place of all causes of death. We also found that age, smoking habits, as well as increased BMI and moderate total serum cholesterol levels (protective) were significantly associated with cancer mortality, after controlling for several potential confounders.

Smoking and Cancer. The risk of developing smoking-related cancers, as well as noncancerous diseases, has been reported in many studies before (1–3). Cigarette smoke contains about 4,000 chemical agents, including over 60 substances that are known to cause cancer in humans (1, 3, 14). Many of these substances, such as carbon monoxide, tar, arsenic, and lead, are poisonous and toxic to the human body. Confirming many previous reports from observational studies, we have found that cigarette smoking was associated with a 2-fold increase of risk of cancer deaths in middle-aged men, and the association between the number of cigarettes smoked and risk of cancer was linear. It is well known that the risk of death from lung cancer increases with the number of cigarettes smoked, and duration of smoking is the strongest determinant of lung cancer in smokers. A recent report of the U.S. Surgeon General suggests that heavy smokers have laryngeal cancer mortality risks 20 to 30 times greater than nonsmokers (15). We confirmed the previous reports by showing that heavy smoking (>30 cigarettes/d) was associated with an 8-fold increase in cancer mortality, after adjusting for several potential confounders. At this point, it should be noted that stopping smoking has been associated with a considerable reduction of the risk of cancer as well as other chronic diseases. Peto et al. (16) reported that stopping smoking before middle age avoids more than 90% of the risk attributable to smoking. Similarly to the previous finding, we observed that middle-aged men who stopped smoking before entering the study experienced 70% lower risk of cancer death as compared with people who reported active smoking at baseline examination. The latter finding provides another strong public health message for cancer prevention.

Total Serum Cholesterol and Cancer. The present study showed that total cholesterol levels between 183 and 218 mg/dL constitute a ''protective'' marker for cancer deaths. However, higher values of total serum cholesterol did not show any significant association with cancer mortality. The association between cancer mortality and total cholesterol levels has been investigated before by several studies. The Multiple Risk Factor Intervention Trial revealed a significant excess of cancer in the lowest decile of serum cholesterol level (17). The investigators suggested that these findings are consistent with the inference that the association between low serum cholesterol level and cancer is at least in part due to an effect of preclinical cancer on serum cholesterol level. Keys and his colleagues (18) from the Seven Countries Study observed that among cancer deaths 5 years after cholesterol measurement, there was a significant excess of lung cancer deaths in the bottom percentiles of the cholesterol

Table 2. Estimates from Cox proportional hazards model predicting 40-year cancer mortality as a function of baseline risk factors levels

Risk factor	Hazard ratio	95% CI
Variables entered in the initial model		
Age at entry (per year)	1.06	1.02-1.10
Physical activity (classes 2-3 vs class 1)	0.82	0.37-1.22
Smoking (yes vs no)	1.93	1.20-3.09
Total serum cholesterol		
<183 mg/dL	1.00	
183-218 mg/dL	0.52	0.33-0.86
>218 mg dL	0.79	0.47-1.52
Diastolic blood pressure (per 5 mm Hg)	1.21	1.05-1.40
Vital capacity (per 1 dL/m)	1.03	0.98-1.09
Force expiratory volume (per 1 dL/m)	0.97	0.92-1.04
BMI (per 1 kg/m^2)	0.93	0.80-1.08
Total skinfold thickness (per 10 mm)	0.90	0.66-1.22
Right arm circumference (per 10 mm)	1.01	0.90-1.11
Variables that remained statistically significant (final model)		
Age at entry (per year)	1.05*	1.01-1.08
Smoking (yes vs no)	1.97†	1.24-3.14
Total serum cholesterol		
<183 mg/dL	1.00	
183-218 mg/dL	0.59*	0.39-0.90
>218 mg/dL	0.82	0.49-1.54
BMI (per 1 kg/m^2)	0.93*	0.87-0.99

*$P < 0.05$.
†$P < 0.01$.

distributions, independently from the effect of age, blood pressure, smoking habits, occupation, vitamin A and ascorbic acid consumption, and relative body weight. Tornberg et al. (19) observed that total cancer incidence and mortality were inversely correlated to serum cholesterol level. The association between serum total cholesterol and cancer mortality was also investigated in a 28-year follow-up study of Dutch middle-aged civil servants and their spouses (20). The investigators suggested that low serum cholesterol might be a risk factor for cancer mortality in men. However, there are studies that showed negative results. For example, MacMahon (21), in a review of 26 trials and 50,000 patients, reported that the increase of cancer deaths was not associated with cholesterol reduction. In accordance to the previous findings, Kromhout et al. (22) in the Zutphen Study, which was carried out in the 1960s and included 829 middle-aged men from the Netherlands, concluded that serum cholesterol level was not related to long-term incidence of and mortality from cancer. It seems that there are some lines of evidence suggesting that low cholesterol levels are a risk factor for cancer, but we cannot rule out the possibility that there is also a direct causal effect. Moreover, from a public health point of view, we have to take into account the strong association between high total cholesterol levels and the burden of coronary heart disease.

Body Mass Index and Cancer. We observed an inverse relationship between BMI and risk of cancer. This effect was independent of age, physical activity status, and smoking habits. Several other studies have investigated the relationship between BMI and cancer risk. The results in these studies seem controversial (23–27). For example, Nieto et al. (23) reported that low BMI was associated with a 3.5-fold higher risk of oral cavity and oropharyngeal cancer. In addition, Giovannucci et al. (24) reported that the risk of prostate cancer in men with a higher BMI was lower than that in men with a lower BMI. Moreover, Kabat and Wynder (25), studying 3,607 lung cancer cases and 9,681 controls, observed an inverse association between incidence of lung cancer and BMI. Similarly, Hu et al. (26) reported that BMI had an inverse association with cancer mortality among 22,528 men and an almost significant direct association among 24,684 women. On the other hand, data from the American Cancer Society study (27) and various other studies (28, 29) support the hypothesis that obesity increases the risk of cancer death and that the relation is stronger and more linear in men than in women. Although it is hard to conclude a causal relationship between decreased BMI and risk of cancer, it could be speculated that low body mass and lung cancer may be due to factors associated with leanness. Moreover, various psychosocial and dietary characteristics may be the link between low BMI and increased risk of cancer (30). It could be also speculated that heavy physical activity levels (mostly from occupational, stressful, unhealthy activities) observed in our study group may be associated with lower BMI and, consequently, increased risk of cancer death.

Predictors of Coronary Heart Disease and Stroke Mortality in Comparison with Cancer Mortality. Previous published reports of this cohort presented the 40-year predictors of coronary heart disease and stroke mortality (12, 31, 32). We have found that age, smoking habits, and increased BMI were significant determinants for coronary heart disease mortality (29), whereas, age, high pulse pressure levels, physical inactivity, and low total serum cholesterol levels were significantly associated with stroke mortality (30). In this work, we found that age and smoking habits constitute risk factors for cancer mortality, too. These findings emphasize the harmful effect of long-term smoking on both cancer and cardiovascular diseases. Potentially, various chemical agents and substances, like carbon monoxide and nicotine, which are known to cause cancer, also favor atherosclerotic process by contributing to the artery-clogging process. Moreover, tar in tobacco, which contains dozens of chemicals that cause cancer, seems to make clots more likely to form in blood vessels (14). We have also observed that moderate total serum cholesterol levels at entry were significantly associated with cancer mortality, which is similar to what has been found about stroke deaths. Whether there are common pathophysiologic mechanisms about the association between serum cholesterol and stroke or cancer mortality cannot be answered by the present study, and the adverse health consequences of high total cholesterol in coronary heart disease should be taken into account. Finally, we have found that coronary heart disease mortality seems to increase with increased BMI, whereas cancer mortality seems to be reduced with increases in body mass. It seems that body mass interacts differently in atherosclerotic diseases and cancer; further studies are needed to confirm and explain these findings. A comparison of the predictors of cancer, coronary heart disease, and stroke mortality is presented in Table 3.

At this point, we have to emphasize that when different diseases share common risk factors, the possibility of competitive death is quite likely. Therefore, men who died due to coronary heart disease are no longer at risk of cancer (competing risks) and the evaluation of smoking, total cholesterol, BMI, physical activity, and other factors may be overestimated or underestimated.

Limitations. The classification of physical activity was based on self-reported occupation and usual activity. This might be a limitation of the study because misclassification is likely to occur with this crude way of ascertainment. However, from a methodologic point of view, this could be an accurate way to assess physical fitness in the long-term evaluation of these middle-aged men. Another limitation is that we have no data about risk factor modification over the 40 years of follow-up. Therefore, changes in physical activity status or BMI were not taken into account in our study. The importance of nutritional habits in cancer epidemiology has been emphasized by many investigators (30). Therefore, absence of dietary information from men enrolled in the study constitutes another limitation of the present analysis, especially with the suggestion that people in the middle tertile of cholesterol levels might have better dietary habits compared with the others. The lack of dietary

Table 3. Comparisons of the estimates predicting 40-year cancer, coronary heart disease (29), and stroke (30) mortality as a function of baseline risk factors levels

	Hazard ratio (95% CI) for cancer	Hazard ratio (95% CI) for CHD	Hazard ratio (95% CI) for stroke
Age at entry (per year)	1.05 (1.01-1.08)*	1.10 (1.06-1.14)*	1.11 (1.07-1.18)*
Smoking (yes vs no)	1.97 (1.24-3.14)*	1.79 (1.15-2.77)*	0.80 (0.49-1.29)
Total serum cholesterol (per 10 mg/dL)	0.95 (0.89-0.98)*	1.04 (0.94-1.16)	0.81 (0.73-0.90)*
BMI (per 1 kg/m^2)	0.93 (0.87-0.99)*	1.05 (1.00-1.10)*	0.62 (0.37-1.02)
Physical activity (yes vs no)	0.82 (0.37-1.22)	1.35 (0.89-2.07)	0.59 (0.32-0.92)*
Pulse pressure (per 5 mm Hg)	—	1.04 (0.95-1.11)	1.16 (1.05-1.28)*

Abbreviation: CHD, coronary heart disease.
*$P < 0.05$.

changes through the four decades of follow-up is another limitation, but, unpublished, self-reported information showed that the majority of these men continued having the similar habits as in the 1960s. Finally, the lack of any data about women, their subsequent anticancer medication, constitutes another limitation of this work.

Conclusions

In this long-term follow-up study, cancer was the second cause of death, after coronary heart disease. Age, moderate total serum cholesterol levels, low BMI, and smoking habits were the best predictors of cancer deaths, after controlling for several potential confounders. The ''paradox'' of the protective effect of total cholesterol levels on cancer risk does not represent an etiologic link, but may reflect the advance of the clinical course of cancer. Moreover, the inverse association between BMI and risk of cancer cannot be explained by the available data; however, it deserves further investigation from other prospective studies.

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