original article

Time-dependent association of total serum cholesterol and cancer incidence in a cohort of 172 210 men and women: a prospective 19-year follow-up study

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Background: The relationship between serum cholesterol and cancer incidence remains controversial.

Patients and methods: We investigated the association of total serum cholesterol (TSC) with subsequent cancer incidence in a population-based cohort of 172 210 Austrian adults prospectively followed up for a median of 13.0 years. Cox regression, allowing for time-dependent effects, was used to estimate adjusted hazard ratios (HRs) with 95% confidence intervals (95% CIs) for the association of TSC with cancer.

Results: We observed pronounced short-term associations of TSC and overall cancer incidence in both men and women. For malignancies diagnosed shortly (<5 months) after baseline TSC measurement, the highest TSC tertile (>235.0 mg/dl in men and >229.0 in women) compared with the lowest tertile (<194.0 mg/dl in men and <190.0 in women) was associated with a significantly lower overall cancer risk [HR = 0.58 (95% CI 0.43–0.78, P_{trend} = 0.0001) in men, HR = 0.69 (95% CI 0.49–0.99, P_{trend} = 0.03) in women]. However, after roughly 5 months from baseline measurement, overall cancer risk was not significantly associated with TSC. The short-term inverse association of TSC with cancer was mainly driven by malignancies of the digestive organs and lymphoid and hematopoietic tissue.

Conclusion: The short-term decrease of cancer risk seen for high levels of TSC may largely capture preclinical effects of cancer on TSC.

Key words: cancer incidence, prospective study, reverse causality, time dependency, total serum cholesterol

introduction

High levels of total serum cholesterol (TSC) are a well-established risk factor for coronary heart disease [1]. The impact of high TSC on cancer incidence is, however, less well understood. Several studies have reported that cancer incidence [2–10] and cancer mortality [7, 8, 11–18] were lower in men with higher baseline levels of TSC. While this inverse association was seen in the majority of previous studies, others found higher cancer risk for those with high TSC concentrations [19], no relation at all [20–28], or a U-shaped association, with both low as well as high TSC levels being significantly related to increased cancer risk [29]. In addition,

in women, most previous investigations failed to detect any association of TSC with cancer incidence [22, 23, 30, 31] and/or cancer mortality [22, 25].

Differences in the study populations, length of follow-up, study end points and statistical adjustment for confounding may all have contributed to the conflicting patterns of association seen in earlier studies; consistent evidence may also be lacking due to small sample sizes and infrequent events in several previous investigations. Moreover, it was speculated that rather than reflecting a true causal relationship, the lower cancer risk seen for high TSC levels may be attributable to an effect of preclinical cancer, i.e. the metabolic depression of TSC due to undiagnosed malignant lesions [6, 32]. This hypothesis has been supported by the observation that the inverse association between higher TSC levels and cancer risk attenuated or even disappeared with increasing time lags between TSC measurement and cancer diagnoses [11, 14, 15, 33, 34].

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However, the inverse association of high baseline TSC levels with cancer risk was also seen for up to 4 or even more years after baseline measurement in some investigations [6, 8, 17, 30, 35].

Motivated by the inconsistencies in the epidemiological literature, we investigated the association of TSC with overall and site-specific cancer incidence in a prospective, population-based cohort of 172 210 Austrian adults, aged 18–99 years with 9958 incident cancers during 19 years of follow-up. To our knowledge, this is the largest population-based study to date to prospectively explore the association of TSC with overall and site-specific cancer incidence in apparently healthy men and women across a wide age range.

patients and methods

study population

The Vorarlberg Health Monitoring and Promotion Program (VHM&PP) [36–39] is one of the world's largest ongoing population-based risk factor surveillance programs. The cohort was initiated in 1985 and is conducted by the Agency for Social and Preventive Medicine in Vorarlberg, the westernmost province of Austria. All adults in the region are invited to participate by a combination of different measures including written invitations and television, radio and newspaper reports. Active follow-up of study participants is carried out through a recall system of written biennial reinvitation letters. Sociodemographic data are recorded, and a voluntary physical examination is conducted regularly in a standardized manner by trained local physicians and internists. During the exam, a fasting blood sample is taken. Costs are covered by the participant's (compulsory) health insurance. A more detailed description of the program methodology has been reported elsewhere [36].

Between 1985 and 2003, a total of 174 852 Vorarlberg residents (aged >18 years) were enrolled in the VHM&PP. After excluding 2642 (1.5%) participants with either missing measurements on TSC at enrollment, malignant cancer before or at enrollment and/or baseline concentrations of TSC >500 mg/dl, the current analysis was based on 172 210 apparently healthy participants, free of cancer at baseline. All participants signed informed consent to have personal data stored and processed. For this study, institutional review board approval was obtained by the Ethics Committee of the province of Vorarlberg.

data collection

Measurements of height, weight, smoking status (current, former and never) and TSC are routinely obtained for each study participant. Individuals who reported smoking of at least one cigarette per day during the year before examination were classified as current smokers. Occupational status (blue collar, white collar or self-employed) was determined by the insurance number of participants and used as a surrogate measure of socioeconomic status. Participants who were retired at baseline were classified according to their former occupation, and housewives were classified according to their husband's job.

cancer ascertainment

Cancers were identified by the Vorarlberg Cancer Registry, which has been accepted for International Agency for Research on Cancer publication since 1993 and has high completeness of recording [40]. Nearly all cancers (96.7%) were histologically confirmed. Cohort data were linked with the Vorarlberg Death Index to identify deaths and to calculate person-years at risk. For analyses, cancers were grouped into the following subgroups according to the International Classification of Diseases, 9th and 10th

Revision (ICD-9, ICD-10) [41]: malignant neoplasms of digestive organs (ICD-9 150–157; ICD-10 C15–C25); respiratory system and intrathoracic organs (ICD-9 160–165; ICD-10 C30–C39); bone, connective tissue, soft tissue and skin (ICD-9 170–173; ICD-10 C40–C49); male genital organs (ICD-9 185–187; ICD-10 C60–C63); breast and female genital organs (ICD-9 174, 179–184; ICD-10 C50–C58); urinary organs (ICD-9 188–189; ICD-10 C64–C68); nervous system and unspecified sites (ICD-9 190–199; ICD-10 C69–C72) and lymphoid, hematopoietic and related tissue (ICD-9 200–208; ICD-10 C81–C96).

laboratory measurements

Two central laboratories undergoing regular internal and external quality procedures determined TSC concentrations on fasting blood samples. Within 60–240 min after venous blood sample collection from a cubital vein, serum was obtained by centrifugation for 15 min at 3309×g at 37° C. Subsequently, TSC concentrations were measured at 37° C and were given as milligrams per deciliter. In order to check calibration, three daily control samples were included. If average values of the control samples of each run were not within 3% of the true value, the run was repeated. Day-by-day variation had to be within 5%.

statistical analyses

Cox proportional hazard models (PROC PHREG, SAS version 9.1; SAS Institute, Cary, NC) were used to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for tertiles of the TSC distribution for men and women separately. The TSC categories were <194, 194–235, >235 mg/dl for men and <190, 190–229, >229 mg/dl for women. Age was used as the underlying time metric in all analyses [42]. Follow-up for a participant started at his/her age at enrollment into the cohort and ended at cancer diagnosis or censoring. Censoring events were death, end of study, loss to follow-up and emigration. Adjustment variables included body mass index (BMI, in quartiles with gender-specific cut-offs), year of entry into the cohort (in quartiles), smoking status (never/former/current) and occupational status (three categories) measured at baseline. The proportional hazards assumption was checked visually by plotting hazard curves for men and women for TSC categorized into tertiles using gender-specific cut-off values and for all other adjustment variables (PROC LIFETEST, SAS version 9.1). The proportional hazards assumption was upheld for all covariates except for TSC in both men and women, with crossing hazards within ∼5 months of follow-up. To accommodate the nonproportional effect of TSC in our regression models an interaction term between time of follow-up and TSC was included in each model, allowing for time-varying effects of TSC [43]. To test for differences between the HRs associated with TSC categories at different follow-up periods, we used a three-degrees of freedom Wald test. A test for log-linear trend was carried out across the TSC tertiles. We evaluated whether the TSC–cancer relationship was modified by age or BMI in stratified analyses. In a sensitivity analysis, we repeated all analyses using calendar time as the time scale, additionally adjusting for participant's age, again allowing for different TSC effects before and after 5 months from baseline. We also repeated all analyses using cut-off values of 12 and 24 months instead of 5 months. Two-sided P values <0.05 were considered statistically significant.

results

baseline characteristics of the study population

Demographic and clinical characteristics of the study population are shown in Table 1. A total of 172 210 participants (79 417 men and 92 793 women), free from cancer at enrollment, were included in the analyses. Median follow-up

time was 13.0 years with a total of 2 004 174 person-years at risk. Most participants (92.8%) were followed up for at least 2 years after baseline TSC measurement and 63.8% had follow-up times of ≥10 years. Mean age at study entry was 41.6 years. During follow-up, a total of 9958 (5.8%) incident cancers were observed, with 5311 in men and 4647 in women. Numbers of cancer incidence according to anatomic sites are shown in Table 2. Median baseline TSC concentrations were 214.0 mg/dl (interquartile range = 62) in men and 209.0 mg/dl (interquartile range = 60) in women (Table 1).

association of TSC with cancer incidence

Plots of the hazard function for overall cancer incidence stratified by tertiles of TSC for men and women (Figure 1, panels A and B) revealed a pronounced time-dependent effect of TSC, with effects changing direction after ~5 months of follow-up. Adjusted HRs with 95% confidence intervals (95% CIs) for the time-dependent association of TSC with overall and site-specific cancer incidence are shown in Table 3 for men and Table 4 for women. Compared with the lowest TSC tertiles, the highest TSC tertiles (>235.0 mg/dl in men and >229.0 mg/dl in women) were associated with a statistically significantly lower overall cancer risk for the first 5 months of follow-up with a HR = 0.58 (95% CI 0.43–0.78, P_{trend} < 0.0001) in men and a HR = 0.69 (95% CI 0.49–0.99, P_{trend} = 0.03) in women. After roughly 5 months from baseline measurement, however,

TSC was not statistically significantly associated with overall cancer risk with a HR = 0.96 (95% CI 0.89–1.03, P_{trend} = 0.23) in men and a HR = 0.93 (95% CI 0.85–1.01; P_{trend} = 0.07) in women (P for heterogeneity of effects between time periods <0.0001).

Analyses of site-specific cancers revealed that for both men and women the short-term inverse association of high TSC levels on overall cancer risk was mainly due to cancers of the digestive organs and lymphoid and hematopoietic tissue (Tables 3 and 4), for which the risk-lowering effects of high baseline TSC lasted past 5 months, albeit less strong, and in men also due to cancers of the respiratory system and intrathoracic organs (Table 3). For cancers of the digestive organs, the HR for the highest TSC tertile compared with the lowest TSC tertile was HR = 0.42 (95% CI 0.24–0.72, P_{trend} = 0.02) in men and HR = 0.37 (95% CI 0.19–0.70, P_{trend} = 0.001) in women within the first 5 months of follow-up, and HR = 0.76 (95% CI 0.65–0.89, P_{trend} = 0.001) in men and HR = 0.87 (95% CI 0.71–1.06, P_{trend} = 0.25) in women after 5 months. The TSC effects before and after 5 months were statistically significantly different for both men and women ($P_{heterogeneity}$ < 0.0001). The corresponding HRs for neoplasms of lymphoid, hematopoietic and related tissue were HR = 0.09 (95% CI 0.01–0.75, P_{trend} = 0.005) in men and HR = 0.08 (95% CI 0.02–0.39, P_{trend} = 0.001) in women for the highest compared with the lowest TSC tertile within the first

Table 1. Characteristics of study population at baseline, VHM&PP, 1985–2003

	Total	Men	Women
All VHM&PP participants 1985–2003, no.	174 852	80 224	94 628
Eligible participants for analyses, no.[a]	172 210	79 417	92 793
Age at entry, mean ± SD (range), y	41.6 ± 15.3 (18–96)	41.7 ± 14.6 (18–96)	41.6 ± 15.9 (18–95)
Body mass index, mean ± SD (median), kg/m^2	24.7 ± 4.2 (24.2)	25.3 ± 3.6 (24.9)	24.2 ± 4.6 (23.3)
Total serum cholesterol, mean ± SD (median), mg/dl	215.4 ± 46.7 (211.0)	217.4 ± 47.2 (214.0)	213.7 ± 46.3 (209.0)
Cigarette smoking, %	25.5	30.1	21.5
Follow-up, mean ± SD (median), y	11.6 ± 5.6 (13.0)	11.3 ± 5.6 (12.5)	12.0 ± 5.6 (13.5)
Total person-years at risk	2 004 174	894 645	1 109 529
Incident cancers, no. (%)	9958 (5.8)	5311 (6.7)	4647 (5.0)
Age at cancer diagnosis, mean ± SD (range), y	56.6 ± 12.9 (19–93)	57.1 ± 12.2 (19–93)	55.4 ± 13.8 (19–93)

[a]Participants with (i) missing measurements on total serum cholesterol at enrollment, (ii) malignant cancer before or at enrollment and/or (iii) baseline concentrations of total serum cholesterol >500 mg/dl were excluded.
SD, standard deviation; VHM&PP, Vorarlberg Health Monitoring and Promotion Program.

Table 2. Incidence of site-specific malignancies in 79 417 men and 92 793 women in the Vorarlberg Health Monitoring and Promotion Program, 1985–2003

	Men	Women
Malignant neoplasms of digestive organs (ICD-9 150–157; ICD-10 C15–C25)	1244	1078
Malignant neoplasms of respiratory system and intrathoracic organs (ICD-9 160–165; ICD-10 C30–C39)	879	226
Malignant neoplasms of bone, connective tissue, soft tissue and skin (ICD-9 170–173; ICD-10 C40–C49)	448	423
Malignant neoplasms of male genital organs (ICD-9 185–187; ICD-10 C60–C63)	1860	–
Malignant neoplasms of breast and female genital organs (ICD-9 174, 179–184; ICD-10 C50—C58)	–	2276
Malignant neoplasms of urinary organs (ICD-9 188–189; ICD-10 C64–C68)	447	219
Malignant neoplasms of lymphoid, hematopoietic and related tissues (ICD-9 200–208; ICD-10 C81–C96)	319	325

ICD, International Classification of Diseases, 9th and 10th Revision. –, not applicable.
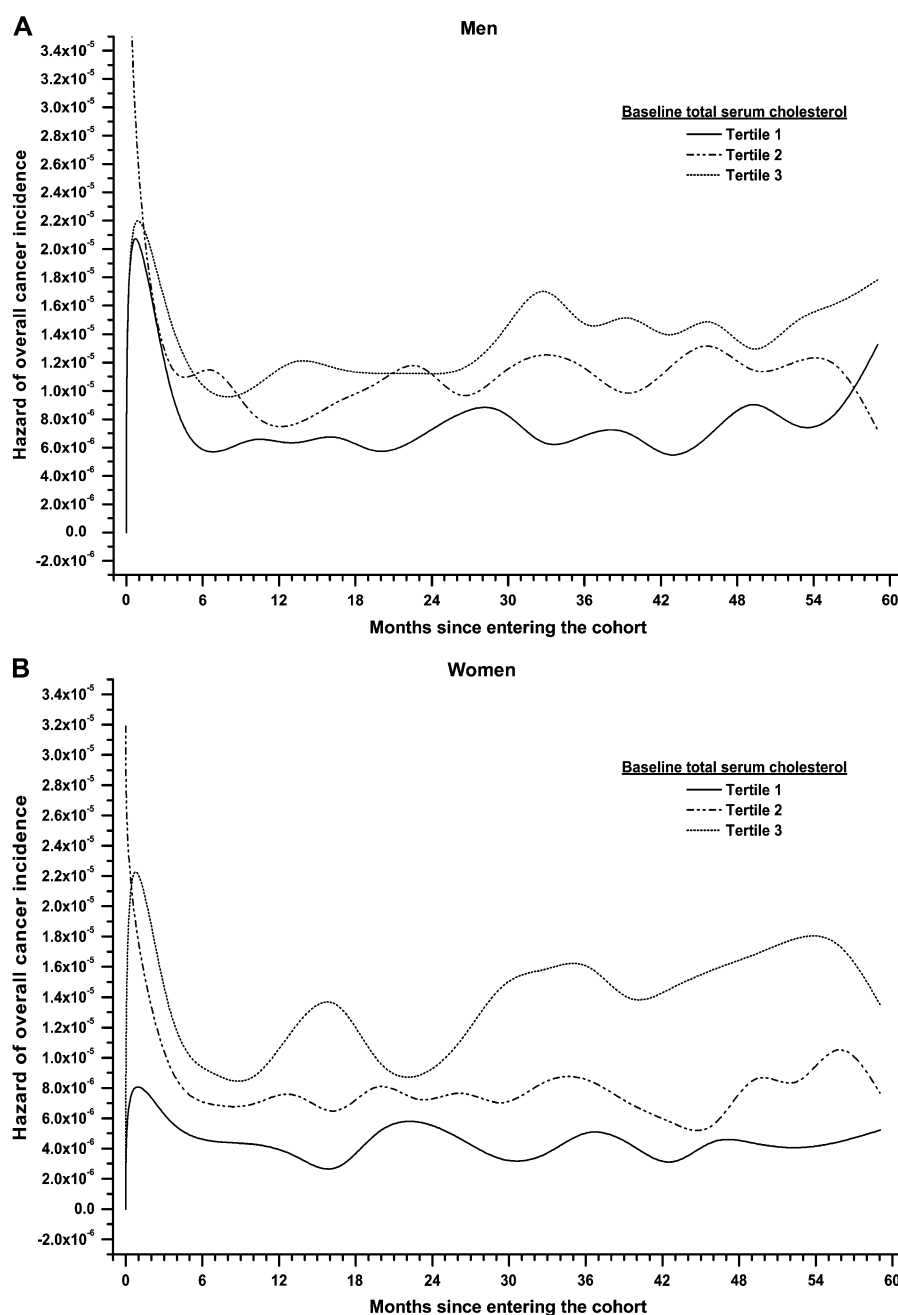
A

Men

B

Women

Figure 1. Panels A and B. Hazard function plot for overall cancer incidence by tertiles of total serum cholesterol (TSC) in 79 417 men (Panel A) and 92 793 women (Panel B) in the Vorarlberg Health Monitoring and Promotion Program, 1985–2003.

5 months of follow-up, and after 5 months HR = 0.69 (95% CI 0.51–0.93, P_{trend} = 0.71) in men and HR = 0.88 (95% CI 0.62–1.27, P_{trend} = 0.12) in women. Again, the estimates for the two time periods were statistically significantly different ($P_{heterogeneity}$ < 0.0001) for both men and women. For men, we further found a short-term protective effect of high TSC on risk of respiratory cancers, with a HR = 0.36 (95% CI 0.17–0.78, P_{trend} = 0.002) for the highest versus lowest TSC tertile within the first 5 months of follow-up and a significant reversal in the direction of this association afterward (Table 3). We found no association of baseline TSC neither for cancers of the bone, connective tissue, soft tissue and skin as well as urinary organs

in both men and women nor for breast cancer or cancers of the female or male genital organs. Results were very similar when we repeated all analyses using calendar time as the time scale and when data were stratified by the BMI categories <20, 20–30, >30 kg/m^2 (data not shown).

sensitivity analyses

When we used a cut-off value of 12 instead of 5 months, the inverse short-term association of TSC with overall cancer incidence remained statistically significant in both men and women. Compared with the lowest TSC tertiles, the HRs for the

Table 3. Estimated adjusted hazard ratios with 95% confidence intervals from Cox regression models with time-dependent effects for total and site-specific cancer incidence according to tertiles of baseline TSC and period of follow-up in 79 417 men, Vorarlberg Health Monitoring and Promotion Program, 1985–2003[a]

	No. of incident cancers	Tertiles of total serum cholesterol (mg/dl)			P for trend across TSC tertiles	P for heterogeneity of effects between time periods
		<194.0	194.0–235.0	>235.0		
Follow-up ≤5 months						
Total cancer incidence	271	1.00 (Ref)	0.77 (0.57–1.04)	0.58 (0.43–0.78)	<0.0001	–
Malignant neoplasms of digestive organs	81	1.00 (Ref)	0.54 (0.32–0.92)	0.42 (0.24–0.72)	0.002	–
Malignant neoplasms of respiratory system and intrathoracic organs	41	1.00 (Ref)	0.58 (0.28–1.18)	0.36 (0.17–0.78)	0.002	–
Malignant neoplasms of bone, connective tissue, soft tissue and skin	13	1.00 (Ref)	0.84 (0.22–3.13)	0.60 (0.15–2.42)	0.45	–
Malignant neoplasms of male genital organs	86	1.00 (Ref)	1.15 (0.63–2.10)	1.12 (0.62–2.00)	0.88	–
Malignant neoplasms of urinary organs	31	1.00 (Ref)	1.16 (0.47–2.84)	0.54 (0.20–1.45)	0.52	–
Malignant neoplasms of lymphoid, hematopoietic and related tissue	15	1.00 (Ref)	0.72 (0.24–2.16)	0.09 (0.01–0.75)	0.005	–
Follow-up >5 months						
Total cancer incidence	5040	1.00 (Ref)	0.96 (0.89–1.04)	0.96 (0.89–1.03)	0.23	<0.0001
Malignant neoplasms of digestive organs	1163	1.00 (Ref)	0.85 (0.73–1.56)	0.76 (0.65–0.89)	0.001	<0.0001
Malignant neoplasms of respiratory system and intrathoracic organs	838	1.00 (Ref)	1.05 (0.86–1.29)	1.30 (1.07–1.57)	0.004	<0.0001
Malignant neoplasms of bone, connective tissue, soft tissue and skin	435	1.00 (Ref)	1.19 (0.91–1.56)	1.12 (0.86–1.47)	0.81	0.07
Malignant neoplasms of male genital organs	1774	1.00 (Ref)	1.01 (0.88–1.16)	1.00 (0.88–1.14)	0.25	<0.0001
Malignant neoplasms of urinary organs	416	1.00 (Ref)	1.07 (0.80–1.44)	1.18 (0.89–1.56)	0.02	<0.0001
Malignant neoplasms of lymphoid, hematopoietic and related tissue	304	1.00 (Ref)	0.82 (0.61–1.10)	0.69 (0.51–0.93)	0.71	<0.0001

[a]Estimated from Cox regression models with time-dependent effects and adjustment for body mass index, smoking status (current, former and never), occupational status (blue collar, white collar and self-employed) and year of entry into the cohort. Age was used as the underlying time metric for all analyses. TSC, total serum cholesterol. –, not applicable.

highest TSC tertiles were 0.56 (95% CI 0.44–0.72) and 0.62 (95% CI 0.47–0.82), in men and women, respectively. For follow-up periods >12 months, TSC was not statistically significantly associated with overall cancer risk, with HR = 0.97 (95% CI 0.90–1.05] in men and 0.95 (95% CI 0.86–1.04) in women; P for heterogeneity of effects between time periods, both <0.0001. Similar results were obtained when we used a cut-off value of 24 months. The inverse short-term associations of TSC with malignancies of digestive organs, the respiratory system and lymphoid, hematopoietic and related tissue, however, were somewhat attenuated in both men and women, but remained statistically significant. Notably, for men, the inverse association of TSC with malignancies of the digestive organs was seen also for follow-up periods >24 months [HR for the highest versus lowest TSC tertile 0.80 (95% CI 0.68–0.94)], while we found no association of TSC with overall and/or other site-specific cancer incidence after 24 months of follow-up in men nor in women.

discussion

The present study, including 172 210 Austrian adults, to our knowledge, is the largest investigation, to prospectively assess the association between baseline TSC levels and subsequent cancer risk in a population-based cohort of healthy men and women across a wide age range. We found that in both men and women overall cancer risk was significantly decreased for those in the highest TSC tertile for malignancies diagnosed shortly after baseline TSC measurement, while after some time (e.g. 5, 12 or 24 months) overall cancer risk was not significantly associated with TSC.

Previous reports of high TSC levels lowering cancer risk raised concerns that an increase in cancer rates might outweigh benefits of decreasing cardiovascular disease risk by cholesterol-lowering drugs [44]. The associations seen in our study, however, support the hypothesis that the cancer risk-lowering effect of high TSC may largely be due to mechanisms of reverse causality, i.e. be caused by cancers in preclinical stages [14, 15, 32–34], e.g. through protean physiological effects, which include the metabolic depression of blood cholesterol [6]. Additionally, leukemic blood and bone marrow cells were shown to have an elevated low-density lipoprotein (LDL) receptor activity that inversely correlated with plasma cholesterol levels [45]. Further evidence that low levels of TSC are the effect rather than the cause of cancer comes from several clinical trials that correlated low cholesterol levels with disease

Table 4. Estimated adjusted hazard ratios with 95% confidence intervals from Cox regression models with time-dependent effects for total and site-specific cancer incidence according to tertiles of baseline TSC and period of follow-up in 92 793 women, Vorarlberg Health Monitoring and Promotion Program, 1985–2003[a]

	No. of incident cancers	Tertiles of total serum cholesterol (mg/dl)			P for trend across TSC tertiles	P for heterogeneity of effects between time periods
		<190.0	190.0–229.0	>229.0		
Follow-up ≤5 months						
Total cancer incidence	236	1.00 (Ref)	0.88 (0.60–1.28)	0.69 (0.49–0.99)	0.03	–
Malignant neoplasms of digestive organs	63	1.00 (Ref)	0.63 (0.32–1.24)	0.37 (0.19–0.70)	0.001	–
Malignant neoplasms of respiratory system and intrathoracic organs[b]	5	1.00 (Ref)	–	–	–	–
Malignant neoplasms of bone, connective tissue, soft tissue and skin	13	1.00 (Ref)	1.63 (0.43–6.16)	0.25 (0.04–1.52)	0.08	–
Malignant neoplasms of breast and female genital organs	134	1.00 (Ref)	1.17 (0.67–2.03)	1.09 (0.65–1.84)	0.88	–
Malignant neoplasms of urinary organs	9	1.00 (Ref)	0.37 (0.02–5.91)	1.15 (0.14–9.38)	0.52	–
Malignant neoplasms of lymphoid, hematopoietic and related tissue	11	1.00 (Ref)	0.24 (0.06–0.96)	0.08 (0.02–0.39)	0.001	–
Follow-up >5 months						
Total cancer incidence	4411	1.00 (Ref)	0.97 (0.89–1.07)	0.93 (0.85–1.01)	0.07	<0.0001
Malignant neoplasms of digestive organs	1015	1.00 (Ref)	0.88 (0.67–1.19)	0.87 (0.71–1.06)	0.25	<0.0001
Malignant neoplasms of respiratory system and intrathoracic organs[b]	221	1.00 (Ref)	–	–	–	–
Malignant neoplasms of bone, connective tissue, soft tissue and skin	410	1.00 (Ref)	0.89 (0.67–1.19)	0.86 (0.65–1.16)	0.36	0.0005
Malignant neoplasms of breast and female genital organs	2142	1.00 (Ref)	0.97 (0.86–1.10)	0.94 (0.83–1.07)	0.32	<0.0001
Malignant neoplasms of urinary organs	210	1.00 (Ref)	1.14 (0.71–1.86)	1.13 (0.71–1.80)	0.69	0.05
Malignant neoplasms of lymphoid, hematopoietic and related tissue	314	1.00 (Ref)	1.28 (0.89–1.83)	0.88 (0.62–1.27)	0.12	<0.0001

[a]Estimated from Cox regression models with time-dependent effects and adjustment for body mass index, smoking status (current, former and never), occupational status (blue collar, white collar and self-employed) and year of entry into the cohort. Age was used as the underlying time metric for all analyses.
[b]Insufficient events for analyses.
TSC, total serum cholesterol. –, not applicable.

activity and showed that TSC concentrations increased after therapy that reduced tumor mass [32]. Still another explanation for the inverse cancer–cholesterol relationship in the literature subsumes subjects with high TSC to be more likely to be censored due to cardiovascular deaths before developing cancer, which might result in an inverse association of high TSC with cancer risk [6, 10]. While in our cohort high baseline TSC levels increased risk of death from coronary heart disease in men of all ages and in women under the age of 50, low TSC levels were significantly associated with all-cause mortality, showing significant associations with death from cancer, liver diseases, and mental diseases in men across the entire age range and in women aged 50 or older [46].

Previous epidemiological investigations of cancer incidence and/or cancer mortality have produced inconsistent results on the effects of TSC. Similar to our findings, Knekt et al. [34] reported the association between TSC and risk of cancer incidence in a Finish cohort of 39 268 men and women, to strongly vary from negative to slightly positive according to anatomic sites of cancer. The strongest inverse associations

were seen during the first years of follow-up, especially for rapidly developing cancers. Similarly, in the largest study of cancer mortality, Sherwin et al. [15] found a significant excess of cancer death in >360 000 men from the United States in the lowest decile of TSC during the early years of follow-up, which attenuated over time. In another large-scale investigation that combined data from 11 studies from eight countries [14], men who died from cancer within 1 year of cholesterol measurement had lower mean cholesterol levels than the rest of the study population; however, this inverse association markedly diminished with time. Finally, Rose and Shipley [33] found the inverse association between plasma cholesterol and non-coronary heart disease deaths to be confided to the first 2 years of follow-up; beyond this time, total mortality and cholesterol levels were positively correlated. Törnberg et al. [19] reported a consistently positive association between TSC and incidence of rectal cancer in a cohort of Swedish men. On the other hand, Schatzkin et al. [35] found lower cancer risk for high baseline TSC levels among 5125 men in the National Health and Nutrition Examination Survey even for malignancies diagnosed

≥5 years after baseline TSC measurement. Similar long-term protective effects of high TSC levels were seen in the Framingham study [30].

Our study had several strengths and some potential limitations. Major strengths are the prospective design, the large sample size, length of follow-up and the standardized protocol carried out by experienced physicians. Limitations are that we were unable to analyze lipid subfractions including LDL cholesterol and high-density lipoprotein cholesterol and to account for some risk factors including alcohol consumption, physical activity and diet that might have residually confounded the relationship between TSC and cancer incidence. We were also not able to examine the effect of cholesterol-lowering drugs on the TSC–cancer relationship. However, in 75% of the VHM&PP study participants, serum for TSC measurement was drawn before 1995, the year of the implementation of statin therapy in Austria. Additionally, recent clinical trials have shown no differences in rates of cancer incidence between subjects undergoing statin treatment and those with no such treatment [47], indicating a minor role of cholesterol-lowering drugs on our risk estimates. Finally, the choice of a cut-off at 5 months of follow-up, used in the main analyses to accommodate the nonproportional, time-dependent effect of TSC on cancer incidence, was data driven and therefore may not apply in a more general fashion.

In summary, the present 19-year follow-up study prospectively investigated the association of TSC with overall and site-specific cancer incidence in a population-based cohort of >172 000 Austrian adults, free of cancer at baseline. Our results indicate a strong time-dependent association of TSC with overall cancer incidence and several site-specific malignancies in both men and women, with a significant risk excess in the lowest TSC tertile for malignancies diagnosed shortly after baseline TSC measurement. While further research is needed to shed light on the underlying pathophysiological mechanisms, the pattern of association seen in the present study supports the hypothesis that the inverse association of high TSC levels with cancer risk may largely be attributable to reverse causation due to preclinical malignancies.

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