Original Article

Prostate Cancer Risk in the Swedish AMORIS Study

The Interplay Among Triglycerides, Total Cholesterol, and Glucose

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BACKGROUND: In a cohort including 5112 prostate cancer (pCa) patients, the authors investigated associations among triglycerides (TG), total cholesterol (TC), and pCa while taking into account glucose. **METHODS:** A cohort (n = 200,660) based on 4 groups of men, according to age at cohort entry, with TG, TC, and glucose measurements was selected from the Apolipoprotein MOrtality RISk (AMORIS) database. Of these, 5112 men developed pCa. Multivariate Cox proportional hazard models were used to analyze associations among TG, TC, and pCa. Competing risks were assessed graphically. **RESULTS:** Age-stratified analyses for quartiles of TG, TC, and glucose showed a negative association between glucose and pCa risk (HR, 0.93; 95% CI, 0.86-1.01), 0.93 (0.86-1.01), 0.87 (0.81-0.94) for the second, third, and fourth quartiles compared with the first (P_{trend} = .001). Stratified analysis by glucose levels (<6.11 or ≥6.11 mmol/L) showed a positive association between hypertriglyceridemia (TG≥1.71 mmol/L) and pCa risk, when there were high glucose levels (HR, 1.23; 95% CI, 1.01-1.48). No association was found for hypercholesterolemia (TC≥6.50 mmol/L). Competing risk analysis showed that protective effects of glucose were overestimated in conventional Cox proportional hazard models and strengthened positive findings between TG and pCa risk. **CONCLUSIONS:** The authors' findings supported the hypothesis that factors of the glucose and lipid metabolism influence pCa risk. Competing risk assessment showed that it is important to take into account the long natural history and age distribution of pCa when interpreting results. The authors' findings indicate another reason to fight the increasing prevalence of obesity and dyslipidemia. ***Cancer*** **2011;117:2086–95.** © *2010 American Cancer Society.*

KEYWORDS: prostate cancer, total cholesterol, triglycerides, glucose, hypercholesterolemia, hypertriglyceridemia.

During the last decade, some studies investigated whether the metabolic syndrome is associated with prostate cancer (pCa) risk.[1,2] Long-term immigrants approach the pCa risk of white men of the country they migrate to,[3] suggesting that changes in lifestyle affect pCa risk. Because the prevalence of pCa and metabolic-related symptoms are growing worldwide, it is important to investigate possible associations among hypertriglyceridemia, hypercholesterolemia, and the risk of developing pCa.

The metabolic syndrome is related to an increased risk of cardiovascular disease and includes, depending on the definition used, at least 3 of the following symptoms: central obesity, raised triglycerides or specific treatment for this lipid abnormality, reduced HDL cholesterol or specific treatment for this lipid abnormality, raised blood pressure or treatment of previously diagnosed hypertension, or raised fasting plasma glucose.[4] Hsing et al indicated in a meta-analysis that men with metabolic syndrome are 1.54 times more likely to develop pCa.[5] However, inconsistent use of the metabolic syndrome definition in different studies can lead to contradicting evidence for a link between the metabolic syndrome and pCa. Therefore, it is interesting to look at different components of the metabolic syndrome: this study focuses on hypertriglyceridemia, hypercholesterolemia, and hyperglycemia in relation to pCa risk.

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Obesity is also linked to lipid changes and may be linked to pCa. In the meta-analysis by Hsing et al, body mass index (BMI) was positively associated with pCa mortality but not with pCa incidence (pooled RRs, 1.25 and 1.03, respectively).[5] It has also been postulated that obesity is associated with reduced risk of low-grade pCa but with increased risk of high-grade pCa,[5,6] also supported by a retrospective analysis of 2303 patients treated with radical prostatectomy in which obese men had higher-grade and larger tumors compared with men with a normal BMI.[7]

From epidemiological studies, diabetes is thought to decrease pCa risk, but underlying mechanisms remain unclear.[8] US Surveillance, Epidemiology, and End Results (SEER) data have shown that after adjustment for confounding variables, self-reported diabetes is not significantly associated with pCa risk (OR, 0.98). Another large study, based on the NIH-AARP Diet and Health study, found that history of diabetes is associated with decreased risk of pCa (RR, 0.71).[9]

Apart from the growing evidence for associations between glucose and pCa, several lines of evidence have led to an augmented interest for the role of TG and TC as possible predictors of pCa risk. Animal studies have shown decreased growth of human prostate LNCaP tumors (androgen-sensitive human prostate adenocarcinoma cells) in nude mice fed a low-fat diet.[10] Furthermore, androgens are believed to stimulate prostate tumor growth via activation of the sterol regulatory element binding protein (SREBP) pathway, which regulates lipogenic gene expression, resulting in accumulation of neutral lipids (triglycerides and cholesteryl esters) and, consequently, tumor growth.[11] Enhanced lipogenesis is thought to play a key role in cancer progression and is, therefore, a promising novel target for antineoplastic intervention.[11] Finally, effects of statin use (cholesterol and triglyceride-lowering drugs) have been studied extensively, but evidence for an association with pCa risk remains inconclusive.[12]

To date, the largest study investigating total cholesterol (TC) levels and pCa risk, a nested case-control study with 698 pCa cases, found a negative association for high-grade and advanced pCa (ORs, 0.61 and 0.42, respectively), whereas a hospital-based retrospective case-control study with 312 cases found a positive association for overall pCa (OR, 1.64).[13,14] Both findings were adjusted for age, family history of pCa, body size, diabetes, smoking, and several dietary components. A prospective cohort study including 1484 pCa cases found a lower incidence of overall pCa with higher levels of TG (HR, 0.94, 0.87, and 0.67, for the second, third, and fourth quartiles compared with the first quartile).[15] Findings were adjusted for body size, gamma-glutamyltransferase, glucose, TC, smoking, and occupational status.

We studied the associations between TG, TC, glucose and pCa risk in detail in the Swedish Apolipoprotein MOrtality RISk (AMORIS) database, which provided measurements for TG, TC, and glucose in a large cohort of men in which 5112 developed pCa.

MATERIALS AND METHODS

Study population and data collection

The AMORIS database recruited 351,487 men and 338,101 women between 1985 and 1996, mainly from the greater Stockholm area, with age ranging from <20 years to >80 years. They were either healthy individuals referred for clinical laboratory testing as part of health checkups, or they were outpatients referred for laboratory testing. All laboratory analyses were performed at the CALAB laboratory, Stockholm.[16,17] No individuals were inpatients at the time their blood samples were analyzed. None were excluded from the database for any possible manifestation of disease or because of treatment. More than 60% were known to be fasting at the time of blood sampling. A more detailed description of the AMORIS study is given elsewhere.[17-20] The AMORIS database was linked to the Swedish National Cancer Register as well as the Cause of Death Register and the consecutive Swedish Censuses during 1970-1990 by using the Swedish 10-digit personal identity number.[21] Socioeconomic characteristics were obtained from the censuses including socioeconomic status (SES). SES is based on occupational groups and classifies gainfully employed subjects into manual workers and nonmanual employees, below denoted as blue-collar and white-collar workers.[22] The National Cause of Death Register records all deaths in Sweden with date and underlying and contributing causes of death since 1953.[21] The Swedish National Cancer Register was founded in 1958 and covers the entire Swedish population. According to Swedish law, every case of primary cancer must be notified to the cancer registry by the responsible clinician and also by the pathologist/cytologist.[23,24] The present study complied with the Declaration of Helsinki, and the ethics review board of the Karolinska Institute approved the study.

For all men included in the present study (n = 200,660), there was information on TG, TC, and glucose available from the same health examination, taken within

Table 1. Descriptive Statistics of the Study Population by PCa Status

	PCa = 5112	No PCa = 195,548
	No. (%)	No. (%)
Age group		
Age group 45	498 (9.74)	90,154 (46.10)
Age group 55	1463 (28.62)	57,995 (29.66)
Age group 65	2619 (51.23)	40,381 (20.65)
Age group 75	532 (10.41)	7018 (3.59)
Socioeconomic status		
White collar	2871 (56.16)	101,805 (52.06)
Blue collar	1814 (35.49)	79,191 (40.50)
Not gainfully employed or missing	427 (8.36)	14,552 (7.45)
Fasting status		
Fasting	115,211 (58.92)	3200 (62.60)
Nonfasting	30,081 (15.38)	346 (6.77)
Missing	50,256 (25.70)	1566 (30.63)
Year of PCa diagnosis		
1985-1991	245 (4.79)	
1991-1997	1364 (26.68)	
>1997	3503 (68.53)	
Time until study entry, y		
Mean (SD)	3.01 (2.54)	3.80 (2.81)
Follow-up time, y		
Mean (SD)	6.96 (4.03)	8.27 (4.29)
Glucose, mmol/L		
Mean (SD)	5.18 (1.27)	5.21 (1.40)
<6.11	4667 (91.29)	178,559 (91.31)
≥6.11	445 (8.71)	16,989 (8.69)
Triglycerides, mmol/L		
Mean (SD)	1.51 (0.96)	1.58 (1.14)
<1.71	3635 (71.11)	136,019 (69.56)
≥1.71	1477 (28.89)	59,529 (30.44)
Total cholesterol, mmol/L		
Mean (SD)	5.93 (1.02)	5.83 (1.07)
<6.50	3674 (71.87)	144,388 (73.84)
≥6.50	1438 (28.13)	51,160 (26.16)

10 years before cohort entry. Because the risk of pCa is strongly age-dependent, we used a cohort based on 4 groups of men allocated according to age at cohort entry (aged 45, 55, 65, and 75 years). All men were free from pCa at time of entry and none were diagnosed with pCa or died within 3 months after entry. Follow-up time was defined as the time from age at cohort entry (aged 45, 55, 65, or 75 years [as above]) until the date of pCa diagnosis, death, or study closing date (December 31, 2002).

The following information was retrieved from the AMORIS database, serum TG (mmol/L), serum TC (mmol/L), serum glucose (mmol/L), age, and fasting status. From the other registers, information was retrieved on socioeconomic status (SES), pCa diagnosis, death, and emigration.

Triglycerides and TC were measured enzymatically as described previously.[16,25] Glucose was measured enzymatically with a glucose-oxidase/peroxidase method. All methods were fully automated with automatic calibration and performed at 1 accredited laboratory.[16]

Data analyses

The associations between quartiles of TG, TC, glucose, and pCa risk were analyzed by using multivariate Cox proportional hazards models in an age-stratified analysis, which allowed for different baseline hazards in the different age groups. A test for trend was conducted by using assignment to quartiles as an ordinal scale. All analyses were repeated for each age cohort separately as well. Based on the statistically significant findings for quartiles of glucose, we then conducted a stratified analysis by levels of glucose (<6.11 or ≥ 6.11 mmol/L, according to the National Cholesterol Education Program [NCEP]). TG and TC were also dichotomized according to the NCEP guidelines (cutoffs, 1.71 and 6.50 mmol/L, respectively).[4] All models took into account glucose and/or TG and/or TC, SES, fasting status, and time between measurements and entry.

Because pCa has a long natural history and is a disease mainly in the elderly, competing risks are involved in the analysis of pCa risk. In general, a competing risk situation arises when an individual can experience not only the event of interest but can also be censored because of other events.[26] It is even more important to consider competing risk when, as in this study, metabolic factors such as hypertriglyceridemia and hypercholesterolemia may be linked to both pCa and early death due to, for instance, cardiovascular diseases.[27] Thus, death from circulatory disease and death from other causes are considered to be competing risks for pCa diagnosis. In a Cox proportional hazard model, as described above, 1 of the main assumptions is that censoring is not informative. We violate this assumption when we censor for death (and not having pCa) as the cause of death may be related to our exposure of interest for pCa risk, such as lipid levels. To find out how our findings in the Cox proportional hazard models are affected by this violation, we created graphs to illustrate the cumulative incidence of pCa, the cumulative incidence of death (due to circulatory disease [ICD-10: I00-I99] and due to other causes), 1 − probability of

pCa-free survival, and the conditional (ie, conditioned on the fact that a person was alive) probability of pCa diagnosis.[28] We considered the probability of reverse causation (ie, blood lipid levels can be affected by an undiagnosed pCa) by conducting a sensitivity analysis in which all men who had their measurements taken within 1.5 years before pCa diagnosis were excluded.[29] All analyses were conducted with Statistical Analysis Systems (SAS) release 9.1.3 (SAS Institute, Cary, NC) and R version 2.7.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 498 of 90,652 men developed pCa in the group aged 45 years, while 1463 of 59,458, 2619 of 43,000, and 532 of 7550 were diagnosed with pCa in the groups aged 55, 65 and 75 years, respectively. All participant characteristics are shown in Table 1. More than 90% of the population was gainfully employed; the measurements were taken as part of health examinations performed at company health checkups. A detailed overview of the metabolic factors (TG, TC, and glucose) by age group is given in Table 2.

Multivariate Cox proportional hazards model for the association between quartiles of TG, TC, and glucose, and pCa risk did not show a clear pattern for TG and TC (Table 3). For glucose, a statistically significant negative association was found (age-stratified HR, 0.93 (95% CI, 0.86-1.01); HR, 0.93 (95% CI, 0.86-1.01); HR, 0.87 (95% CI, 0.81-0.94) for the second, third, and fourth quartiles compared with the first quartile; $P_{trend} = .001$; Table 3).

Based on the findings for glucose in Table 3 and the current body of evidence for an association between glucose and pCa risk, we conducted a stratified analysis by levels of glucose (<6.11 or ≥6.11 mmol/L) in which TG and TC were also dichotomized (Table 4). We found a positive association between hypertriglyceridemia and pCa risk for men with high glucose levels (age-stratified HR, 1.23; 95% CI, 1.01-1.48). No association was found for hypercholesterolemia, but a combination of hypertriglyceridemia and hypercholesterolemia was associated with a statistically nonsignificant increased pCa risk for men with high glucose levels (age-stratified HR, 1.09; 95% CI, 0.91-1.32).

We further considered the long natural history and age distribution of pCa as well as competing risks. The

Table 2. Descriptive Statistics of the Metabolic Variables in Each Age Cohort

	PCa = 5112	No PCa = 195,548
	No. (%)	No. (%)
Age group 45		
Glucose, mmol/L		
Mean (SD)	4.97 (1.05)	5.03 (1.13)
<6.11	474 (95.18)	85,286 (94.60)
≥6.11	24 (4.82)	4868 (5.40)
Triglycerides, mmol/L		
Mean (SD)	1.46 (0.97)	1.55 (1.16)
<1.71	364 (73.09)	63,904 (70.88)
≥1.71	134 (26.91)	26,250 (29.12)
Total cholesterol, mmol/L		
Mean (SD)	5.68 (1.06)	4.97 (1.05)
<6.50	378 (75.90)	70,517 (78.22)
≥6.50	120 (24.10)	19,637 (21.78)
Age group 45		
Glucose, mmol/L		
Mean (SD)	5.12 (1.11)	5.27 (1.46)
<6.11	1364 (93.23)	52,343 (90.25)
≥6.11	99 (6.77)	5652 (9.75)
Triglycerides, mmol/L		
Mean (SD)	1.57 (1.02)	1.64 (1.17)
<1.71	1005 (68.69)	39,101 (67.42)
≥1.71	458 (31.31)	18,894 (32.58)
Total cholesterol, mmol/L		
Mean (SD)	5.94 (0.99)	5.95 (1.06)
<6.50	1052 (71.91)	40,873 (70.48)
≥6.50	411 (28.09)	17,122 (29.52)
Age group 65		
Glucose, mmol/L		
Mean (SD)	5.23 (1.29)	5.43 (1.69)
<6.11	2364 (90.26)	35,121 (86.97)
≥6.11	255 (9.74)	5260 (13.03)
Triglycerides, mmol/L		
Mean (SD)	1.50 (0.92)	1.58 (1.06)
<1.71	1881 (71.82)	28,041 (69.44)
≥1.71	738 (28.18)	12,340 (30.56)
Total cholesterol, mmol/L		
Mean (SD)	5.97 (1.03)	5.99 (1.05)
<6.50	1838 (70.18)	27,872 (69.02)
≥6.50	781 (29.82)	12,509 (30.98)
Age group 75		
Glucose, mmol/L		
Mean (SD)	5.33 (1.66)	5.61 (1.86)
<6.11	465 (87.41)	5809 (82.77)
≥6.11	67 (12.59)	1209 (17.23)
Triglycerides, mmol/L		
Mean (SD)	1.49 (0.93)	1.54 (1.03)
<1.71	385 (72.37)	4973 (70.86)
≥1.71	147 (27.63)	2045 (29.14)
Total cholesterol, mmol/L		
Mean (SD)	5.83 (0.99)	5.86 (1.06)
<6.50	406 (76.32)	5126 (73.04)
≥6.50	126 (23.68)	1892 (26.96)

Table 3. Hazard Ratios (HR) for Risk of PCa by Quartile

	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile	P_{trend}
	HR	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Triglycerides	<0.9 mmol/L	0.9-1.3 mmol/L	1.3-1.9 mmol/L	>1.9 mmol/L	
All age groups[a]	1.00 (Ref)	1.00 (0.93-1.08)	0.89 (0.83-0.97)	1.01 (0.93-1.10)	.542
Age group 45	1.00 (Ref)	1.03 (0.82-1.31)	0.75 (0.58-0.98)	0.91 (0.70-1.19)	.168
Age group 55	1.00 (Ref)	1.03 (0.89-1.20)	0.97 (0.83-1.13)	1.11 (0.95-1.30)	.294
Age group 65	1.00 (Ref)	0.99 (0.88-1.10)	0.89 (0.78-0.98)	0.96 (0.86-1.09)	.221
Age group 75	1.00 (Ref)	0.97 (0.77-1.23)	0.95 (0.74-1.22)	1.07 (0.82-1.39)	.687
Total cholesterol	<5.1 mmol/L	5.1-5.8 mmol/L	5.8-6.5 mmol/L	>6.5 mmol/L	
All age groups[a]	1.00 (Ref)	1.08 (0.99-1.17)	1.06 (0.98-1.15)	0.99 (0.91-1.08)	.583
Age group 45	1.00 (Ref)	1.19 (0.94-1.51)	0.99 (0.76-1.30)	1.12 (0.86-1.46)	.726
Age group 55	1.00 (Ref)	1.10 (0.94-1.28)	1.11 (0.95-1.30)	1.01 (0.87-1.19)	.992
Age group 65	1.00 (Ref)	1.03 (0.92-1.16)	1.03 (0.91-1.16)	0.98 (0.87-1.11)	.650
Age group 75	1.00 (Ref)	1.11 (0.87-1.43)	1.13 (0.88-1.45)	0.91 (0.70-1.18)	.448
Glucose	<4.6 mmol/L	4.6-5.0 mmol/L	5.0-5.5 mmol/L	>5.5 mmol/L	
All age groups[a]	1.00 (Ref)	0.93 (0.86-1.01)	0.93 (0.85-1.01)	0.87 (0.81-0.94)	.001
Age group 45	1.00 (Ref)	1.00 (0.79-1.25)	0.93 (0.72-1.19)	0.91 (0.69-1.18)	.390
Age group 55	1.00 (Ref)	0.93 (0.80-1.08)	0.93 (0.80-1.09)	0.93 (0.80-1.08)	.406
Age group 65	1.00 (Ref)	0.95 (0.85-1.07)	0.97 (0.87-1.09)	0.88 (0.79-0.98)	.034
Age group 75	1.00 (Ref)	0.76 (0.59-0.99)	0.73 (0.56-0.94)	0.68 (0.54-0.86)	.003

Hazard ratios (HR) for risk of PCa with 95% confidence intervals (CI) by triglyceride quartiles, total cholesterol quartiles, glucose quartiles, and age groups. All HRs are adjusted for fasting status, glucose (continuous) and/or triglycerides (continuous) and/or total cholesterol (continuous), SES, and time between measurement taken and cohort entry.
[a] Age group stratified analysis.

Table 4. Hazard Ratios (HR) for Risk of PCa by Level of Glucose

	Glucose <6.11 mmol/L	Glucose ≥6.11 mmol/L
	HR (95% CI)	HR (95% CI)
Hypertriglyceridemia, Triglycerides ≥1.71 mmol/L		
All age groups[a]	1.01 (0.94-1.08)	1.23 (1.01-1.48)
Age group 45	0.95 (0.76-1.18)	1.59 (0.66-3.82)
Age group 55	1.04 (0.92-1.18)	1.39 (0.91-2.11)
Age group 65	1.00 (0.91-1.10)	1.04 (0.81-1.34)
Age group 75	0.98 (0.78-1.22)	1.69 (1.03-2.76)
Hypercholesterolemia, Total Cholesterol ≥6.50 mmol/L		
All age groups[a]	1.05 (0.97-1.12)	0.96 (0.77-1.20)
Age group 45	0.99 (0.81-1.21)	1.58 (0.58-4.34)
Age group 55	1.13 (0.98-1.29)	0.86 (0.53-1.37)
Age group 65	1.02 (0.92-1.13)	0.98 (0.73-1.32)
Age group 75	1.03 (0.83-1.28)	0.96 (0.58-1.64)
Hypertriglyceridemia and Hypercholesterolemia, Triglycerides ≥1.71 mmol/L and Total Cholesterol ≥6.50 mmol/L		
All age groups[a]	1.00 (0.93-1.07)	1.09 (0.91-1.32)
Age group 45	0.89 (0.71-1.11)	1.76 (0.78-3.97)
Age group 55	1.02 (0.90-1.15)	1.09 (0.74-1.62)
Age group 65	1.03 (0.93-1.13)	1.01 (0.79-1.29)
Age group 75	0.91 (0.72-1.14)	1.32 (0.80-2.16)

Hazard ratios (HR) for risk of PCa with 95% confidence intervals (CI) by levels of glucose, adjusted for fasting status, triglycerides, or total cholesterol (continuous), SES, and time between measurement taken and cohort entry.
[a] Age group stratified analysis.

age distribution was accounted for by analyzing the association between TG or TC and pCa in different age groups. The competing-risk problem is especially important in the oldest age group.

Fig. 1 shows the results for the cohort aged 75 years. The unconditional probability for pCa diagnosis (light gray dashed line in Fig. 1) is lower for those with glucose ≥6.11 mmol/L compared with those with glucose <6.11

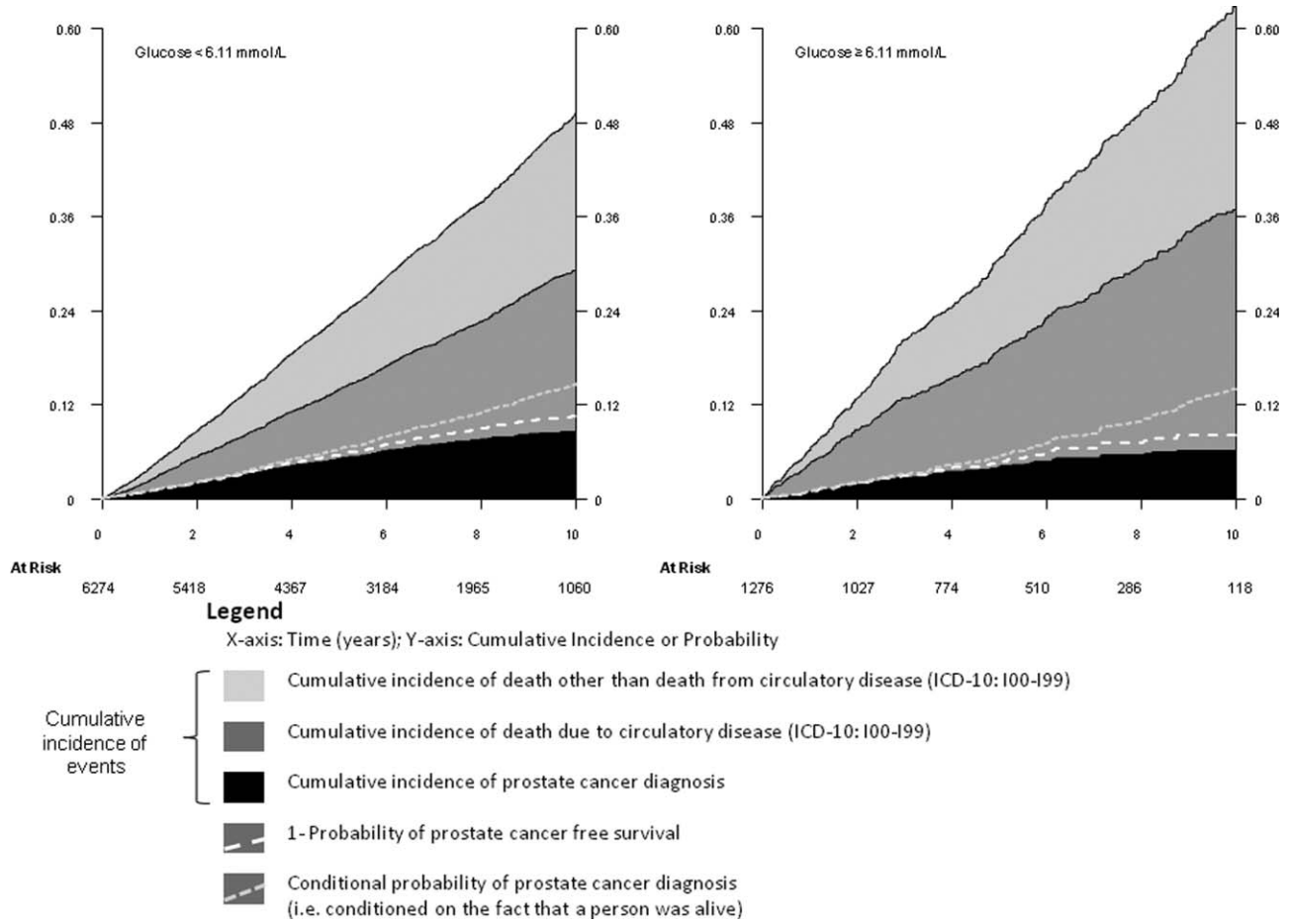

Figure 1. Competing risks in the age 75 cohort are shown for levels of glucose: cumulative incidence of death due to circulatory disease (dark gray area), cumulative incidence of death other than death from circulatory disease (light gray area), cumulative incidence of pCa (black area), 1−probability of pCa-free survival (white dashed line), and conditional probability (ie, conditioned on the fact that a person was alive) of pCa diagnosis (gray dotted line).

mmol/L, as previously shown in Table 2. However, when taking into account the competing risk of early death, the difference in conditional probabilities for pCa diagnosis (ie, conditioned on the fact that a person was alive; white dotted line in Fig. 1) between those with glucose ≥6.11 mmol/L and <6.11 mmol/L became much smaller (Fig. 1). In the 75-year-old age cohort, about 31.37% of all deaths (n = 2875) that occurred during follow-up were due to circulatory disease (dark gray for cumulative incidence in Fig. 1), 2.75% due to pCa, 12.38% due to other cancers, and 53.50% due to other diseases (death due to other causes than circulatory disease are shown in light gray for cumulative incidence in Fig. 1). No strong effects of competing risks were found for the associations among TG, TC, and pCa risk (results not shown).

To illustrate the effect of competing risk on the results by glucose levels in Table 4, the above competing risk analysis for the 75-year-old age cohort was repeated for different levels of TG. Figure 2 shows that, by taking into account competing risks, the association between hypertriglyceridemia and pCa risk for men with glucose ≥6.11 mmol/L may be even stronger (white dotted line vs light gray dashed line in Fig. 2) than the association found in Table 4.

Only 42 men had their measurements of TG, TC, and glucose taken within 1.5 years before their pCa diagnosis, resulting in no changes in the previous findings when excluding these men (results not shown).

DISCUSSION

In the AMORIS study, we found evidence for an association between metabolic factors, like TG, TC, and glucose, and pCa risk. When we assessed the possible competing risks, especially among the elderly, quartiles of glucose

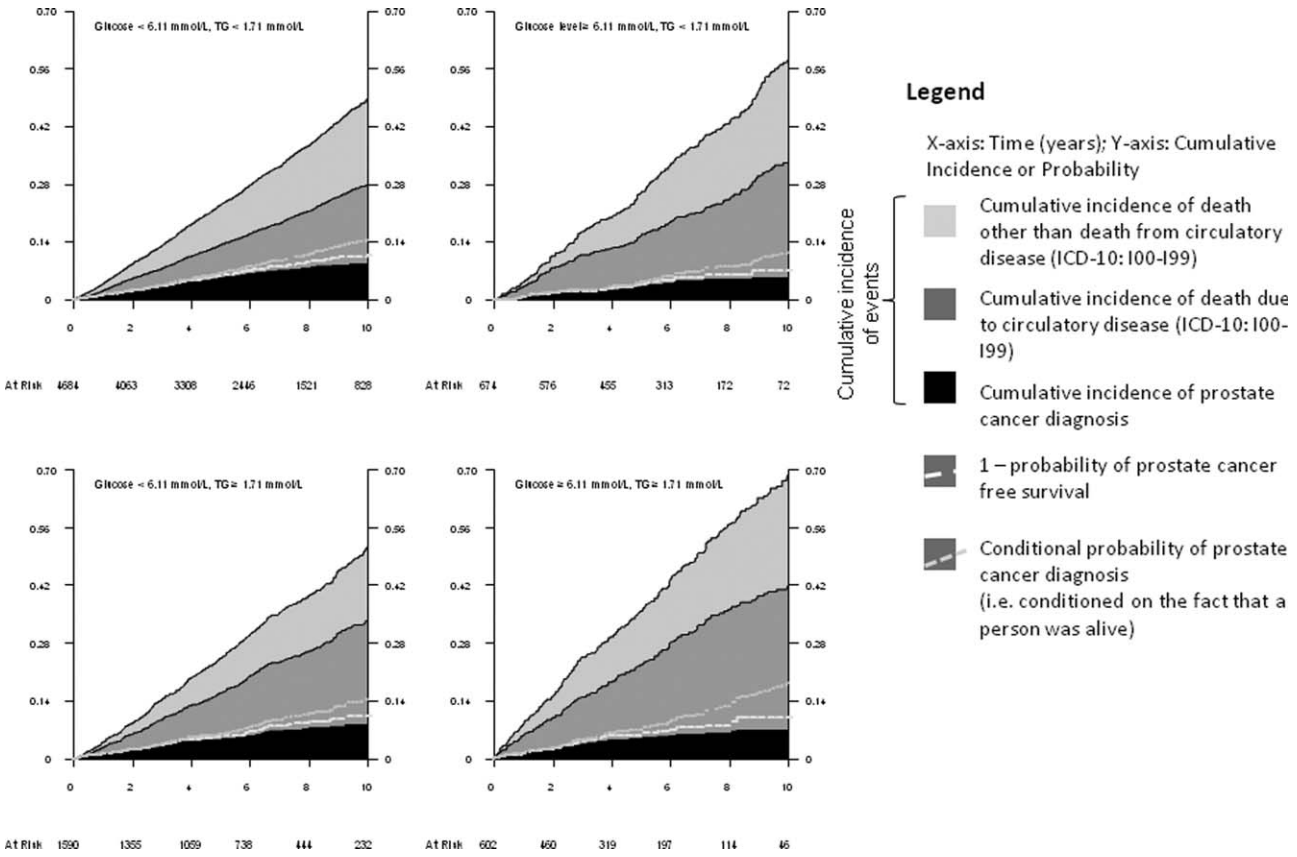

Figure 2. Competing risks in the age 75 cohort are shown for levels of glucose and TG: cumulative incidence of death due to circulatory disease (dark gray area), cumulative incidence of death other than death from circulatory disease (light gray area), cumulative incidence of pCa (black area), 1–probability of pCa-free survival (white dashed line), and conditional probability (ie, conditioned on the fact that a person was alive) of pCa diagnosis (gray dotted line).

were less strongly associated with pCa risk than in a Cox proportional hazards model. Also, the positive association between hypertriglyceridemia and risk of pCa for men with hyperglycemia became stronger when taking into account competing risks.

Based on epidemiological studies, it is thought that diabetes decreases the risk for pCa but underlying mechanisms and supporting evidence remain unclear or contradictory.[8] Moreover, some study findings suggest that pCa risk differs by time since diabetes diagnosis or occurrence of metabolic aberrations associated with impaired glucose tolerance.[30] In a prospective cohort study of 47,209 men, Darbinian et al showed that during the first 10 years of follow-up, risk was increased among those with serum glucose $\geq$200 mg/dL (RR, 1.42). However, an inverse association between serum glucose and pCa risk was observed when follow-up began 10 years after study entry (RR, 0.87). Long-term diabetic patients that experience reduced levels of circulating insulin may be at a reduced risk of developing pCa,[8] as experimental studies have shown that insulin is positively associated with the growth of normal and cancerous prostate cells. Our findings corroborate the majority of epidemiological studies and show an inverse association between glucose levels and risk of pCa. Nevertheless, it is likely that competing risks are overestimating these findings (see below).

Several lines of experimental and epidemiological evidence have also indicated that lipids are involved in the development, maintenance, and progression of pCa. Cancer cells overexpress key enzymes involved in lipid biosynthesis and produce new lipids resulting in membrane synthesis and tumor growth. In pCa cells, this de novo synthesis is mainly stimulated by androgens.[11] Moreover, it is hypothesized that hormone refractory pCa is not independent of androgen-driven activity and that androgens may be synthesized de novo in these tumors via cholesterol and progesterone, leading to androgen-receptor activation and tumor growth.[31] Finally, several observational

studies investigating dietary habits, metabolic diseases, and use of statins have also suggested a link between dyslipidemia and risk of pCa.[12,32-34]

The findings of the most recently published prospective cohort study on levels of TG and cancer have shown a protective effect by quartiles of TG.[15] In the AMORIS study, we could not show such a trend by quartiles. However, stratified analyses by glucose levels and conditional probability analyses showed that results can be misleading when not taking into account competing risks of early death, especially among the elderly. Stratification by levels of glucose showed that hypertriglyceridemia is associated with an increased risk of pCa but only for men with high levels of glucose. In addition, when taking into account competing risks for the older age group, we found even more evidence for a positive association between hypertriglyceridemia and risk of pCa in men with high glucose levels.

Using the same methods, we did not find strong evidence for an association between TC and risk of pCa. Only among men with high levels of glucose did a combination of hypercholesterolemia with hypertriglyceridemia increase the risk of pCa in the AMORIS study. In the most recent case-control study, using the same cutoffs for hypercholesterolemia, an odds ratio of 1.29 (95%CI, 0.75-2.12) was found.[13] However, the American Prostate Cancer Prevention Trial did not find an association between TC and pCa risk either, but they found a reduced risk for high-grade pCa among men with low TC.[35]

The lack of competing risk analysis may partly explain why results from previous studies are contradictory. From our graphical representation, one can observe that high glucose levels increase the likelihood that early death may mask pCa risk when one does not consider the competing risk of death as shown in the conditional probability analysis. Thus, our competing risk assessment suggests an overestimation of the protective effect of high glucose levels that has been shown in previous studies.[5]

A major strength of the present study was the large number of men with prospective measurements of TG, TC, and glucose in AMORIS, all measured at the same clinical laboratory. The database also provided complete follow-up for each individual, as well as linkage to other registers allowing for detailed information on cancer diagnosis, time of death, and emigration. The AMORIS population consists of nonhospitalized individuals referred for laboratory testing. During the study period, the all-cause mortality was about 14% lower in the AMORIS population than in the general population of Stockholm county when taking age, gender, and calendar year into account.[36] This "healthy cohort effect" may influence the generalizability of the results but not the internal validity, ie, the hazard ratios given a certain level of lipids for example. In addition, the impact on the generalizability is likely to be minor because it has been shown that the AMORIS cohort is similar to the general working population of Stockholm county in terms of SES and ethnicity. However, a limitation of this study was that no data were available on other risk factors linked to metabolic diseases, such as smoking habits, hypertension, or family history of metabolic disease, but none of these factors have been strongly linked to pCa risk and are, thus, unlikely to produce substantial residual confounding.[37] We had no data on obesity, but obesity is likely to be on the same causal pathway as the factors studied and is, therefore, not a confounding variable in our analyses. However, lipid changes may be an intermediate in a pathway between obesity and risk of pCa. No information was available on medication or diagnosis for diabetes or dyslipidemia; thus, we could not adjust for medication and diagnosis in our analyses. However, we caution that our study focused on the impact of serum glucose levels rather than diabetes. Moreover, at the time of blood sampling, statins were not commonly used. Finally, no information was available on tumor severity, so it was impossible to distinguish between low-risk and aggressive disease. From the Swedish National Prostate Cancer Register (NPCR), we know that the number of men with screening-detected disease and disease with low Gleason score increased with time, while there were stable trends of decreasing numbers of men with advanced disease at time of diagnosis.[38] It may be that metabolic changes are linked to a specific type of pCa, but that cannot be estimated from the current findings.[5]

CONCLUSIONS

Our findings support the hypothesis that factors of the lipid and glucose metabolism influence the risk of developing pCa. The associations are modest, and the nature of these associations is still unclear: changes in metabolic components could lead to direct tumor effects or effects related to host characteristics. From our competing risk assessment, it can be seen that it is important to take into account the long natural history and age distribution of pCa when interpreting the results, as for instance, the protective effective of glucose was overestimated in the conventional survival analysis. If confirmed in future studies,

our results add yet another reason to fight the worldwide rapidly rising prevalence of obesity and dyslipidemias.

CONFLICT OF INTEREST DISCLOSURES

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