Interaction of Factors Related to the Metabolic Syndrome and Vitamin D on Risk of Prostate Cancer

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Abstract

Background: **Factors related to the metabolic syndrome and low levels of vitamin D have been implicated as risk factors for prostate cancer. Insofar, no studies have assessed their joint effects on prostate cancer risk.**
Methods: **We studied (*a*) the associations of vitamin D with the metabolic syndrome factors body mass index, systolic and diastolic blood pressure, and high-density lipoprotein cholesterol (HDL-C) and (*b*) the prostate cancer risk associated with these factors and especially their joint effects with vitamin D on risk of prostate cancer. We did a longitudinal nested case-control study on 132 prostate cancer cases and 456 matched controls from a cohort of 18,939 Finnish middle-aged men from the Helsinki Heart Study. The odds ratios (OR) of prostate cancer were assessed via conditional logistic regression analysis.**
Results: **Apart from HDL-C, there was no linear association between the metabolic syndrome factors and vitamin D levels. In univariate analysis, men in the highest quartiles of body mass index (>28 kg/m^2) and systolic blood pressure (>150 mmHg) showed a modest increase in risks of prostate cancer, with ORs of 1.37 (P = 0.16) and 1.53 (P = 0.05) when compared with the three lower quartiles, but low HDL-C entailed no prostate cancer risk. However, with all three factors present, the OR was 3.36 (P = 0.02), and jointly with low vitamin D (≤40 nmol/L), the OR was 8.03 (P = 0.005) compared with those with no metabolic syndrome factors and intermediate levels of vitamin D. There was an interaction between vitamin D and the metabolic syndrome factors so that a clustering of these factors entailed high risk of prostate cancer but only if vitamin D level was low (≤40 nmol/L). If it was at intermediate levels, the metabolic syndrome factors entailed no prostate cancer risk.**
Conclusions: **We conclude that the prostate cancer risk associated with factors related to the metabolic syndrome is strongly conditioned by levels of vitamin D.** (Cancer Epidemiol Biomarkers Prev 2007;16(2):302–7)

Introduction

Obesity is a central feature in the metabolic syndrome, the epidemic in the affluent societies of today. This cluster of disorders was originally described by Reaven (1) as the syndrome X. Reaven postulated that insulin resistance underlies syndrome X and is thus a necessary requisite for syndrome X to be present. Later, several other definitions have been presented for the metabolic syndrome (e.g., in the National Cholesterol Education Program's Adult Treatment Panel III definition of the metabolic syndrome, more emphasis is laid on obesity as the underlying cause for the development of the metabolic syndrome factors). For the clinical identification of the metabolic syndrome, Adult Treatment Panel III lists five characteristics: abdominal obesity, elevated triglycerides, low levels of high-density lipoprotein cholesterol (HDL-C), hypertension, and elevated levels of fasting glucose. When three of five of these criteria are present, the diagnosis of metabolic syndrome can be made (2). All obese are not insulin resistant and all insulin resistant are not necessarily obese; the degree of overlapping is population dependent (3).

Two recent Nordic studies have reported a significant association between the metabolic syndrome and increased risk of prostate cancer (4, 5). However, obesity, the principal factor in the metabolic syndrome, has been inconsistently linked to prostate cancer risk (6, 7). In two large Scandinavian follow-up studies, a modest positive overall association was found (8, 9), but in the latter, a Norwegian study, a clear positive association was found among those diagnosed before age of 60 years but not among those diagnosed at a later age. Interestingly, Giovannucci et al. found a quite contrasting result when studying the prostate cancer risk by age using data from the U.S. Health Professionals Follow-up Study: they found a significant inverse association between body mass index (BMI) and prostate cancer risk among men <60 years but a weak positive association among men ≥60 years (10). The metabolic consequence of metabolic syndrome, diabetes, has mostly been found to be inversely associated with risk of prostate cancer (11), although, also in this relation, a conditioning has been presented: the decreased risk of prostate cancer was seen only among those treated for diabetes, not among untreated patients (12). Recently, it was found that the metabolic syndrome is associated with a reduced risk of prostate (13), but in the same journal, an article with opposite results was published (14).

Several epidemiologic studies have reported that high serum vitamin D levels or sunlight may protect against prostate cancer (15-21). Factors that affect prostate cancer include age, dark skin, and environmental factors, such as latitude and diet (22). These factors may all be linked to vitamin D bioavailability (23, 24). Furthermore, high consumption of fish (rich in vitamin D) seems to be related to decreased prostate cancer risk (25). In addition, vitamin D receptor gene polymorphism may contribute to the risk of prostate cancer (26-30). There are also studies showing no or only a weak

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association between serum vitamin D metabolites and prostate cancer risk (31-33). We have recently described a U-shaped risk for prostate cancer by serum 25(OH)-vitamin D in three Scandinavian countries (Finland, Sweden, and Norway): the risk was higher with both low and high serum vitamin D (34).

Low levels of vitamin D, in turn, seem to be connected with the metabolic syndrome (35) and obesity (36). A recent large-scale study on a subpopulation of the participants in the Third National Health and Nutrition Examination Survey reported an inverse association between concentrations of serum vitamin D and prevalence of the metabolic syndrome (37). In addition, vitamin D deficiency or vitamin D receptor gene polymorphism seems to be associated with both type 1 and type 2 diabetes (38, 39).

Here, we first studied the associations of vitamin D with the metabolic syndrome factors obesity, hypertension, and low level of HDL-C and, second, the prostate cancer risk associated with increasing clustering of the metabolic syndrome factors and, in particular, the joint effects (interactions) of vitamin D and these factors on risk of prostate cancer.

Materials and Methods

The Baseline Cohort. The cohort from which the present case-control study was drawn consisted of ~19,000 men who attended the first screening visit within the Helsinki Heart Study. In this clinical trial, the effect of gemfibrozil, a drug modulating lipid levels, was investigated with regard to coronary heart disease (18, 40). The participants, middle-aged (40-58 years at the onset) employees in two governmental agencies and five industrial companies, were recruited between 1981 and 1982. A blood sample was drawn from the participants in the morning, and serum samples were stored at −20°C. Most of the samples were collected during the winter months.

Case Ascertainment and Control Selection. All incident cases of prostate cancer and all cases of death were identified through linkage with the Finnish Cancer Registry in 1997 using a nationwide individual identification number as the identity link. If several samples were available for the same case subject, the first sample was chosen. The study design was that four control subjects for each case subject were selected within each cohort from all members alive and free of cancer at the time of diagnosis of the case by matching on age (±2 year) and date (±2 months) of the blood sampling and the region inside the country. As the subjects were from a clinical trial with a lipid-lowering drug, treatment status was also a matching criterion. Some of the stored frozen samples were accidentally thawed and matched for thawing. Of the 132 case/control sets, 54 were among those thawed. The matching ensured that the samples of the controls had been stored in the same freeze room as those of the corresponding cases. The mean (SD) levels of calcidiol among thawed cases were 38.2 (17.4) nmol/L and 42.2 (17.1) nmol/L among controls, whereas among those not thawed the levels were 40.3 (20.5) nmol/L and 43.5 (18.4) nmol/L, respectively. Antoniucci et al. (41) found that serum calcidiol is unaffected by multiple freeze-thaw cycles.

If four control subjects were not found in this procedure, less than four control subjects were accepted. Due to great seasonal variation in the vitamin D levels, it was additionally required that the blood from the case subject and its controls should be sampled during the same season of the year. This restriction entailed that 132 case subjects with 456 controls from originally 140 cases and 560 matched controls were available for this study.

Factors Related to the Metabolic Syndrome. Obesity was measured in terms of BMI (kg/m^2). Blood pressure was measured by specially trained nurses in 37 local clinics where also the blood samples were collected.

Serum samples from the local clinics were mailed daily to the central laboratory (at the National Public Health Institute in Helsinki) where the lipid determinations were done daily. HDL-C was measured with an enzymatic method (kit 236691; Boehringer Mannheim, Mannheim, Germany). The measurements of BMI, blood pressure, and HDL-C were done at the same screening visit where also the blood samples were collected and stored at −20°C for later use.

Serum Vitamin D. Serum concentrations of 25-hydroxyvitamin D_3/D_2 were analyzed by RIA (Incstar Corp., Stillwater, MN). The samples were analyzed blinded, without knowledge of the case-control status, during the same day and using the same lot of assay kit. The coefficients of intra-assay and interassay variations for the assay of 25(OH)-vitamin D were 8.5% and 16%, respectively.

Statistical Methods. The associations between vitamin D and the metabolic syndrome factors were described by presenting Pearson correlation coefficients and the means of the metabolic syndrome factors by categories of the vitamin D levels. ANOVA was used to test for differences of the means. When studying the associations of vitamin D and the metabolic syndrome factors with prostate cancer risk, we used conditional logistic regression analysis so that the matching status could be maintained. In the analyses, we dichotomized the metabolic syndrome variables at the cutoff points for the highest (lowest for HDL) quartiles, which were as follows: BMI, >28 kg/m^2; systolic blood pressure (SBP), >150 mmHg; diastolic blood pressure (DBP), >95 mmHg; and HDL, ≤1.05 mmol/L. As the association of vitamin D and prostate cancer risk was found to be U shaped (34), we used a three-level variable for vitamin D, with cutoff points of 40 and 60 nmol/L.

To gain an understanding of the joint effect of vitamin D and the metabolic syndrome factors on prostate cancer risk, we first explored the univariate associations, next the joint effects of vitamin D with the metabolic syndrome factors were analyzed separately one by one, and finally the joint effect of vitamin D and a clustering of the metabolic syndrome factors. Likelihood ratio test was used to test for interactions. To avoid problems with convergence when estimating the interactions, the variables indicating degree of clustering of the metabolic syndrome factors were compressed to two levels: 0 = none of the factors at high level; 1 = at least one of the factors at high level. The analyses were done using the statistical package Egret for Windows.

Results

Study Characteristics. We have in the study 588 observations with 132 matched case-control sets. The mean age at serum sampling was 51.3 years among the cases and the mean age at diagnosis was 62.1 years, with a mean lag time of 10.8 years between sampling and diagnosis (Table 1).

Table 1. Characteristics of the sampling procedure and mean levels of vitamin D and some factors related to the metabolic syndrome among cases and controls

Characteristic	Cases (N = 132), mean (SD)	Controls (N = 456), mean (SD)
Age at serum sampling (y)	51.3 (3.8)	51.0 (3.7)
Age at diagnosis (y)	62.1 (4.9)	
Lag between sampling and diagnosis (y)	10.8 (3.5)	
Vitamin D (nmol/L)	39.5 (19.3)	42.9 (17.8)
BMI (kg/m^2)	26.4 (3.1)	26.3 (3.1)
SBP (mmHg)	143.1 (17.4)	142.0 (17.1)
DBP (mmHg)	91.2 (10.0)	90.0 (10.1)
HDL-C (mmol/L)	1.28 (0.32)	1.27 (0.29)

Table 2. Mean values of BMI, SBP, DBP, and serum HDL-C by vitamin D levels in the control group and among cases

Vitamin D level (nmol/L)	*n*	BMI (kg/m^2), mean (SD)	SBP (mmHg), mean (SD)	DBP (mmHg), mean (SD)	HDL-C (mmol/L), mean (SD)
Controls					
<40	224	26.3 (3.1)	141.1 (16.7)	89.5 (10.5)	1.23 (0.29)
40-59	154	26.3 (2.9)	140.8 (17.0)	89.9 (9.4)	1.30 (0.28)
≥60	78	26.5 (3.4)	147.2 (17.5)	91.4 (10.3)	1.33 (0.30)
ANOVA for difference of means		$P = 0.84$	$P = 0.02$	$P = 0.36$	$P = 0.007$
Cases					
<40	81	26.6 (3.2)	144.0 (17.4)	92.2 (10.6)	1.24 (0.32)
40-59	29	25.3 (2.0)	140.2 (15.3)	88.1 (8.1)	1.39 (0.32)
≥60	22	27.4 (3.6)	143.4 (19.8)	91.8 (9.7)	1.31 (0.31)
ANOVA for difference of means		$P = 0.05$	$P = 0.59$	$P = 0.16$	$P = 0.10$

Associations between Vitamin D and the Metabolic Syndrome Factors. Vitamin D levels correlated moderately with levels of HDL ($r = 0.15$; $P = 0.001$) but not with the levels of the other metabolic syndrome factors considered, the correlation coefficients being <0.1 and statistically not significant. Instead, BMI correlated clearly with the other metabolic syndrome factors as could be expected. However, a closer study of the association of vitamin D with the metabolic syndrome factors revealed that, among cases, the association was not linear, as the mean values of these factors (except for HDL-C) had their minimum at vitamin D concentration of 40 to 59 nmol/L (Table 2).

Main Effects of the Metabolic Syndrome Factors and Vitamin D on Risk of Prostate Cancer. When using the range of 40 to 59 nmol/L as the reference, we found odds ratios (OR) of 1.93 ($P = 0.007$) for vitamin D levels <40 nmol/L and 1.32 ($P = 0.35$) for levels >60 nmol/L (Table 3). There was no significant association between the metabolic syndrome factors as continuous variables and prostate cancer risk (data not shown). However, there was some suggestion of increased prostate cancer risk in the highest quartiles of BMI and SBP compared with the three lower quartiles: by BMI the excess risk was 37% ($P = 0.16$) and by SBP the excess risk was 53% ($P = 0.05$). By low HDL, no excess risk of prostate cancer was present. The ORs for the metabolic syndrome factors were slightly decreased if adjusted for vitamin D, and vice versa, the OR for vitamin D was slightly curtailed when adjusted for the metabolic syndrome factors (Table 3).

Joint Effects of Vitamin D and the Factors Related to Metabolic Syndrome on Risk of Prostate Cancer. Men with BMI in the highest quartile (>28 kg/m^2) and low vitamin D level (<40 nmol/L) had an OR of 2.28 ($P = 0.01$) compared with the reference group of intermediate levels of vitamin D (40-60 nmol/L) and BMI (≤28 kg/m^2; Table 4). An even stronger joint effect was seen in men with low level of vitamin D and high level of SBP: the OR was 3.33 [95% confidence interval (95% CI), 1.72-6.44] when compared with the intermediate level of vitamin D and lower level of SBP. High levels of SBP increased the risk of prostate cancer only if vitamin D was at low level, and vitamin D was associated with significant prostate cancer risk only in the presence of high SBP. A similar pattern was seen by DBP but not with HDL.

Joint Effects of a Clustering of the Metabolic Syndrome Factors and Vitamin D on Risk of Prostate Cancer. We explored the prostate cancer risk by increasing number of the metabolic syndrome factors BMI, SBP, and HDL present, first without taking into account the vitamin D levels and finally by studying them jointly.

When considering the factors BMI and SBP, there was a significant increase in the prostate cancer risk (OR, 2.35) only when both factors were at high level (Table 5). If even low HDL was present in the cluster, the risk was considerably increased (OR, 3.36; $P = 0.02$). The prostate cancer risk attributed to the metabolic syndrome factors was considerably reduced if vitamin D was simultaneously considered in the model (Table 5).

When studying the joint effects (Table 6), we see that neither low vitamin D alone nor a clustering of the metabolic syndrome factors alone entailed any notable effect on prostate cancer risk, but when low vitamin D was present simultaneously with both high BMI and high SBP, the OR was 3.85 ($P = 0.003$; $P = 0.07$ for interaction between vitamin D and the compressed 0 and 1 variable for the presence of high BMI or high SBP). When low vitamin D level was present simultaneously with high BMI, high SBP, and low HDL, the OR was 8.03 ($P = 0.005$) when compared with the respective reference groups with normal level of vitamin D and no metabolic syndrome factors at risk level ($P = 0.21$ for interaction).

Discussion

We studied prospectively the joint effects of factors related to the metabolic syndrome and vitamin D on risk of prostate cancer. The metabolic syndrome factors obesity, hypertension, and low HDL-C were assessed both separately and in clusters. Our main finding was that a clustering of factors related to the metabolic syndrome substantially increased the prostate cancer risk but only if the level of vitamin D was low, and vice versa, the risk due to low levels of vitamin D was curtailed if no metabolic syndrome factors were present. The significant effect of vitamin D level on the prostate cancer risk of metabolic syndrome might explain why variable results have been obtained (13, 14). With adequate circulating levels of vitamin D, the metabolic syndrome factors were not risk

Table 3. Univariate associations of vitamin D levels and levels of BMI, SBP, DBP, and HDL-C with risk of prostate cancer in terms of ORs with 95% CIs

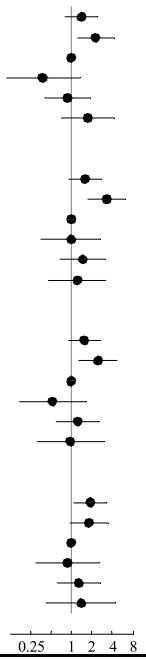
Factor	OR (95% CI), not adjusted	OR (95% CI), adjusted*
Vitamin D (nmol/L)		
<40	1.93 (1.19-3.13)	1.88 (1.15-3.08)
40-59	1 (reference)	1 (reference)
≥60	1.32 (0.69-2.56)	1.25 (0.64-2.43)
BMI > 28 (kg/m^2)	1.37 (0.89-2.10)	1.30 (0.84-2.01)
SBP > 150 (mmHg)	1.53 (1.00-2.33)	1.47 (0.96-2.26)
DBP > 95 (mmHg)	1.19 (0.76-1.86)	1.14 (0.73-1.78)
HDL-C ≤ 1.05 (mmol/L)	1.06 (0.68-1.65)	0.95 (0.60-1.50)

NOTE: The analyses were based on 587 observations with 132 case-control sets. The cases and controls were matched on age (±2 years) and season of the blood sampling, region, accidental thawing, and treatment with gemfibrozil, the drug used in this trial population.

*The effect of vitamin D was adjusted for BMI, SBP, and HDL-C; the effects of BMI, SBP, DBP, and HDL-C were adjusted for vitamin D.

Table 4. ORs of prostate cancer by combined levels of vitamin D and some factors related to the metabolic syndrome

Vitamin D (nmol L)	Quartile of BMI	OR (95% CI)	*P* for interaction
<40	I, II, and III	1.41 (0.82-2.43)	0.05
	IV	2.28 (1.22-4.25)	
40-59	I, II, and III	1 (reference)	
	IV	0.38 (0.11-1.34)	
≥60	I, II, and III	0.88 (0.4-1.94)	
	IV	1.73 (0.7-4.28)	
	SBP		
<40	I, II, and III	1.6 (0.93-2.76)	0.20
	IV	3.33 (1.72-6.44)	
40-59	I, II, and III	1 (reference)	
	IV	0.98 (0.36-2.66)	
≥60	I, II, and III	1.48 (0.68-3.2)	
	IV	1.23 (0.47-3.21)	
	DBP		
<40	I, II, and III	1.55 (0.91-2.64)	0.18
	IV	2.47 (1.3-4.69)	
40-59	I, II, and III	1 (reference)	
	IV	0.53 (0.17-1.67)	
≥60	I, II, and III	1.25 (0.6-2.6)	
	IV	0.97 (0.31-3.02)	
	HDL-C		
<40	II, III, and IV	1.92 (1.11-3.34)	0.97
	I	1.82 (0.97-3.42)	
40-59	II, III, and IV	1 (reference)	
	I	0.87 (0.3-2.52)	
≥60	II, III, and IV	1.27 (0.61-2.64)	
	I	1.38 (0.42-4.53)	



NOTE: BMI IV quartile > 28 (kg/m^2), SBP IV quartile > 150 (mmHg), DBP IV quartile > 95 (mmHg), and HDL-C I quartile ≤ 1.05 (mmol/L).

factors for prostate cancer. This finding points to the protective role of vitamin D in prostate carcinogenesis (42).

The Association of the Metabolic Syndrome Factors with Vitamin D. No clear-cut linear correlations between factors of metabolic syndrome and vitamin D levels were observed in this study except for the moderate correlation between HDL-C and vitamin D. However, among cases, a nonlinear association was seen for all the factors, with a minimum (maximum for HDL-C) when vitamin D values were 40 to 59 nmol/L. In the study of Ford et al. (37), a significant inverse association was observed between vitamin D and prevalence of metabolic syndrome and several of its separate components, especially abdominal obesity. In our study, obesity was measured in terms of BMI, which is a less accurate measure of central obesity. It is also to note that, in the study by Ford et al., subjects had far higher levels of vitamin D than in our study; the range in our study did not cover even the three lowest quintiles in their study.

Metabolic Syndrome Factors, Vitamin D, and Prostate Cancer Risk—Analogies with Other Studies. Our study suggests that there is no overall association between the metabolic syndrome factors as continuous variables and prostate cancer risk. However, a slightly increased risk was suggested to exist in the highest quartiles of BMI and SBP. On the other hand, clustering of the metabolic syndrome factors revealed that simultaneous presence of all the factors, high BMI, high SBP, and low HDL, entailed >3-fold risk. Both hypertension and low HDL cholesterol are multifactorial in origin, so when considered separately, they may not represent metabolic syndrome. However, when occurring together with obesity, the probability that they stand for metabolic syndrome is increased. It is even probable that this cluster of metabolic syndrome factors entails also elevated levels of other metabolic syndrome-related putative risk factors for prostate cancer. If the measured factors are links to prostate cancer risk or if they are only innocent bystanders only indicating the presence of the true culprit(s) cannot be evaluated in our study. In addition, another Finnish study (4) has reported an association between the metabolic syndrome and risk of prostate cancer, but as far as we know, no other study has assessed the role of vitamin D in that association.

The joint effect of BMI and vitamin D showed an interesting pattern: with intermediate levels of vitamin D, high BMI entailed no increased risk of prostate cancer, but with low or high levels of vitamin D, it was a risk factor. In their study on BMI and risk of prostate cancer in U.S. Health Professionals, Giovannucci et al. (37) found that high BMI entailed a decreased risk of prostate cancer (relative risk, 0.52) but only among men <60 years of age, not among those ≥60 years (10). In the study by Ford et al. on a U.S. population, the vitamin D levels were much higher than in our study, with <20% having levels <40 nmol/L. It is thus reasonable to assume that the Health Professionals in the Giovannucci et al. study had mostly adequate levels of vitamin D. For comparison with our findings, we list the facts: (*a*) our study population was fairly young, with mean 62.1 years at diagnosis, and (*b*) we have previously shown that, in this material, the vitamin D gradient of prostate cancer risk was most marked among younger men (18). It thus lies close to speculate that the protective effect of high BMI in Giovannucci's study as in ours was related to adequate levels of vitamin D.

In the Norwegian study by Engeland et al. (9), quite contrasting findings were seen: BMI entailed increased risk of prostate cancer especially among younger men (relative risk, 1.58). Even this finding may be related to vitamin D levels. In our previous Nordic study on vitamin D and prostate cancer, we found that vitamin D levels were far higher in Norway than in Finland, with 14% >80 nmol/L compared with 3% in the Finnish material (28). In our present study, BMI emerged as a risk factor both when vitamin D levels were very low or very high.

Possible Pathways for the Vitamin D-Metabolic Syndrome Factor Interactions in Prostate Cancer Risk. The interaction of vitamin D and metabolic syndrome factors on prostate cancer risk suggests existence of a common putative pathway(s). Possible factors explaining this interaction include those among endocrine systems that are affected both by metabolic syndrome and inadequate vitamin D status and play a central role in the regulation of prostatic growth. The interactions seen are not quite unexpected, as analogous findings have been found at the transcriptional level. Among the nuclear hormone receptor family, the peroxisome proliferator-activated receptors play regulatory roles in the metabolic syndrome, including adipogenesis, lipid metabolism, insulin sensitivity, and

Table 5. ORs and 95% CIs of prostate cancer by increasing clustering of the factors high BMI, high SBP, and low HDL-C level

	No. cases	OR (95% CI), no adjustment	OR (95% CI), adjusted for vitamin D
No. factors high BMI and high SBP present			
0	70	1 (reference)	1 (reference)
1	43	1.11 (0.73-1.69)	1.11 (0.73-1.68)
2	19	2.35 (1.25-4.43)	2.12 (1.11-4.04)
Test for trend		$P = 0.03$	$P = 0.05$
No. factors high BMI, high SBP, and low HDL-C present			
0	59	1 (reference)	1 (reference)
1	39	0.85 (0.55-1.33)	0.83 (0.53-1.30)
2	27	1.43 (0.85-2.38)	1.29 (0.77-2.18)
3	7	3.36 (1.19-9.44)	2.86 (1.00-8.19)
Test for trend		$P = 0.06$	$P = 0.15$

NOTE: High BMI > 28 (kg/m^2), high SBP > 150 (mmHg), and low HDL-C ≤ 1.05 (mmol/L) representing the highest quartiles of these variables.

Table 6. Joint effect of vitamin D and clustering of factors related to the metabolic syndrome on risk of prostate cancer

Vitamin D level (nmol/L)	No. factors* high BMI and high SBP	No. cases	OR (95% CI)
<40	0	38	1.20 (0.66-2.20)
	1	30	1.88 (0.99-3.55)
	2	13	3.85 (1.57-9.41)
40-59	0	21	1 (reference)
	1-2	8	0.56 (0.23-1.36)
≥60	0	11	1.05 (0.44-2.50)
	1-2	11	1.20 (0.52-2.79)

Vitamin D level (nmol/L)	No. factors* high BMI, high SBP, and low HDL-C	No. cases	OR (95% CI)
<40	0	31	1.23 (0.63-2.38)
	1	26	1.26 (0.64-2.47)
	2	18	1.79 (0.85-3.76)
	3	6	8.03 (1.89-34.09)
40-59	0	19	1 (reference)
	1-3	10	0.53 (0.23-1.21)
≥60	0	9	0.91 (0.35-2.38)
	1-3	13	1.12 (0.50-2.53)

NOTE: ORs with 95% CIs by combinations of vitamin D levels and different degrees of clustering of the factors: high BMI, high SBP, and low HDL-C.
*High BMI > 28 (kg/m^2), high SBP > 150 (mmHg), and low HDL-C ≤ 1.05 (mmol/L).

inflammation. Fatty acids and oxidized lipids are endogenous ligands of peroxisome proliferator-activated receptor-γ, whereas some of its synthetic ligands are used as antidiabetic treatments (43). These receptors bind to the retinoid X receptor to form a heterodimer. In addition, the vitamin D receptor forms a heterodimer with retinoid X receptor, and these two complexes have common signaling pathway, thus influencing tightly each other's effect on the target gene (43). Both these receptors are highly expressed in prostate cancer cells where they are involved in regulation of growth and induction of apoptosis (44). Several nuclear receptor ligands have interactions with vitamin D signaling pathway in prostate cancer (45), and peroxisome proliferator-activated receptor-γ ligands have been reported to have synergistic anticancer effects with other agents (45), although to date no reports exist on vitamin D and peroxisome proliferator-activated receptor interactions in prostate cancer.

Another suggested pathway goes via involvement of vitamin D in the insulin-like growth factor (IGF) signaling axis (46). The same mechanism seems to be involved in the action of factors of metabolic syndrome (47). A high concentration of calcitriol [1,25-$(OH)_2$ vitamin D_3] causes an insulin resistance without lipid accumulation (48-50). Circulating IGF-I levels have been shown to associate with the prostate cancer risk, although contradictory data have also been reported (51). *In vitro* studies have shown IGF-I to act as mitogen for prostate cancer cells, and up-regulation of IGF-binding protein-3 by vitamin D has in turn seemed to be one mechanism mediating antiproliferative effect of this hormone on prostatic epithelial cells (52-54). Compensatory hyperinsulinemia that characterizes adolescent obesity is suggested to suppress levels of IGF-binding protein-1, which may serve to increase the bioavailability of free IGF-I in the body (47). Thus, vitamin D insufficiency with prevalent hyperinsulinemia could contribute to prostate carcinogenesis, permitting unbalanced mitotic effect of free IGF-I on prostatic cells. It is thus possible that both vitamin D insufficiency and hyperinsulinemia act through the same mechanism in prostate carcinogenesis, an increased action of IGF-I.

Vitamin D can also indirectly modify the insulin signaling system. Vitamin D and peroxisome proliferator-activated receptor-γ ligands up-regulate antiaging hormone, Klotho, expression (49, 55). Klotho binds to a cell surface receptor through which it represses autophosphorylation of receptors for insulin and IGF-I and the consecutive signaling steps, thus leading to an insulin resistance. Furthermore, vitamin D can directly affect blood pressure via negative regulation of renin-angiotensin system, which is also suggested to play a role in metabolic syndrome (56). Therefore, long-lasting vitamin D insufficiency may contribute to the development of metabolic syndrome. In our study, the metabolic syndrome emerged more clearly among those with low level of vitamin D than among those with normal level (40-59 nmol/L), only among cases.

Methodologic Considerations and Limitations of the Study. In the analyses, we used the limits for the highest quartiles of the three metabolic syndrome factors as cutoff points. These limits were much higher than the limits recommended by the Adult Treatment Panel III panel for the presence of factors related to the metabolic syndrome (2). The measurements were made at the beginning of the 1980, at a time when the coronary heart disease mortality in Finland was among the highest in the world and, accordingly, the level of risk factors was high. By using the Adult Treatment Panel III limits, we would thus hardly have an appropriate reference group.

The metabolic syndrome-related factors were measured at the time the sample was drawn, but vitamin D measurements were based on stored samples. The sera were stored for 15 to 16 years at a temperature of −20°C. We have not found any notable effect of the storage time on vitamin D levels when samples are stored properly and protected against UV light. In fact, our previous study in Finland suggests that serum concentrations of vitamin D are lower today than 20 years ago (18, 57). Some of the samples were accidentally thawed during the storage; the thawing status was therefore used as a matching criterion.

The effect of the Finnish habits of high intake of milk fat on increased risk of prostate cancer (4, 58) might be partly mediated via the metabolic syndrome. However, we cannot exclude the possibility that even other pathways could exist for the effect of the diet on prostate cancer risk. The dietary factors would thus form a putative confounding factor that we were not able to adjust.

The size of this pilot study is its greatest limitation. As the vitamin D levels in the Finnish material were centered at the lower end of the distribution, we had too few cases at the upper end of the distribution of vitamin D to allow some conclusions on the pattern of prostate cancer risks. Moreover, it is well known that the tests for interaction are of low power so that large data sets are usually required to detect an interaction. The consistency in the pattern of risks and the fact that some interactions were significant despite the small size of the study strengthen the plausibility of our findings.

Today, much research is devoted to curtail the epidemic of the metabolic syndrome with its effect on diabetes, coronary heart disease, and cancer. Lately, combinations of treatments against metabolic syndrome and diabetes, the statins and the glitazones, have been found to have powerful anticancer effects (59, 60). Vitamin D may be one possible component (45). Population-based epidemiologic studies on the interactions of naturally occurring vitamin D levels, especially high levels, with factors related to metabolic syndrome would form an important background for development of such combined therapies.

Conclusions. Our study suggests that a clustering of factors related to the metabolic syndrome substantially increases the prostate cancer risk but only when the level of vitamin D is low (<40 nmol/L), but normal vitamin D concentration (40-60 nmol/L) may offer some protection against the prostate cancer risk associated with the factors related to metabolic syndrome.

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