Research Article

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Total Serum Cholesterol and Pancreatic Cancer: A Nested Case–Control Study

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Abstract

Background: Pancreatic cancer is the third leading cause of cancer-related death in the United States. Total serum cholesterol (TSC) may predict cancer risk, although its role independent of statins remains elusive. We examined the association between TSC and pancreatic cancer risk independent of statins.

Methods: A nested case–control analysis was conducted among statin-naïve patients within The Health Improvement Network (THIN), a United Kingdom–based general practice database. Cases were >40 years old and diagnosed with pancreatic cancer after at least 6 months of follow-up. Controls were selected by incidence density sampling and matched by age, sex, practice site, and follow-up. Primary exposure was TSC (mmol/L) prior to index date. Conditional logistic regression estimated ORs for pancreatic cancer risk associated with TSC. Sensitivity analyses were conducted among nondiabetics.

Results: Among 1,241 cases and 3,307 matched controls, an average 8% reduction was observed in pancreatic cancer risk per mmol/L increase in TSC [OR 0.92, 95% confidence interval (CI): 0.85–1.00; nondiabetics: OR 0.91, 95% CI: 0.83–0.99]. When TSC was measured at 12-month intervals prior to diagnosis, the OR between TSC and pancreatic cancer was 0.88 at 0 to 12 months (95% CI: 0.77–1.00; nondiabetics: OR 0.81, 95% CI: 0.68–0.96). No significant association was seen at subsequent discrete intervals before index date.

Conclusions: TSC is a significant predictor of short-term risk for pancreatic cancer. This risk increase associated with lower TSC was independent of statins.

Impact: TSC could serve as a biomarker for risk stratification, screening, and early diagnosis of pancreatic cancer in future clinical prediction models.

Introduction

Pancreatic ductal adenocarcinoma is one of the most prevalent and lethal cancers, with an estimated 55,440 new diagnoses of and 44,330 deaths due to pancreatic cancer expected to occur in the United States in 2018 (1). Current projections make it the second leading cause of cancer-related death in the United States by 2030, overtaking breast, prostate, and colorectal cancers (2). Its advanced stage at diagnosis, limited response to existing therapies, and resistance to early detection, confer a particularly poor prognosis. Patients with stage I or II disease undergoing the only potentially curative treatment, surgical resection, face a median survival of 24 to 25 months status postsurgery, even with adjuvant or neoadjuvant chemotherapy (3). Currently, no effective screening method exists to detect premalignant or early-stage tumors (4). There remains a significant need to improve understanding of risk factors and biomarkers to facilitate early detection.

Previous studies have suggested that total serum cholesterol (TSC) could be a predictor of cancer risk. Multiple epidemiologic observations since the 1980s have shown an inverse association between TSC and overall or site-specific cancer incidence and mortality (5–13), including a meta-analysis of 33 prospective studies predating the marketing of statins (14). Our group recently discovered that TSC was inversely related in a dose–response fashion to short-term colorectal cancer risk regardless of statin use, implying that cholesterol-lowering in a reverse causality fashion may be a marker of occult colorectal cancer (15).

Examining TSC levels as a predictor of pancreatic cancer could enable its timely diagnosis and treatment. Two small studies suggested a negative association between TSC and pancreatic cancer (16, 17). Meanwhile, several population-based investigations found no correlation between TSC and pancreatic cancer (18–20). However, no study has accounted for the potential influence of statins, which are widely prescribed, cholesterol-lowering drugs indicated for cardiovascular disease prevention (21) with pleotropic and potentially chemopreventive properties (22–32), in defining the association between TSC and pancreatic cancer risk.

Given the paucity and inconsistency of existing literature on the role of TSC in pancreatic cancer, and the need to exclude the effect of statins, we conducted a nested case–control study within a robust UK general practice–based database to explore the associations of TSC levels and change in TSC with pancreatic cancer risk, independent of statin therapy.

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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Materials and Methods

Data source

Data were extracted from The Health Improvement Network (THIN), a general practice electronic medical records database from the United Kingdom (https://www.iqvia.com/en/locations/uk-and-ireland/thin). THIN comprises deidentified electronic records of over 12 million patients enrolled in over 550 general practices in the United Kingdom. Available THIN data encompasses demographic information, medical diagnoses, prescriptions, lifestyle habits, biometric measurements, and laboratory testing. Medical diagnoses are recorded as Read codes, the standard diagnosis classification system in the United Kingdom (33). THIN data are routinely monitored, analyzed, and audited for quality assurance (34). Average follow-up time per patient is over 5 years. The database was demonstrated to be high quality and generalizable to the UK population (35). Rates of cancer incidence in THIN, including pancreatic cancer, were comparable with those reported in cancer registries in the United Kingdom (36).

Study design and population

A nested case–control study within THIN was conducted to investigate the associations of pancreatic cancer risk with TSC, time of TSC measurement, and change in TSC. Eligible study population consisted of those who had registered with a THIN practice between 1995 and 2013. Follow-up began either when the practice started transferring the electronic medical record to THIN or when the patient registered with their general practitioner, whichever date came later, and finished on the index date (described below). We excluded patients with any prescription history of statins, to isolate the effect of TSC on pancreatic cancer.

Cases

Cases were selected to be patients with $\geq$1 diagnostic code(s) for pancreatic cancer during follow-up, and who were at least 40 years old at the time of pancreatic cancer diagnosis. In a recent study, the positive predictive value of Read codes for pancreatic cancer in THIN was 97% based on manual chart review (37). Diagnostic codes for pancreatic cancer were not specific for histologic subtype, and encompassed exocrine and endocrine tumors. However, given the overwhelming majority (~85%) of pancreatic cancers are ductal adenocarcinomas (3), the dominant exocrine tumor, and only 6% of pancreatic cancers are pancreatic neuroendocrine tumors, which are typically diagnosed younger and carry better prognosis (1), the minor misclassification bias was deemed to be acceptable.

Patients diagnosed with pancreatic cancer within the first 6 months of THIN follow-up were excluded as these may represent prevalent pancreatic cancers (38). The index date for cases was the date of pancreatic cancer diagnosis.

Controls

Controls were selected using incidence density sampling (39). Specifically, for each case, up to four controls who were alive and pancreatic cancer–free at the time of the case's diagnosis were randomly selected after matching by age (within 5 years), sex, practice location, calendar period (within 6 months), and length of follow-up (within 6 months). The matched controls were assigned the same index date as their corresponding case. The OR estimate from a case–control study with incidence density sampling are interpretable as unbiased estimates of incidence rate ratios (40).

Exposures

The primary exposure was TSC (mmol/L), using the last available TSC level prior to index date. As secondary exposures, we also examined TSC levels measured at different time points (0–12, 12–24, 24–36, and >36 months) prior to index date, as well as changes in TSC levels.

Statistical analyses

We used conditional logistic regression models to estimate adjusted ORs and 95% confidence intervals (CI) for pancreatic cancer risk associated with TSC levels. TSC was modeled first as a continuous variable, then as a categorical variable (i.e., <4, 4–5, 5–6, 6–7, and >7 mmol/L, corresponding to 154, 154–193, 193–232, 232–270, and >270 mg/dL). When treated as a categorical variable, the reference group for TSC level was <4 mmol/L, consistent with UK guidelines for target TSC levels (41). Each model adjusted *a priori* for variables known to contribute to pancreatic cancer risk, including obesity [body mass index (BMI) $\geq$ 30 kg/m^2], smoking status (ever vs. never), alcohol consumption (ever vs. never), diabetes mellitus, and aspirin use (ever vs. never). Personal history of chronic pancreatitis and family history of pancreatic cancer were not reliably reported in THIN and thus, not included. All covariates were measured before the index date.

To determine whether the association between TSC and pancreatic cancer risk is affected by time of measurement, we calculated adjusted ORs and 95% CIs for pancreatic cancer risk associated with TSC levels measured during different time intervals (0–12, 12–24, 24–36, and >36 months) before index date. Because recent evidence has suggested a potential association between diabetes mellitus medications and the risk of pancreatic cancer (42), we conducted a sensitivity analysis restricted among a nondiabetic subpopulation.

We also performed an exploratory analysis to examine the association between change in TSC and pancreatic cancer risk. We calculated the adjusted ORs for pancreatic cancer risk associated with per-unit (mmol/L) decrease in TSC (modeled as a continuous variable) and for <1 unit and >1 unit decreases in TSC (modeled as a categorical variable). These analyses were conducted among subjects with $\geq$2 TSC measurements, separated by $\geq$1 year, and with the last measurement occurring $\geq$1 year or <1 year before the index date. Subjects with no change or increases in TSC between the measurements comprised the reference group for the categorical analysis. The conditional logistic regression models in these analyses were adjusted for the aforementioned and following additional confounders: weight loss during follow-up and first available TSC measurement recorded during follow-up.

All statistical analyses were performed using STATA version 13.1 (StataCorp). All statistical tests were two-sided. The study was approved by the University of Pennsylvania's Institutional Review Board and the United Kingdom's Scientific Review Committee.

Results

The study included 1,241 subjects with pancreatic cancer and 3,307 matched controls with acceptable cholesterol data. A comparison of the baseline characteristics between cases and controls is shown in Supplementary Table S1. Mean duration from onset of

Table 1. Characteristics of pancreatic cancer cases and control subjects

	Cases ($n = 1,241$)	Controls ($n = 3,307$)
Age at index date, mean, y (IQR)	70.5 (62.3–79.3)	69.6 (61.0–78.7)
Male sex, *N* (%)	596 (48.0)	1,300 (43.2)
Duration of follow-up, mean, y (IQR)[a]	7.2 (4.0–10.2)	7.3 (4.1–10.2)
Cigarette smoking history, *N* (%)		
Ever-smoker	644 (51.9)	1,378 (45.8)
Diabetes mellitus, *N* (%)	234 (18.9)	227 (7.6)
Obesity (BMI $\geq$ 30 kg/m^2), *N* (%)	278 (22.4)	668 (22.2)
Alcohol use, *N* (%)[b]	742 (59.8)	1,787 (59.4)
Aspirin use, *N* (%)[b]	309 (24.0)	636 (21.2)
TSC level, mean, mmol/L/mg/dL (IQR)[c]	5.4/208 (4.6–6.0/178–232)	5.6/216 (4.9–6.2/189–239)

Abbreviation: y, years.
[a]Before index date.
[b]Any use.
[c]Last available TSC level prior to index date.

follow-up to the index date was 7.2 years in cases and 7.3 years in controls. Case subjects were more likely than controls to be older, male, and have a history of smoking, diabetes, obesity, alcohol use, and aspirin use. Mean TSC level prior to index date was 5.4 mmol/L or 208 mg/dL [interquartile range (IQR): 4.6–6.0 mmol/L or 178–232 mg/dL] in cases, and 5.6 mmol/L or 216 mg/dL (IQR: 4.9–6.2 mmol/L or 189–239 mg/dL) in controls.

Among all subjects, there was a statistically significant decreased risk of pancreatic cancer with increasing TSC (OR 0.92, 95% CI: 0.85–1.00; Supplementary Table S1). A comparable inverse association between TSC and pancreatic cancer was seen in the nondiabetic sensitivity analysis (Supplementary Table S2).

To further elucidate the association between TSC and pancreatic cancer risk, the risk of pancreatic cancer was calculated at multiple time intervals of TSC measurement preceding cancer diagnosis (Supplementary Table S2A). The link between elevated TSC and decreased pancreatic cancer risk became stronger when absolute TSC levels were measured closer to cancer diagnosis (0–12 months: OR 0.88, 95% CI: 0.77–1.00). In contrast, no significant association was seen at subsequent, discrete 12-month time intervals prior to diagnosis (12–24 months: OR 0.99, 95% CI: 0.82–1.18; 24–36 months: OR 1.10, 95% CI 0.86–1.41; >36 months: OR 1.03, 95% CI: 0.89–1.18). A similar temporal trend was observed in the nondiabetic sensitivity analysis, with a significant OR observed only at 0 to 12 months before diagnosis (OR 0.81, 95% CI: 0.68–0.96; Supplementary Table S2B).

Additional exploratory analyses examined whether decreasing TSC was associated with an increased risk of pancreatic cancer, including only subjects with $\geq$2 TSC measurements separated by $\geq$1 year, the last of which occurred $\geq$1 year or <1 year before cancer diagnosis (Supplementary Table S3). Adjusting for baseline TSC level and weight loss during follow-up, in addition to the *a priori* variables, pancreatic cancer risk increased almost 2-fold per mmol/L decrease in TSC (OR 1.94; 95% CI: 0.86–4.39), when the last TSC was measured $\geq$1 year prior, compared with an OR of 1.14 (95% CI: 0.83–1.58), when the last TSC was measured <1 year prior to index date. Compared with the subjects with no change or increase in TSC, the adjusted OR for those with a >1 mmol/L decrease was 5.02 (95% CI: 0.76–33.25) versus 2.41 (95% CI: 0.90–6.46), when the last TSC was measured $\geq$1 year versus <1 year prior to diagnosis, respectively.

Discussion

In this large nested case–control analysis, we observed an inverse association between TSC levels and pancreatic cancer risk. Specifically, a lower risk of pancreatic cancer was observed with higher TSC (above our reference range of 4 mmol/L or 154 mg/dL). Our continuous analysis indicated an average 8% decrease in pancreatic cancer risk per unit increase in TSC. However, this association was likely limited to mildly elevated TSC levels (4–6 mmol/L or 154–232 mg/dL), as per our categorical analysis, which did not display a clear trend at higher TSC levels of >6 mmol/L. A similar inverse association was observed when the analysis was restricted among nondiabetics. Furthermore, the inverse relationship between absolute TSC and pancreatic cancer risk was present only within the 12 months before index date, whereas change in TSC, especially a >1 mmol/L (or 38.6 mg/dL) decrease, may have an effect >1 year prior to diagnosis.

The inverse association between TSC prior to index date and pancreatic cancer risk is unlikely due to chance in light of the dose–response relationship (8% decreased risk per mmol/L increase in TSC). Direct causation seems biologically implausible, as only one study has demonstrated improved host antitumor immunity in subjects with hyperlipidemia compared with hypolipidemia (43). Instead, similar to our group's findings in colorectal cancer (15), this inverse association is likely attributable to "preclinical" pancreatic cancer, with carcinogenesis-promoting metabolic depression of serum cholesterol (17, 44). According to this proposed reverse causality hypothesis (17, 45, 46), cholesterol lowering presumably reflects cancer cells' reliance on enhanced cholesterol and lipid metabolism to construct new membranes and facilitate signaling (44). In addition to recent Mendelian randomization studies (47, 48), reverse causation is supported by our finding that the inverse association disappeared as time interval between absolute TSC measurement and cancer diagnosis broadened from <12 months (OR 0.88; 95% CI: 0.77–1.00) to >12 months (nonsignificant ORs $\sim$1.0–1.1 for 12–24, 24–36, and >36 months).

This remains consistent with preceding studies, most of which examined overall or nonpancreatic sites of cancer, where the negative relationship between TSC and cancer risk or mortality was attenuated with increasing time prior to diagnosis (15), or upon excluding the first few years of study follow-up (2, 5, 13, 45, 46, 49). Some studies, though, have reported inverse associations persisting despite lag times of $\geq$4 years between baseline TSC and cancer diagnosis (11, 16, 17, 50), implying some direct effect of cholesterol on cancer cannot be entirely excluded. Only two previous groups, separated by 25 years, have demonstrated a negative association specifically between TSC and pancreatic

Table 2A. ORs for association between pancreatic cancer risk associated with TSC levels measured at different time intervals before pancreatic cancer diagnosis

	Adjusted OR[b] (95% CI) by time period											
	0–12 months ($n = 736$)			12–24 months ($n = 499$)			24–36 months ($n = 366$)			>36 months ($n = 571$)		
TSC[a]	Cases	Controls	OR (95% CI)[b]	Cases	Controls	OR (95% CI)[b]	Cases	Controls	OR (95% CI)[b]	Cases	Controls	OR (95% CI)[b]
<4 mmol/L	87	91	Reference	38	70	Reference	22	41	Reference	32	69	Reference
4–5 mmol/L	217	358	0.61 (0.34–1.09)	145	283	1.54 (0.67–3.58)	109	224	1.96 (0.71–5.38)	147	325	1.00 (0.54–1.86)
5–6 mmol/L	252	561	0.43 (0.24–0.77)	185	463	1.41 (0.60–3.33)	135	359	1.78 (0.63–5.05)	220	581	0.85 (0.46–1.59)
6–7 mmol/L	119	357	0.38 (0.20–0.71)	95	270	1.48 (0.60–3.63)	84	212	1.91 (0.65–5.58)	133	359	0.92 (0.48–1.74)
>7 mmol/L	61	132	0.55 (0.27–1.13)	36	111	1.37 (0.48–3.89)	16	84	2.01 (0.50–8.17)	39	117	0.98 (0.46–2.12)
Continuous[c]	736	1499	0.88 (0.77–1.00)	499	1,197	0.99 (0.82–1.18)	366	920	1.10 (0.86–1.41)	571	1,451	1.03 (0.89–1.18)

[a]Last TSC value measured in each specified time period prior to the index date of pancreatic cancer diagnosis.
[b]Adjusted for obesity (BMI $\geq$ 30 kg/m^2), ever smoking, alcohol consumption, diabetes mellitus, and aspirin use.
[c]Per 1 unit (mmol/L) increase in TSC. 1 mmol/L = 38.6 mg/dL.

Table 2B. ORs for association between pancreatic cancer risk and TSC levels measured at different time intervals before pancreatic cancer diagnosis, among nondiabetics

	Adjusted OR[b] (95% CI) by time period											
	0 to 12 months ($n = 534$)			12 to 24 months ($n = 374$)			24 to 36 months ($n = 278$)			>36 months ($n = 481$)		
TSA[a]	Cases	Controls	OR (95% CI)[b]	Cases	Controls	OR (95% CI)[b]	Cases	Controls	OR (95% CI)[b]	Cases	Controls	OR (95% CI)[b]
<4 mmol/L	39	56	Reference	17	40	Reference	11	24	Reference	20	49	Reference
4–5 mmol/L	149	241	0.42 (0.18–0.99)	96	202	1.64 (0.45–5.97)	73	159	2.51 (0.55–11.42)	111	251	0.99 (0.46–2.11)
5–6 mmol/L	194	449	0.28 (0.12–0.65)	147	370	1.94 (0.54–6.96)	107	288	2.37 (0.50–11.35)	195	488	0.79 (0.37–1.70)
6–7 mmol/L	105	297	0.25 (0.10–0.58)	82	228	2.12 (0.57–7.98)	75	174	3.01 (0.61–14.88)	119	308	0.90 (0.41–1.97)
>7 mmol/L	47	112	0.32 (0.12–0.85)	32	94	1.53 (0.36–6.45)	12	72	3.01 (0.44–20.64)	36	105	0.79 (0.32–1.95)
Continuous[c]	534	1,155	0.81 (0.68–0.96)	374	934	1.05 (0.85–1.29)	278	717	1.18 (0.87–1.61)	481	1,201	1.02 (0.87–1.19)

[a]Last TSC value measured in each specified time period prior to the index date of pancreatic cancer diagnosis.
[b]Adjusted for obesity (BMI $\geq$ 30 kg/m^2), ever smoking, alcohol consumption, and aspirin use.
[c]Per 1 unit (mmol/L) increase in TSC. 1 mmol/L = 38.6 mg/dL.

Table 3. ORs for pancreatic cancer risk by change in TSC

Last TSC measurement >1 year prior to diagnosis						
Model	**Cases[a]**	**Controls[a]**	**OR (95% CI) for no change or increase[b]**	**OR (95% CI) for <1 mmol/L decrease**	**OR (95% CI) for >1 mmol/L decrease**	**OR (95% CI) per 1 mmol/L decrease**
Adjusted[c]	62	83	1.000	1.36 (0.59–3.15)	3.04 (0.97–9.58)	1.54 (0.92–2.59)
Most fully adjusted[d]	40	48	1.000	0.98 (0.28–3.42)	5.34 (0.81–35.04)	1.94 (0.86–4.39)
Last TSC measurement <1 year prior to diagnosis						
Model	**Cases[e]**	**Controls[e]**	**OR (95% CI) for no change or increase[b]**	**OR (95% CI) for <1 mmol/L decrease**	**OR (95% CI) for >1 mmol/L decrease**	**OR (95% CI) per 1 mmol/L decrease**
Adjusted[c]	177	210	1.000	1.16 (0.72–1.87)	1.73 (0.92–3.26)	1.10 (0.88–1.37)
Most fully adjusted[d]	113	126	1.000	1.27 (0.68–2.38)	2.41 (0.90–6.46)	1.14 (0.83–1.58)

[a]Limited to cases and controls with at least two total cholesterol measurements, separated by at least 1 year, with the last measurement occurring at least 1 year before the index date of pancreatic cancer diagnosis.

[b]Reference group includes subjects with no change or increase in TSC between the first and last total cholesterol measurement recorded.

[c]Adjusted for age, sex, duration of follow-up, calendar period, obesity (BMI $\geq$ 30 kg/m^2), ever smoking, alcohol consumption, diabetes mellitus, and aspirin use.

[d]Adjusted for variables in adjusted model, as well as weight loss during follow-up and first available TSC measurement during follow-up.

[e]Limited to cases and controls with at least two total cholesterol measurements, separated by at least 1 year, with the last measurement occurring within 1 year of the index date of pancreatic cancer diagnosis.

cancer risk (16, 17). The largest such study, 844 incident cases across seven European cohorts in the Metabolic Syndrome and Cancer Project, reported decreased pancreatic cancer risk among men between the highest and lowest TSC quintile (HR 0.52; 95% CI: 0.33–0.81; ref. 16). Interestingly, three other population-based studies in the last decade, including the United Kingdom, Korea, and Asia-Pacific regions, failed to uncover any association (18–20).

To our knowledge, our study is the first to have stratified by time interval between TSC measurement and pancreatic cancer diagnosis to detect reverse causality, whereas prior studies differed fundamentally by deliberately incorporating longer follow-up since TSC measurement to determine etiology, not reverse causation. Notably, we are the first group to define this primary relationship divorced from statins. Statins are a class of lipid-lowering drugs indicated for cardiovascular disease prevention (21). Currently used by a quarter of adults in the United States and United Kingdom, statins could be prescribed to millions more adults under revised guidelines for cholesterol management (41, 51). The pleiotropy of statins, including antiinflammatory (22, 23), antiangiogenic (24, 25), proapoptotic (26–28), and growth-suppressive properties (29), has stimulated substantial interest in their chemopreventive and therapeutic potential. Recent studies of statins and pancreatic cancer have yielded conflicting data, with some suggesting a modest protective effect in general U.S. clinic patients (30), male U.S. veterans (31), and U.K. male smokers (32). By restricting our cohort to statin-naïve patients, we effectively controlled for the possibilities that statin use could arise as both a byproduct of and alter the trajectory of TSC levels, as well as exert an independent effect on pancreatic cancer risk. In addition, we also adjusted for potential confounding by aspirin use, which is often comorbid with statin use for cardiovascular risk prophylaxis, and itself may be inversely associated with pancreatic cancer risk (52, 53).

Importantly, our study factored in the complex association between diabetes mellitus and pancreatic cancer (42, 54, 55) through a restriction analysis among nondiabetics, which yielded similar results as the primary analysis. This internal validity is especially critical given recent discoveries of paraneoplastic diabetes mellitus mediated by adrenomedullin (56), metformin-associated risk reductions (57, 58), and a 30% increased risk persisting >20 years after diabetes mellitus diagnosis suggesting a causal role (42). Furthermore, the accuracy of our outcome of interest has been previously validated in the THIN database with a 97% positive predictive value of diagnostic codes for pancreatic cancer (37), minimizing the risk of misclassification bias.

Our study had several potential limitations. To exclude the complex effect of statin therapy on our primary association of interest, we restricted our analysis to statin-naïve patients. Nevertheless, our cohort of statin nonusers represented the full spectrum of TSC levels (Supplementary Table S1). We were unable to perform a meaningful sensitivity analysis in the diabetic subpopulation given the small number of diabetic subjects (18.9% of cases, 7.6% of controls). Our sample size also limited our ability to perform higher resolution analyses of the relationship between timing of TSC measurement and pancreatic cancer risk. Ideally, we could have identified a more precise duration cutoff (e.g. 6-month intervals) within which absolute TSC is negatively associated with pancreatic cancer risk. Further studies with larger sample sizes will be needed to better delineate the time window within which absolute TSC predicts pancreatic cancer risk. Because of the extent of patient-level data available in the THIN database, we were unable to account for confounding by personal history of chronic pancreatitis or family history of pancreatic cancer, both established risk factors for pancreatic cancer (3, 4), nor dietary patterns, which could alter TSC levels and possibly pancreatic cancer risk (59, 60).

Our primary analyses focused on an individual's absolute TSC, rather than change in TSC over time. Our exploratory analyses of TSC change suggested a decline in TSC was more strongly associated with pancreatic risk when detected $\geq$1 year versus <1 year prior to diagnosis (OR 1.94 vs. 1.14 per mmol/L TSC decrease), but were limited by very small sample sizes. At first glance, this finding seems discordant with our earlier assertion that an inverse, reverse-causal association was only detected with absolute TSC measurements <1 year prior to diagnosis. However, these two analyses capture different factors, as change in TSC accounts for baseline TSC values, unlike the snapshot of absolute TSC. It is thus conceivable that an effect could be seen $\geq$1 year prior for the former, and not the latter variable. One assumes *a priori* that change in TSC serves as a more direct and powerful predictor of occult disease than absolute TSC, because a cancer-induced

change in TSC is the true signal in question. Given the challenge of obtaining multiple TSC measurements prior to cancer diagnosis, an individual's absolute TSC level still serves as a useful predictor of clinical interest, and a reasonable proxy for change in TSC. Nonetheless, further studies with larger sample sizes and serial TSC measurements will be needed to elucidate the effect of timing of TSC decline on pancreatic cancer risk.

Pancreatic cancer remains an extremely lethal disease with incidence mirroring mortality, and 5-year survival dipping to 6% in the United States (4, 61). There is a pressing clinical need to develop a paradigm for screening and early diagnosis in average- and high-risk individuals. The only routinely used serum tumor marker, carbohydrate antigen (CA) 19-9, has shown utility in prognosticating and surveilling patients with known disease, but lacks sufficient sensitivity and specificity for screening purposes (3, 62). TSC and its components are routinely surveilled in the primary care setting under revised U.S. and UK guidelines for lipid management in cardiovascular disease prevention (41, 51). Our study suggests that TSC could serve as a clinically useful biomarker given its low cost, ease of testing, routine use, widespread availability, and feasibility of incorporating into future screening, risk stratification, and decision-making tools. Interestingly, our group recently published a clinical prediction model of pancreatic cancer risk, which included TSC as a key variable, among adults with new-onset diabetes mellitus (63). Our findings here suggest that TSC could determine risk in a broader population, beyond just diabetes mellitus–associated pancreatic cancer. Moreover, our exploratory analysis showed a nonsignificant 2-fold increased risk per unit decrease in TSC $\geq$1 year prior to index date, implying that TSC trend could facilitate timely detection of pancreatic cancer. Further studies would be needed to establish the clinical significance of 1 to 12 months' earlier diagnosis given pancreatic cancer's highly aggressive course, with over 90% of diagnosed patients dying of the cancer (3).

Conclusion

In summary, TSC is a significant predictor of short-term risk for pancreatic cancer. This risk increase associated with lower TSC was independent of statin use, a crucial novel discovery given statins' potential chemoprotective role in pancreatic cancer. Our study lends insight into the natural history of pancreatic cancer, offering a biomarker that could be combined with other clinical and genetic information for risk stratification and screening efforts.

Disclosure of Potential Conflicts of Interest

R. Mamtani is a consultant/ advisory board member for Roche. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: W.C.-Y. Chen, B. Boursi, R. Mamtani, Y.-X. Yang
Development of methodology: W.C.-Y. Chen, B. Boursi, Y.-X. Yang
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): W.C.-Y. Chen, B. Boursi, Y.-X. Yang
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): W.C.-Y. Chen, B. Boursi, Y.-X. Yang
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): W.C.-Y. Chen, B. Boursi, Y.-X. Yang
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