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Citation for the published paper:
Wallstrom, Peter and Bjartell, Anders and Gullberg, Bo and Olsson, Hakan and Wirfalt, Elisabet.

"A prospective study on dietary fat and incidence of prostate cancer (Malmö, Sweden)"
Cancer causes & control, 2007, Vol: Aug 29.

<http://dx.doi.org/10.1007/s10552-007-9050-4>

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A prospective study on dietary fat and incidence of prostate cancer (Malmö, Sweden)

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Abbreviated title: Dietary fat and prostate cancer

Financial support has been received from the Swedish Cancer Society, the Swedish Medical Research Council, Region Skåne, The Swedish Nutrition Foundation and the Ernhold Lundström Research Foundation.

Suggested MeSH terms: Prostatic-Neoplasms, Cohort-Studies, Dietary-Fats, Fatty-Acids

Conflicts of interest: None.

Abstract

Objective: To study the associations between intake of various types of fat and risk of prostate cancer (PCa) in a population-based cohort.

Methods: We studied 10,564 initially cancer-free men of the Malmö Diet and Cancer cohort, aged 45-73 years. Diet was assessed by a modified diet history method. Cases and clinical characteristics were ascertained via national and regional registry data.

Results: During a mean follow-up of 11.0 years, 817 incidental PCa cases were diagnosed. Of these, 281 were classified as advanced. There were 202 cases occurring before 65 years of age. After adjustment for age and energy intake, there was no association between intake of any types of fat and risk of PCa, or between fat intake and advanced PCa or PCa occurring in persons aged < 65 years. However, we observed positive associations between intakes of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and risk of PCa. After adjustment for multiple confounders, the latter associations were weakened, but the results were otherwise virtually unchanged.

Conclusions: This large study, with high-validity dietary data, does not support an association between intake of total, saturated, or mono-unsaturated fat and PCa risk. The observed associations between EPA/DHA intakes and PCa are difficult to interpret.

Introduction

Prostate cancer is the third most common cancer in men globally; it represents almost 10% of all cancer cases. However, both incidence, prevalence and mortality vary considerably between countries and populations; e.g. in the Western world, it is the most common male cancer (1-3).

Several studies have reported positive associations between a high intake of total and saturated fat and incidence of prostate carcinoma. Similar claims have been made for polyunsaturated fatty acids (PUFA) (2,4,5). However, methodological weaknesses and differences among studies (retrospective designs, lack of adjustment for total energy intake, inadequate diet assessment methods or no calculations of actual fat intake (4)) make many of these results difficult to interpret. Among epidemiological studies that have avoided these design problems (6-15), results have been mixed.

Concerning PUFA, a growing body of evidence suggests that the associations of individual fatty acids (FA) with prostate cancer are different from one another. For example, a recent study from Finland observed decreased risk in persons with higher serum levels and dietary intakes of linoleic acid (LA; *cis*-18:2, ω -6) (14). This was in agreement with a case-control study that examined adipose tissue fatty acid composition, which is reported to be a good marker of long-term intake (9). However, most previous evidence speaks against any association (8,10,11,13,15,16). α -linolenic acid (ALA; 18:3, ω -3) has in some studies been a relatively strong predictor of cancer risk (6,8-10,15), but has shown no association in others (13,14), and a meta-analysis (17) concluded that the heterogeneity between studies was too large for proper evaluation. Long-chain ω -3 FA (mainly eicosapentaenoic acid (EPA; 22:5) and docosahexaenoic acid (DHA; 22:6)), of which the dominant source is fatty fish, were

associated with lower risk in some studies (14,15), but not in others (6,8,10,13). Similarly, fish consumption *per se* appeared protective in some studies (18-20), but not in all (13,16,21). Further, some researchers argue that dietary fat, e.g. ALA, may be more strongly associated with more aggressive tumors than with indolent tumors (15). Similarly, it is often hypothesized that there are differences between factors associated with tumors occurring at younger and older ages (e.g. 22-24).

We here present the results from an examination of these issues, based on an 11-year follow-up of a population-based cohort in Malmö, Sweden.

Methods

Study population

The Malmö Diet and Cancer (MDC) study is set in Malmö, Sweden's third largest city (25). The background population consisted of all men born between 1923 and 1945 and all women born between 1923 and 1950 who were living in Malmö during the screening period 1991 to 1996 (n=74,138). This population was identified through the Swedish national population registries. The final cohort consisted of 28,098 individuals (participation rate 40.8 percent). The subjects were recruited through advertisements in local media and through invitation by mail. The only exclusion criteria were inadequate Swedish language skills and mental incapacity (26,27). The Ethics Committee at Lund University approved the design of the MDC study (LU 51-90).

Data collection

The study subjects visited the MDC study center twice. At the first visit project staff provided information on the background and aim of the project, and detailed instructions about the dietary assessment and the other procedures of the study, including the lifestyle questionnaire.

Height and weight were also measured. At the second visit, a dietary interview was performed (see below), and the lifestyle questionnaires were checked for incomplete answers.

Dietary assessment

The MDC study used an interview-based, modified diet history method that combined (i) a 7-day menu-book for registration of lunch and dinner meals, cold beverages including alcohol, drugs, natural remedies, and nutrient supplements, (ii) a 168-item questionnaire for assessment of meal pattern, consumption frequencies and portion sizes of regularly eaten foods, and (iii) a 45-minute complementary interview. The consistency of the information provided was carefully checked so that the questionnaire and menu-book did not overlap.

The mean daily intake of foods was calculated based on frequency and portion size estimates from the questionnaire and menu-book. The food intake was converted to energy and nutrient intakes using the MDC nutrient database, wherein the majority of the nutrient information comes from PC-KOST2-93 (National Food Administration, Uppsala, Sweden). The method method is described in more detail elsewhere (28).

Data on the validity (29,30) and reproducibility (31) of the method have been published. The relative validity of the method (compared to 14 days of weighed food records), is, in men, for saturated FA (SFA) 0.56, monounsaturated FA (MUFA) 0.59, polyunsaturated FA 0.26, palmitoleic acid (16:1) 0.51; oleic acid (18:1) 0.58, LA (18:2) 0.23, ALA (18:3 ω -3) 0.22; arachidonic acid (AA; 20:4 ω -6) 0.55; EPA (20:5) 0.24; and DHA (22:6) 0.20.

In September 1994, the coding procedures of the dietary assessment were slightly altered in order to reduce interview time. An evaluation of these changes has been published (28); it was shown that the effects of the alterations were very small. We still chose to adjust for this alteration in the analyses, as described below.

Case ascertainment and staging

Cancer cases were ascertained by record linkage with the National Cancer Register. Cancer cases from the year 2005, and additional data on tumor stage and grade, pre-diagnostic serum PSA value, and reason for diagnosis (symptoms, health examination, or other), was obtained from the National Prostate Cancer Register (NPCR) (South Region). In the South Region, to which Malmö belongs, registration was started in 1996. For cases diagnosed between 1991 and 1995, the same data was manually extracted from medical records using standard routines. The South Region register is at least 95% complete; the National Cancer Register is known to be at least 98% complete. A validation of the NPCR data from another region showed high validity for all variables, including the variables used in the classification of non-advanced and advanced tumors (32).

There are 11,063 men in the MDC cohort. Among these, 485 men were already diagnosed with cancer (excluding basal cell carcinomas) when entering the study, and were therefore excluded from further analysis. Fourteen other men were excluded because of obtaining a diagnosis of prostate cancer at autopsy. This left 10,564 men for analysis. They were followed until date of death, date of prostate cancer diagnosis, or December 31, 2005, whichever came first. No participants were lost to follow-up of vital status. Among them, 817 incident cases of prostate cancer (“total prostate cancer”; ICD-9 code 185) occurred from the time of the baseline examinations until the end of follow-up. The average follow-up time in participants free of prostate cancer at death (n=1,321) or at the end of follow-up (n=8,426) was 11.0 years.

An advanced case (“advanced prostate cancer”) was defined as a having a tumor with a clinical T stage of 3 or higher *or* tumor-positive lymph nodes (N1) *or* one or more distant metastases (M1) *or* a Gleason score of 8 or higher *or* a pre-treatment serum prostate specific antigen (PSA) value of at least 50 ng/mL (24). Tumors were also classified as advanced if WHO grade was 3, and Gleason score was unavailable (n=6). In cases where at least two of T stadium, Gleason score or PSA serum value was reported, and none of these factors indicated

an advanced tumor, the tumor was classified as non-advanced. We thus defined 281 incident cases as being advanced, and 530 cases as non-advanced. Staging data was unavailable or insufficient for 6 of the incident cases. These 6 cases, and the 530 cases of non-advanced cancers, were excluded from analyses comparing men with advanced tumors with other men.

In order to analyse prostate cancer occurring in younger people, we repeated all analyses in a sub-cohort, where the end of follow-up occurred either at date of death, date of prostate cancer diagnosis, December 31, 2005, or the man's 65th birthday, whichever came first. This younger sub-cohort consisted of 8,194 men, among whom 202 incident prostate cancers (54 advanced) occurred. Mean follow-up time for non-cases was 7.7 years.

Dietary variables

The dietary variables used in this study were mean daily intakes of dietary total energy, fat, saturated FA, monounsaturated FA, polyunsaturated FA, palmitoleic acid, oleic acid, LA, ALA, AA, EPA, DHA, the sum of EPA and DHA, sum of ω 3 FA (20:5+22:5+22:6+18:3) and ω 6 FA (20:4+18:2), and the ω 3: ω 6 intake ratio. Calcium intake, and consumption of red meat, fruits, and vegetables were included as potential confounders. Intake from EPA- and DHA-containing supplements were included in some analyses, for which variables on total EPA and DHA intakes were created.

In the statistical analyses, the food and nutrient variables were adjusted for total energy intake (residual method) (33). This procedure allows comparison of intakes independently of energy requirements, and also diminishes the influence of measurement errors (33,34).

Other variables

A structured multiple-choice questionnaire was used in the MDC study to collect information on sociodemographic factors, smoking status, alcohol habits, health status, and several other

factors. The agreement between the baseline questionnaire and the same questionnaire when repeated after three weeks was high for most variables (kappa values > 0.75) (27).

Statistical methods

We examined the associations between prostate cancer incidence (total, advanced, and occurring before age 65 y) and intake of groups of fatty acids, and of individual fatty acids. The energy-adjusted intake variables were divided into quintile groups. The hazard ratios of each distribution quintile (compared to the lowest), and trends across the quintiles, were assessed with Cox' proportional hazards regression, with adjustment for age at baseline. The time variable was number of days of follow-up after baseline. All fat analyses were stratified on dietary assessment method version.

We then repeated the analyses above with adjustment for a number of potential confounders (age, diabetes, waist circumference, height, living alone/with partner/with other, educational level, alcohol habits, BMI, smoking history, birth country (Sweden/other), total calcium intake, consumption of fruits, vegetables, and red meat), selected from a survey of the current scientific literature.

All EPA- and DHA-related analyses were repeated with the inclusion of intake of EPA and DHA from supplements.

In a series of sensitivity analyses, we repeated all analyses after exclusion of men who reported having changed dietary habits (630 cases remaining), cases in which the cause of the diagnosis was not symptoms (478 cases remaining), persons not born in Sweden (748 cases remaining), persons who were considered to be misreporters of total energy intake (as described previously (35)) (714 remaining cases) and cases occurring within two years of the beginning of follow-up (691 remaining cases). We also analysed the effect of adjustment for dietary interviewer and season of dietary interview.

We also performed Cox regressions in which age (in quarters of years) was used as a stratification variable, with adjustment for the year of entry into the cohort, in order to assess the effects of using a more thorough adjustment for age.

Statistical tests resulting in *p* values lower than, or equal to, 0.050 were considered statistically significant. All statistical analyses were performed with SPSS for Windows, version 12.0.1 (SPSS Inc., Chicago, IL, U.S.A.).

Results

Table 1 shows the ages of the cases and non-cases, and some clinical characteristics of the tumors. In the entire cohort, cases were older than non-cases at the start of the study, particularly men with advanced disease. In the younger sub-cohort, cases were younger than non-cases.

The associations between the risk of prostate cancer, and the different dimensions of fat intake, are given in Table 2. Higher intake of EPA and DHA, alone or in combination, was associated with increased total risk of prostate cancer. For example, the hazard ratio for highest vs. lowest quintile of DHA was 1.35 (95% confidence interval 1.07-1.69; *p* for trend = 0.021). No other examined dimension of fat intake was significantly associated with total prostate cancer risk. After adjustment for potential confounders, the risk estimates between EPA and DHA and total prostate cancer risk were similar, but the associations were weaker (Table 2). EPA and the sum of EPA and DHA were no longer significant (*p* for trend=0.067 and 0.063, respectively).

None of the fat intake variables were significantly associated with risk of advanced or younger prostate cancer (Tables 3-4).

The number of men who used EPA/DHA supplements at least once during the 7-day registration period was 327. There were no statistically significant differences in frequency of

supplement use between cases, advanced cases and non-cases (Fisher's exact test, data not shown). Adding the supplemental intake from the 327 men to the dietary data did not change the results on total prostate cancer to any great extent, neither in the age-adjusted analysis, nor in the multivariate analysis (Table 5). The same was true of the analyses featuring advanced cases and younger cases (data not shown).

Sensitivity analysis

Exclusion of asymptomatic cases resulted in slightly higher risk estimates for increasing intakes of age-adjusted DHA (RR for highest quintile of DHA = 1.49, 95% CI 1.10-2.02; $p=0.018$) with total prostate cancer. The same was true of the EPA+DHA combination (data not shown). Similarly, exclusion of cases occurring within two years of the beginning of follow-up resulted in virtually unchanged results for these fatty acids, only with slightly higher p values. However, all other exclusions (men who changed dietary habits, men not born in Sweden, and men who were considered to be misreporters of total energy intake) yielded weaker, non-significant trends for these and other fat intake variables. This was also true of the sensitivity analyses featuring adjustments for multiple potential confounders. Adjustment for interviewer and season of dietary interview did not change the results appreciably (data not shown).

The age- and energy-adjusted results on dietary+supplementary EPA/DHA and total prostate cancer (Table 5) were slightly more robust than the corresponding data without supplements (Table 2); they remained significant even after exclusion of cases without symptoms, cases occurring within two years of follow-up and (for EPA only) persons who had changed their diet (data not shown).

Using age (in quarters of years) as a stratification variable (as described above) did not change the results appreciably (data not shown).

Discussion

Total and saturated fat intake are often considered established risk factors of prostate cancer, although they were judged to be only “possible” causes of increased risk in a major review (36). Few studies with validated methods and adequate energy adjustment have confirmed this association (6,15). We found no association between intake of total, saturated or mono-unsaturated fat and risk of prostate cancer, in spite of high relative validity, good power and reasonably wide ranges of intake (the 95th percentiles being circa 3 times greater than the 5th for the major FA groups; not shown). The upper limit of the 95-percent confidence intervals for the relative risk estimates for the highest quintile of total and saturated fat intakes was only 1.19. Considering the CI:s for the other quintiles, this translates into a maximum attributable fraction for saturated fat of about 4 percent (37). This, in turn, implies that a major role of these nutrients in prostate cancer etiology is unlikely, although it is plausible that non-differential misclassification due to measurement errors deflates this number.

We observed positive associations between EPA/DHA intakes and risk, although the current literature generally points towards either no association or inverse associations (4,15,38). The meta-analysis by Dennis et al. (17) also reported a positive association; however, this result was based on two studies only, none of which reported statistically significant trends (12,13). Further, since the publication of this meta-analysis, at least two studies have reported significant inverse associations (15,20). The associations in our study were rather weak, but quite robust. For example, they were only slightly weakened by multiple adjustments for potential confounders (Table 2). The associations disappeared after most relevant exclusions (see above), but not consistently. It could also be argued that the disappearing associations are partly the effect of lower power due to fewer cases, since the estimates were often similar to the ones in the main analyses. On the other hand, we have not been able to find any reports of experimental work claiming EPA or DHA to be involved in prostate carcinogenesis.

EPA and DHA in the diet originates almost exclusively from fatty fish. It may be worth noting that fatty fish, not least from the Baltic Sea, is a source of environmental toxins such as polychlorinated biphenyls (PCBs) (39), which are known to disrupt estrogen, androgen, and other endocrine systems (40). There are reports associating PCB exposure with risk of prostate cancer (41), which means that the EPA/DHA-prostate cancer association could be confounded by environmental toxins. Further, in a recent prospective study from Japan, a country with traditionally high fish consumption, fish consumption was associated with increased risk (21).

The associations between EPA/DHA and prostate cancer were not significant in the analyses of more advanced disease and disease at younger ages. This suggests that detection bias may be involved – men reporting higher levels of EPA/DHA intakes may be more health-conscious, and may therefore be more likely to visit a doctor. This could lead to a higher chance of early diagnosis. On the other hand, the trend for total prostate cancer was still significant after exclusion of asymptomatic cases.

Another possibility is Berksonian bias (42) – in this case, health-conscious men could conceivably have a greater chance of surviving long enough for a detectable prostate cancer to develop. However, in a post-hoc analysis, EPA/DHA intake was still significantly associated with increased total risk of prostate cancer even after adjusting for all variables significantly associated with mortality (data not shown).

Finally, it is of course always possible that the finding is either an effect of residual confounding, or a spurious result of multiple comparisons.

We observed no association between risk of prostate cancer and ALA intake. The relative validity of the MDC dietary assessment method is generally very good, compared to methods used in similar studies (43). However, the relative validity of ALA (and LA) intake in men is

comparatively low in the MDC study. The most important sources of ALA (and LA) are fats and vegetable oils. It is likely that many participating men did not know the type of fats used in the cooking of their meals or which brand of butter/margarine spread was used on their sandwiches. Because of the highly variable fatty acid composition of these fats, this may have resulted in misclassification. Thus, our findings on ALA and prostate cancer risk can hardly be said to either support or contradict an association.

Similar validity problems exist with regard to EPA/DHA intakes. As noted above, the dominant source of EPA and DHA is fatty fish. The diet method was designed to capture information on main courses by having them registered for one consecutive week, but most consumers of fatty fish in Malmö do not have it every week. This could lead to misclassification. Further, participants may not always know the kind of fish consumed during the 7-day registration. However, it must be stressed that a low validity normally does not distort measured associations; instead, it tends to make them weaker. Thus, the positive association between EPA/DHA intake and prostate cancer in this study is probably not directly caused by low validity.

It might seem strange that the cancer cases were younger than the non-cases at screening in the <65 subcohort (Table 1). However, this result is most likely an artifact produced by differences in follow-up time. The average follow-up time in men aged 45-49 was around 4500 days, compared to only 900 days for those aged 60-64, since the latter group obviously were much closer to the censoring point, their 65th birthday. Therefore, even if the relative risk in the older group was much higher than in the younger groups, the absolute risk was smaller.

We did not observe any significant associations between fat intake and advanced or younger-age cancer. The findings in these groups were mostly similar to those in the overall group, but since there were far fewer cases in these groups than in the total prostate cancer group, the

statistical power was obviously correspondingly lower. Further, several PUFA variables suffered from low relative validity in men, which also lowers power.

Conclusions

This large prospective study showed no association between incidence of total and advanced prostate cancer and intake of total, saturated and mono-unsaturated fat. We found no evidence of a protective role of EPA or DHA in total or advanced prostate cancer; indeed, we observed a modestly increased risk of total prostate cancer at higher intakes, a result we find difficult to interpret. We found no support for a causative role of ALA, but for this fatty acid, the validity of our dietary method is suboptimal. Finally, we observed no association between fat intake and incidence of advanced prostate cancer, or prostate cancer in men < 65 y.

Acknowledgments: We would like to thank Ulla Lindström, RN, Dept of Urology, Malmö University Hospital for retrieval of clinical data. We also thank the staff and participants of the Malmö Diet and Cancer Study.

Table 1. Age distribution of the study groups, and characteristics of the prostate cancer cases.

	Entire cohort (n=10,564)			Young sub-cohort (< 65 y; n=8,194)	
	Non-cases (n=9,747)	All cases (n=817)	Advanced cases (n=281)	Non-cases (n=7,992)	Cases (n=202)
	Mean (SD) / n	Mean (SD) / n	Mean (SD) / n	Mean (SD) / n	Mean (SD) / n
Age (y)	58.7 (7.0)	61.8 (6.3)	63.3 (6.0)	56.2 (5.2)	54.4 (3.9)
Tumor stage					
T1		337	35		95
T2		273	49		63
T3		179	179		33
T4		16	16		6
Tx		9	2		4
Sum		814	281		201
N0		215	86		67
N1		15	15		2
Nx		573	177		130
Sum		803	278		199
M0		437	168		112
M1		62	62		12
Mx		304	47		75
Sum		803	277		199
Gleason score					
≤ 6		402	48		119
7		188	89		30
≥ 8		89	89		13
Sum		679	226		162
WHO grade					
G1		198	26		54
G2		366	92		101
G3		184	135		32
GX		44	12		13
Sum		792	265		200
Serum PSA (ng/mL)^a					
< 20.0		582	116		156
20.0-49.9		130	68		27
≥ 50.0		90	90		18
Sum		802	274		201

^a Pre-treatment value.

Table 2. Quintiles of dietary fat intake (medians), adjusted for energy intake,^b with number of incident cases of prostate cancers. Hazard ratios with 95% confidence intervals. Rates and *p* values further adjusted for age (“age-adjusted RR”) and for selected background factors (“multivariate RR”) ^c.

	Q1 (n=2112)	Q2 (n=2113)	Q3 (n=2113)	Q4 (n=2113)	Q5 (n=2113)	<i>p for trend</i>
Fat, g	86.1	98.3	106.5	114.7	127.6	
Range	11.2-93.3	93.3-102.6	102.6-110.4	110.4-120.0	120.0-188.6	
Cases (n)	174	162	152	159	170	
Age-adjusted RR	1.00	0.92	0.85	0.90	0.96	0.69
95% CI		0.74-1.14	0.68-1.05	0.73-1.12	0.78-1.19	
Multivariate RR ^d	1.00	0.91	0.84	0.90	0.99	0.89
95% CI		0.73-1.13	0.67-1.05	0.72-1.13	0.79-1.24	
Saturated fat, g	33.1	39.2	43.7	49.2	58.8	
Range	2.1-36.6	36.6-41.6	41.6-46.2	46.2-52.9	53.0-103.1	
Cases (n)	182	163	154	139	179	
Age-adjusted RR		0.87	0.83	0.76	0.97	0.46
95% CI		0.70-1.07	0.67-1.03	0.61-0.95	0.79-1.19	
Multivariate RR	1.00	0.84	0.80	0.75	0.98	0.57
95% CI		0.68-1.04	0.65-1.00	0.60-0.94	0.79-1.22	
Mono-unsaturated fat, g	29.6	34.3	37.3	40.4	45.1	
Range	1.2-32.4	32.4-35.8	35.8-38.8	38.8-42.3	42.4-74.1	
Cases (n)	162	164	168	161	162	
Age-adjusted RR		0.98	0.99	0.97	0.99	0.90
95% CI		0.79-1.22	0.80-1.23	0.78-1.21	0.80-1.23	
Multivariate RR	1.00	0.97	0.97	0.97	1.01	0.93
95% CI		0.78-1.21	0.78-1.22	0.77-1.22	0.80-1.29	
Poly-unsaturated fat, g	12.0	14.6	16.7	19.0	23.0	

^b Adjusted to the geometric mean energy intake (2523 kcal per day).

^c Age, diabetes, waist circumference, height, living alone/with partner/with other (categorical), educational level (ordinal), alcohol habits (categorical), BMI (categorical), smoking history (ordinal), birth country (Sweden/other; categorical), total calcium intake, consumption of fruits, vegetables, and red meat. All dietary variables were energy-adjusted.

^d Sixty-five men had missing values for one or more of the included variables. Therefore, the total number of cases was reduced to 814 in these analyses.

Range	4.9-13.5	13.5-15.7	15.7-17.8	17.8-20.6	20.6-41.6	
Cases (n)	176	154	161	144	182	
Age-adjusted RR		0.85	0.90	0.78	1.02	0.88
95% CI		0.68-1.05	0.73-1.12	0.63-0.97	0.83-1.25	
Multivariate RR	1.00	0.85	0.89	0.79	1.05	0.90
95% CI		0.68-1.06	0.72-1.11	0.63-0.99	0.84-1.30	
Palmitoleic acid (16:1), g	1.5	1.9	2.1	2.4	2.8	
Range	0.1-1.7	1.7-2.0	2.0-2.2	2.2-2.5	2.5-5.7	
Cases (n)	159	157	155	178	168	
Age-adjusted RR	1.00	0.95	0.93	1.10	1.03	0.41
95% CI		0.76-1.19	0.75-1.16	0.88-1.36	0.83-1.28	
Multivariate RR	1.00	0.92	0.89	1.05	0.99	0.66
95% CI		0.73-1.15	0.71-1.12	0.84-1.31	0.78-1.25	
Oleic acid (18:1), g	26.4	30.5	33.4	36.2	40.5	
Range	1.0-28.8	28.8-32.0	32.0-34.7	34.7-37.9	37.9-67.4	
Cases (n)	169	171	160	159	158	
Age-adjusted RR	1.00	1.00	0.92	0.94	0.96	0.56
95% CI		0.81-1.23	0.74-1.15	0.76-1.17	0.77-1.19	
Multivariate RR	1.00	0.98	0.91	0.94	0.97	0.70
95% CI		0.79-1.22	0.73-1.13	0.75-1.18	0.76-1.24	
Linoleic acid (18:2), g	9.0	11.3	13.2	15.3	18.9	
Range	1.7-10.3	10.3-12.3	12.3-14.3	14.3-16.8	16.8-37.2	
Cases (n)	180	147	164	156	170	
Age-adjusted RR		0.81	0.92	0.86	0.96	0.90
95% CI		0.65-1.01	0.74-1.14	0.69-1.06	0.78-1.19	
Multivariate RR	1.00	0.79	0.90	0.85	0.98	0.95
95% CI		0.63-0.98	0.73-1.12	0.68-1.06	0.79-1.22	
α-linolenic acid (18:3), g	1.4	1.7	2.0	2.3	2.7	
Range	0.5-1.6	1.6-1.9	1.9-2.1	2.1-2.4	2.4-10.7	
Cases (n)	178	156	157	165	161	
Age-adjusted RR		0.85	0.88	0.90	0.88	0.40
95% CI		0.69-1.05	0.71-1.09	0.73-1.12	0.71-1.09	
Multivariate RR	1.00	0.85	0.88	0.91	0.92	0.66

95% CI		0.69-1.06	0.71-1.10	0.73-1.13	0.73-1.15	
Arachidonic acid (20:4), g	0.11	0.15	0.18	0.21	0.27	
Range	0.00-0.13	0.13-0.16	0.16-0.19	0.19-0.23	0.23-0.90	
Cases (n)	144	182	162	171	158	
Age-adjusted RR	1.00	1.29	1.13	1.20	1.10	0.68
95% CI		1.04-1.60	0.90-1.41	0.96-1.50	0.88-1.38	
Multivariate RR	1.00	1.25	1.09	1.15	1.07	0.98
95% CI		1.00-1.57	0.86-1.37	0.91-1.45	0.83-1.37	
EPA (20:5), g	0.03	0.08	0.14	0.23	0.44	
Range	0.00-0.05	0.05-0.11	0.11-0.18	0.18-0.31	0.31-2.01	
Cases (n)	125	144	185	160	203	
Age-adjusted RR	1.00	1.09	1.33	1.09	1.33	0.026
95% CI		0.86-1.38	1.06-1.68	0.86-1.38	1.07-1.67	
Multivariate RR	1.00	1.06	1.27	1.05	1.28	0.067
95% CI		0.83-1.35	1.01-1.60	0.82-1.33	1.02-1.61	
DHA (22:6), g	0.12	0.20	0.30	0.48	0.86	
Range	0.00-0.16	0.16-0.25	0.25-0.38	0.38-0.63	0.63-3.37	
Cases (n)	118	158	168	179	194	
Age-adjusted RR	1.00	1.26	1.29	1.32	1.35	0.021
95% CI		1.00-1.60	1.02-1.63	1.05-1.67	1.07-1.69	
Multivariate RR	1.00	1.23	1.26	1.29	1.29	0.048
95% CI		0.96-1.56	0.99-1.60	1.02-1.63	1.02-1.64	
EPA+DHA, g	0.16	0.28	0.44	0.72	1.30	
Range	0.00-0.22	0.22-0.35	0.35-0.56	0.56-0.94	0.94-5.38	
Cases (n)	119	152	178	175	193	
Age-adjusted RR	1.00	1.22	1.37	1.27	1.33	0.026
95% CI		0.96-1.55	1.08-1.72	1.00-1.60	1.06-1.68	
Multivariate RR	1.00	1.18	1.33	1.23	1.28	0.063
95% CI		0.93-1.50	1.05-1.68	0.97-1.56	1.01-1.62	
Total ω-3, g	1.8	2.3	2.6	3.0	3.8	
Range	0.6-2.1	2.1-2.5	2.5-2.8	2.8-3.3	3.3-11.2	
Cases (n)	157	145	158	165	192	
Age-adjusted RR	1.00	0.91	0.96	0.95	1.08	0.39
95% CI		0.72-1.14	0.77-1.19	0.77-1.19	0.87-1.33	

Multivariate RR	1.00	0.91	0.95	0.94	1.09	<i>0.39</i>
95% CI		0.72-1.14	0.76-1.19	0.75-1.18	0.87-1.35	
Total ω-6, g	9.2	11.5	13.4	15.5	19.1	
Range	1.8-10.5	10.5-12.5	12.5-14.4	14.4-17.0	17.0-37.4	
Cases (n)	180	144	170	152	171	
Age-adjusted RR	1.00	0.80	0.96	0.84	0.97	<i>0.93</i>
95% CI		0.64-0.99	0.78-1.18	0.67-1.04	0.79-1.20	
Multivariate RR	1.00	0.77	0.94	0.83	0.99	<i>0.91</i>
95% CI		0.62-0.97	0.76-1.17	0.66-1.03	0.79-1.23	
ω-3:ω-6 ratio	0.14	0.17	0.19	0.23	0.30	
Range	0.05-0.15	0.15-0.18	0.18-0.21	0.21-0.25	0.25-1.67	
Cases (n)	159	148	174	156	180	
Age-adjusted RR	1.00	0.88	0.99	0.87	0.96	<i>0.75</i>
95% CI		0.70-1.10	0.80-1.24	0.70-1.09	0.77-1.19	
Multivariate RR	1.00	0.85	0.96	0.84	0.94	<i>0.60</i>
95% CI		0.68-1.07	0.77-1.19	0.67-1.05	0.75-1.17	

Table 3. Quintiles of dietary fat intake (medians), with number of incident cases of advanced prostate cancers.^e Hazard ratios with 95% confidence intervals. Rates and *p* values further adjusted for age (“age-adjusted RR”) and for selected background factors (“multivariate RR”) ^f.

	Q1	Q2	Q3	Q4	Q5	<i>p</i> for trend
Fat, g						
Cases (n)	53	57	50	59	62	
Age-adjusted RR	1.00	1.04	0.89	1.07	1.11	0.55
95% CI		0.71-1.51	0.60-1.31	0.74-1.55	0.77-1.61	
Multivariate RR ^g	1.00	1.02	0.89	1.07	1.11	0.57
95% CI		0.70-1.50	0.60-1.31	0.73-1.58	0.75-1.66	
Saturated fat, g						
Cases (n)	57	52	52	54	66	
Age-adjusted RR	1.00	0.85	0.87	0.91	1.10	0.52
95% CI		0.59-1.24	0.60-1.27	0.62-1.32	0.77-1.57	
Multivariate RR	1.00	0.83	0.87	0.90	1.08	0.57
95% CI		0.57-1.22	0.59-1.27	0.61-1.32	0.74-1.57	
Mono-unsaturated fat, g						
Cases (n)	50	54	57	58	62	
Age-adjusted RR	1.00	1.02	1.05	1.10	1.20	0.30
95% CI		0.70-1.50	0.72-1.54	0.75-1.60	0.83-1.74	
Multivariate RR	1.00	1.01	1.04	1.10	1.22	0.31
95% CI		0.68-1.49	0.70-1.53	0.74-1.63	0.80-1.84	
Poly-unsaturated fat, g						
Cases (n)	63	59	51	45	63	
Age-adjusted RR	1.00	0.90	0.80	0.67	1.00	0.52
95% CI		0.63-1.28	0.56-1.16	0.46-0.99	0.70-1.42	
Multivariate RR	1.00	0.89	0.80	0.68	1.04	0.67
95% CI		0.62-1.27	0.55-1.16	0.46-1.01	0.72-1.50	

^e An advanced case was defined as being either stage T3+ or N1 or M1 or having a Gleason score of 8+ or having a prediagnostic serum PSA value of at least 50 ng/mL or being of WHO grade 3 in the absence of a Gleason score (see Methods).

^f Age, diabetes, waist circumference, height, living alone/with partner/with other (categorical), educational level (ordinal), alcohol habits (categorical), BMI (categorical), smoking history (ordinal), birth country (Sweden/other; categorical), total calcium intake, consumption of fruits, vegetables, and red meat. All dietary variables were energy-adjusted.

^g Sixty-five men had missing values for one or more of the included variables. Therefore, the total number of cases was reduced to 280 in these analyses.

Palmitoleic acid, (16:1), g

Cases (n)	58	48	52	52	71	0.29
Age-adjusted RR	1.00	0.78	0.84	0.87	1.16	
95% CI		0.53-1.14	0.57-1.22	0.60-1.26	0.82-1.64	
Multivariate RR	1.00	0.73	0.78	0.80	1.03	0.64
95% CI		0.50-1.08	0.53-1.15	0.54-1.18	0.71-1.51	

Oleic acid (18:1), g

Cases (n)	53	56	58	55	59	
Age-adjusted RR	1.00	1.02	1.04	1.02	1.12	0.58
95% CI		0.70-1.48	0.72-1.51	0.70-1.49	0.77-1.63	
Multivariate RR	1.00	1.01	1.02	1.03	1.13	0.59
95% CI		0.69-1.47	0.69-1.50	0.69-1.53	0.74-1.70	

Linoleic acid, g (18:2)

Cases (n)	71	47	48	53	62	
Age-adjusted RR	1.00	0.67	0.70	0.75	0.93	0.83
95% CI		0.46-0.96	0.48-1.01	0.52-1.07	0.66-1.31	
Multivariate RR	1.00	0.64	0.69	0.75	0.95	0.99
95% CI		0.44-0.93	0.48-1.00	0.52-1.08	0.67-1.36	

 α -linolenic acid (18:3), g

Cases (n)	61	42	54	66	58	
Age-adjusted RR	1.00	0.66	0.87	1.02	0.89	0.71
95% CI		0.44-0.98	0.60-1.25	0.72-1.44	0.62-1.27	
Multivariate RR	1.00	0.66	0.87	1.01	0.93	0.57
95% CI		0.44-0.98	0.60-1.27	0.70-1.45	0.64-1.36	

Arachidonic acid (20:4), g

Cases (n)	56	60	52	54	59	
Age-adjusted RR	1.00	1.11	0.93	0.99	1.08	0.91
95% CI		0.77-1.59	0.64-1.36	0.68-1.43	0.75-1.56	
Multivariate RR	1.00	1.05	0.87	0.88	0.98	0.65
95% CI		0.72-1.52	0.59-1.29	0.59-1.32	0.65-1.47	

EPA (20:5), g

Cases (n)	49	55	61	51	65	
Age-adjusted RR	1.00	1.03	1.06	0.83	0.99	0.61
95% CI		0.70-1.51	0.73-1.54	0.56-1.23	0.68-1.44	

Multivariate RR	1.00	0.99	1.00	0.79	0.95	0.50
95% CI		0.67-1.45	0.68-1.46	0.53-1.18	0.65-1.40	
DHA (22:6), g						
Cases (n)	43	66	56	61	55	
Age-adjusted RR	1.00	1.39	1.13	1.16	0.96	0.42
95% CI		0.94-2.04	0.76-1.68	0.78-1.71	0.64-1.43	
Multivariate RR	1.00	1.30	1.08	1.11	0.91	0.34
95% CI		0.88-1.92	0.72-1.61	0.75-1.65	0.61-1.37	
EPA+DHA, g						
Cases (n)	46	59	60	61	55	
Age-adjusted RR	1.00	1.19	1.13	1.07	0.90	0.42
95% CI		0.81-1.75	0.77-1.66	0.73-1.57	0.61-1.34	
Multivariate RR	1.00	1.12	1.09	1.04	0.86	0.34
95% CI		0.76-1.66	0.74-1.61	0.70-1.53	0.58-1.28	
Total ω-3, g						
Cases (n)	57	47	43	68	66	
Age-adjusted RR	1.00	0.80	0.70	1.02	0.94	0.72
95% CI		0.54-1.17	0.47-1.03	0.72-1.45	0.66-1.34	
Multivariate RR	1.00	0.78	0.68	0.98	0.95	0.71
95% CI		0.53-1.15	0.45-1.01	0.68-1.41	0.65-1.37	
Total ω-6, g						
Cases (n)	70	47	49	53	62	
Age-adjusted RR	1.00	0.67	0.73	0.76	0.95	0.91
95% CI		0.47-0.98	0.51-1.05	0.53-1.09	0.67-1.33	
Multivariate RR	1.00	0.65	0.72	0.76	0.97	0.92
95% CI		0.44-0.94	0.50-1.05	0.53-1.09	0.68-1.39	
ω-3:ω-6 ratio, g						
Cases (n)	51	53	67	50	60	
Age-adjusted RR	1.00	0.93	1.11	0.79	0.89	0.35
95% CI		0.63-1.36	0.77-1.61	0.53-1.17	0.61-1.29	
Multivariate RR	1.00	0.88	1.05	0.74	0.85	0.27
95% CI		0.60-1.30	0.73-1.52	0.49-1.09	0.58-1.25	

Table 4. Quintiles of dietary fat intake (medians), adjusted for energy intake,^h with number of incident cases of prostate cancers in persons aged < 65 years. Hazard ratios with 95% confidence intervals. Rates and *p* values further adjusted for age (“age-adjusted RR”) and for selected background factors (“multivariate RR”) ⁱ.

	Q1 (n=1638)	Q2 (n=1639)	Q3 (n=1639)	Q4 (n=1639)	Q5 (n=1639)	<i>p for trend</i>
Fat, g	85.8	98.2	106.2	114.5	127.5	
Range	11.2-92.9	92.9-102.5	102.5-110.1	110.1-119.9	119.9-188.6	
Cases (n)	46	36	33	40	47	
Age-adjusted RR	1.00	0.77	0.72	0.84	1.06	0.69
95% CI		0.50-1.19	0.46-1.12	0.55-1.28	0.70-1.59	
Multivariate RR ^j	1.00	0.74	0.69	0.80	1.04	0.76
95% CI		0.48-1.15	0.44-1.09	0.51-1.24	0.67-1.62	
Saturated fat, g	32.8	39.0	43.5	48.8	58.3	
Range	2.1-36.4	36.4-41.3	41.3-45.9	45.9-52.6	52.6-103.1	
Cases (n)	45	46	33	30	48	
Age-adjusted RR	1.00	1.02	0.74	0.66	1.08	0.64
95% CI		0.67-1.53	0.47-1.15	0.41-1.04	0.72-1.63	
Multivariate RR	1.00	0.97	0.71	0.63	1.07	0.63
95% CI		0.64-1.47	0.45-1.12	0.39-1.01	0.70-1.65	
Mono-unsaturated fat, g	29.5	34.2	37.3	40.4	45.1	
Range	1.2-32.2	32.2-35.8	35.8-38.8	38.8-42.3	42.3-74.1	
Cases (n)	42	34	46	38	42	
Age-adjusted RR	1.00	0.82	1.11	0.90	1.04	0.75
95% CI		0.52-1.28	0.73-1.69	0.58-1.40	0.68-1.59	
Multivariate RR	1.00	0.81	1.04	0.84	1.02	0.89
95% CI		0.51-1.28	0.67-1.60	0.53-1.34	0.63-1.64	
Poly-unsaturated fat, g	12.1	14.8	16.8	19.1	23.1	

^h Adjusted to the geometric mean energy intake (2523 kcal per day).

ⁱ Age, diabetes, waist circumference, height, living alone/with partner/with other (categorical), educational level (ordinal), alcohol habits (categorical), BMI (categorical), smoking history (ordinal), birth country (Sweden/other; categorical), total calcium intake, consumption of fruits, vegetables, and red meat. All dietary variables were energy-adjusted.

^j Forty-six men had missing values for one or more of the included variables. However, the total number of cases was still 202 in these analyses.

Range	4.9-13.6	13.6-15.8	15.8-17.9	17.9-20.7	20.7-41.6	
Cases (n)	33	41	47	34	47	
Age-adjusted RR	1.00	1.30	1.44	1.06	1.46	0.26
95% CI		0.82-2.05	0.92-2.25	0.66-1.72	0.94-2.29	
Multivariate RR	1.00	1.25	1.38	1.04	1.42	0.34
95% CI		0.79-1.99	0.88-2.17	0.64-1.70	0.89-2.25	
Palmitoleic acid (16:1), g	1.5	1.9	2.1	2.4	2.8	
Range	0.1-1.7	1.7-2.0	2.0-2.2	2.2-2.5	2.5-5.0	
Cases (n)	42	40	37	35	48	
Age-adjusted RR	1.00	0.89	0.86	1.20	0.89	0.53
95% CI		0.57-1.39	0.55-1.35	0.79-1.81	0.57-1.39	
Multivariate RR	1.00	0.90	0.84	0.81	1.14	0.72
95% CI		0.58-1.41	0.53-1.32	0.51-1.30	0.72-1.80	
Oleic acid (18:1), g	26.3	30.5	33.3	36.3	40.6	
Range	1.0-28.7	28.7-32.0	32.0-34.7	34.7-38.0	38.0-67.4	
Cases (n)	42	38	38	41	43	
Age-adjusted RR	1.00	0.90	0.91	0.97	1.02	0.81
95% CI		0.58-1.40	0.59-1.41	0.63-1.50	0.67-1.57	
Multivariate RR	1.00	0.88	0.86	0.90	1.00	0.97
95% CI		0.56-1.37	0.55-1.35	0.57-1.42	0.62-1.60	
Linoleic acid (18:2), g	9.2	11.5	13.4	15.5	19.1	
Range	1.7-10.4	10.4-12.4	12.4-14.4	14.4-17.0	17.0-37.2	
Cases (n)	40	34	48	35	45	
Age-adjusted RR	1.00	0.87	1.21	0.87	1.11	0.66
95% CI		0.55-1.37	0.80-1.85	0.55-1.37	0.73-1.71	
Multivariate RR	1.00	0.82	1.15	0.84	1.06	0.79
95% CI		0.52-1.30	0.75-1.76	0.53-1.33	0.68-1.64	
α-linolenic acid (18:3), g	1.4	1.7	2.0	2.2	2.7	
Range	0.5-1.6	1.6-1.9	1.9-2.1	2.1-2.4	2.4-6.4	
Cases (n)	40	48	40	28	46	
Age-adjusted RR	1.00	1.25	1.01	0.71	1.20	0.80
95% CI		0.82-1.90	0.65-1.57	0.44-1.16	0.79-1.84	
Multivariate RR	1.00	1.22	0.97	0.68	1.16	0.67

95% CI		0.80-1.86	0.62-1.51	0.42-1.12	0.74-1.82	
Arachidonic acid (20:4), g	0.12	0.15	0.18	0.21	0.27	
Range	0.00-0.13	0.13-0.16	0.16-0.19	0.19-0.23	0.23-0.75	
Cases (n)	41	35	43	45	38	
Age-adjusted RR	1.00	0.87	1.07	1.13	0.94	0.78
95% CI		0.56-1.37	0.70-1.65	0.74-1.73	0.61-1.47	
Multivariate RR	1.00	0.85	1.00	1.06	0.88	0.98
95% CI		0.53-1.34	0.64-1.56	0.67-1.67	0.54-1.44	
EPA (20:5), g	0.03	0.07	0.13	0.22	0.43	
Range	0.00-0.05	0.05-0.10	0.10-0.17	0.17-0.30	0.30-1.55	
Cases (n)	44	31	46	37	44	
Age-adjusted RR	1.00	0.75	1.15	0.98	1.20	0.22
95% CI		0.47-1.19	0.76-1.73	0.63-1.52	0.79-1.83	
Multivariate RR	1.00	0.75	1.09	0.96	1.16	0.32
95% CI		0.47-1.19	0.72-1.66	0.61-1.50	0.75-1.78	
DHA (22:6), g	0.12	0.19	0.29	0.46	0.83	
Range	0.00-0.16	0.16-0.24	0.24-0.36	0.36-0.60	0.60-2.84	
Cases (n)	41	35	41	40	45	
Age-adjusted RR	1.00	0.91	1.11	1.15	1.32	0.11
95% CI		0.58-1.43	0.72-1.71	0.74-1.78	0.86-2.02	
Multivariate RR	1.00	0.89	1.08	1.13	1.26	0.17
95% CI		0.56-1.40	0.70-1.68	0.72-1.76	0.81-1.95	
EPA+DHA, g	0.16	0.27	0.43	0.69	1.25	
Range	0.00-0.21	0.21-0.34	0.34-0.54	0.54-0.89	0.89-4.30	
Cases (n)	40	37	41	38	46	
Age-adjusted RR	1.00	0.98	1.12	1.12	1.39	0.11
95% CI		0.63-1.54	0.73-1.74	0.72-1.76	0.90-2.12	
Multivariate RR	1.00	0.98	1.09	1.11	1.33	0.16
95% CI		0.62-1.54	0.70-1.70	0.71-1.75	0.86-2.06	
Total ω-3, g	1.8	2.3	2.6	3.0	3.7	
Range	0.6-2.1	2.1-2.4	2.4-2.8	2.8-3.3	3.3-7.4	
Cases (n)	40	34	43	41	44	
Age-adjusted RR	1.00	0.90	1.13	1.14	1.27	0.16
95% CI		0.57-1.42	0.74-1.74	0.73-1.76	0.83-1.95	

Multivariate RR	1.00	0.89	1.11	1.08	1.26	<i>0.21</i>
95% CI		0.56-1.41	0.71-1.72	0.69-1.69	0.81-1.96	
Total ω-6, g	9.3	11.6	13.5	15.7	19.3	
Range	1.8-10.6	10.6-12.6	12.6-14.5	14.5-17.1	17.1-37.4	
Cases (n)	38	37	48	34	45	
Age-adjusted RR	1.00	1.00	1.27	0.89	1.17	<i>0.66</i>
95% CI		0.63-1.57	0.83-1.94	0.56-1.41	0.76-1.81	
Multivariate RR	1.00	0.94	1.20	0.86	1.11	<i>0.78</i>
95% CI		0.60-1.49	0.78-1.85	0.53-1.38	0.71-1.75	
ω-3:ω-6 ratio	0.14	0.16	0.19	0.22	0.29	
Range	0.05-0.15	0.15-0.17	0.17-0.20	0.20-0.25	0.25-1.67	
Cases (n)	46	33	50	38	35	
Age-adjusted RR	1.00	0.75	1.19	0.91	0.88	<i>0.88</i>
95% CI		0.48-1.17	0.80-1.78	0.59-1.40	0.57-1.37	
Multivariate RR	1.00	0.82	1.20	0.91	0.88	<i>0.81</i>
95% CI		0.53-1.25	0.80-1.78	0.59-1.40	0.55-1.40	

Table 5. Quintiles of total EPA and DHA intake, including dietary supplements, adjusted for energy intake,^k with number of incident cases of prostate cancer. Hazard ratios with 95% confidence intervals. Rates and *p* values further adjusted for age (“age-adjusted RR”) and for selected background factors (“multivariate RR”)^l.

	Q1	Q2	Q3	Q4	Q5	<i>p</i> for trend
EPA (20:5), g	0.04	0.09	0.16	0.26	0.47	
Range	0.01-0.06	0.06-0.12	0.12-0.20	0.20-0.34	0.34-3.55	
Cases (n)	122	146	179	168	202	
Age-adjusted RR	1.00	1.13	1.32	1.17	1.35	0.014
95% CI		0.89-1.43	1.05-1.67	0.93-1.48	1.08-1.70	
Multivariate RR ^m	1.00	1.09	1.26	1.12	1.30	0.043
95% CI		0.86-1.39	0.99-1.59	0.88-1.42	1.03-1.64	
DHA (22:6), g	0.13	0.21	0.32	0.50	0.88	
Range	0.01-0.17	0.17-0.26	0.26-0.40	0.40-0.64	0.64-3.27	
Cases (n)	121	161	157	184	194	
RR	1.00	1.25	1.17	1.32	1.31	0.027
95% CI		0.99-1.58	0.92-1.48	1.05-1.66	1.04-1.65	
Multivariate RR	1.00	1.21	1.13	1.28	1.26	0.062
95% CI		0.95-1.53	0.89-1.44	1.02-1.62	1.00-1.59	
EPA+DHA, g	0.16	0.29	0.45	0.74	1.33	
Range	0.00-0.22	0.22-0.36	0.36-0.58	0.58-0.95	0.95-6.06	
Cases (n)	123	149	173	176	196	
RR	1.00	1.15	1.27	1.23	1.31	0.023
95% CI		0.90-1.46	1.01-1.60	0.97-1.55	1.04-1.64	
Multivariate RR	1.00	1.11	1.23	1.18	1.26	0.056
95% CI		0.87-1.41	0.97-1.55	0.94-1.50	1.00-1.59	

^k Adjusted to the geometric mean energy intake (2523 kcal per day).

^l Age, diabetes, waist circumference, height, living alone/with partner/with other (categorical), educational level (ordinal), alcohol habits (categorical), BMI (categorical), smoking history (ordinal), birth country (Sweden/other; categorical), total calcium intake, consumption of fruits, vegetables, and red meat. All dietary variables were energy-adjusted.

^m Sixty-five men had missing values for one or more of the included variables. Therefore, the total number of cases was reduced to 814 in these analyses.

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