

# **Prostate cancer risk related to foods, food groups, macronutrients and micronutrients derived from the UK Dietary Cohort Consortium food diaries**

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**Short running head:** Dietary intake and prostate cancer risk

## ABSTRACT

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**Background/Objectives:** The influence of dietary factors remains controversial for screen-detected prostate cancer and inconclusive for clinically-detected disease. We aimed to examine these associations using prospective food records.

**Methods:** 1 717 prostate cancer cases in middle-aged and older UK men were pooled from four prospective cohorts with clinically-detected disease (n = 563) with routine data follow-up (means 6.6-13.3 years) and a case-control study with screen-detected disease (n = 1 054) nested in a randomised trial of prostate cancer treatments (ISCTRN 20141297). Multiple-day food diaries (records) completed by men prior to diagnosis were used to estimate intakes of 37 selected nutrients, food groups and items including carbohydrate, fat, protein, dairy products, fish, meat, fruit and vegetables, energy, fibre, alcohol, lycopene and selenium. Cases were matched on age and diary date to at least one control within study (n = 3 528). Prostate cancer risk was calculated using conditional logistic regression (adjusted for baseline covariates) and expressed as odds ratios per intake quintile ( $\pm$  95% confidence intervals). Prostate cancer risk was also investigated by localised or advanced stage and by cancer detection method.

**Results:** There were no strong associations between prostate cancer risk and 37 nutrients. Potentially heterogeneous associations of Vitamin D and fruit and vegetables with clinical or screen-detected disease, cheese reducing localised disease risk and high energy intake increasing advanced cancer risk require confirmation.

**Conclusions:** Prostate cancer risk, including by disease stage, was not strongly associated with dietary factors measured by food diaries in middle-aged and older UK men.

**Keywords:** prostate neoplasms; diet, food diary, cohort study, food records

## Introduction

Prostate cancer is the most commonly detected life-threatening cancer amongst men in most Western countries, and accounted for over 300 000 deaths worldwide in 2012 (1). The incidence of prostate cancer is increasing worldwide largely due to screening programmes and has doubled in the UK from 1984-2007 (2). The established risk factors for prostate cancer risk factors are age, ethnicity, family history of the disease and some genetic factors (3). Increasingly, obesity has been linked to aggressive prostate cancer risk (4). Prostate cancer incidence and mortality varies globally suggesting that diet and environmental factors may explain some geographic variation (5). Several hypotheses have been explored, including that prostate cancer risk may be elevated by diets rich in meat, dairy products or fat and may be lowered by diets high in fibre, fruit, vegetables and various micronutrients (5,6). The epidemiological evidence for selenium and vitamin E was judged sufficient to commence a randomised supplementation trial, but this was stopped early due to no benefit (7) with subsequent follow-up indicating an increased prostate cancer risk with vitamin E supplementation (8). The American Institute for Cancer Research/World Cancer Research Fund (AICR/WCRF) guidelines currently identify the carotenoid lycopene, a pigment found in tomatoes and other fruits as having a “probable” protective effect on prostate cancer risk (5) whilst diets rich in calcium as “probably” increasing prostate cancer risk.

Epidemiological studies of diet and cancer have predominantly utilised food-frequency questionnaires (FFQ) to measure intake (9). The greater measurement error associated with FFQs in relation to multiple day food diaries (records) has been suggested to account for some null findings for diet and cancer risk (10-11), although this is contested (12).

The UK Dietary Cohort Consortium was established in 2006 (13) to understand diet and cancer relationships using eight population-based studies with food diaries (records). We have utilised the consortium data to analyse prostate cancer risk in relation to dietary intake of food groups, meat, fish and dairy products, fruit and vegetables, lycopene, macronutrients and micronutrients potentially associated with disease.

## **PARTICIPANTS AND METHODS**

### **Study population**

Table 1 summarises the five UK Dietary Cohort Consortium studies that contributed data: European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk (14), EPIC-Oxford (15), Medical Research Council National Survey of Health and Development (NSHD) (16), Prostate testing for cancer and Treatment study ( ProtecT (17)) and Whitehall II (18). Two additional cohorts only recruited females and one focused on vegetarians so were excluded from this analysis. The study designs, ethical approvals and conduct have been described in detail elsewhere (14-18). Information on demographic and lifestyle factors was collected either during participant interviews or questionnaires administered prior to, or contemporaneously with, the completion of the food diary.

### **Ascertainment of prostate cancer and follow-up**

Four prospective cohort studies (EPIC-Norfolk, EPIC-Oxford, NSHD and Whitehall II) obtained prostate cancer diagnoses through record linkage with the UK National Health Service Office for National Statistics and cancer registries. Case participants were individuals who were undiagnosed with cancer (except non-melanoma skin cancer) at the time of diary completion and who were diagnosed with prostate cancer at least 12 months later (six months in EPIC-Oxford) but before the closure date for each cohort (latest date of complete follow-up for cancer incidence and vital status which was the same for cases and controls) (Table 1). The 9<sup>th</sup> and 10<sup>th</sup> Revisions of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD) were used to define prostate cancer (codes 185 or C61). Clinical staging data from cancer registries (where available) utilised the TNM system with T1-T2 (N0 or Nx, M0 or Mx) categorised as localised disease and advanced disease as T3-4.

ProtecT is an ongoing randomised controlled trial of treatments in men diagnosed with localised prostate cancer following community-based prostate specific antigen (PSA) testing in nine centres across the UK (17). Men aged 50-69 years registered at randomly selected general practices were invited to attend recruitment/PSA-testing clinics. There was no selection by symptoms or PSA status (13% had received a prior test) and the UK does not have a prostate cancer screening programme (19). Around 40% of invited men attended clinics between 2003-2009. Food diaries were distributed by trial nurses at recruitment to men also participating in the ProMPT translational study with over 75% returned prior to receipt of PSA results. Participants with an elevated PSA result ( $\geq 3.0$  ng/ml) underwent 10-core prostate biopsies (87% of those eligible received a biopsy) and those with a negative biopsy were offered a second biopsy. All men diagnosed with prostate cancer were cases with clinical stage categorised as described previously.

### **Selection of matched controls**

Cases were matched within an individual study to up to four control participants selected at random from all control participants within the matching criteria. Cohort controls were without notified prostate cancer at closure date for follow-up whilst ProtecT controls either had a PSA result of  $<3.0$  ng/ml or negative prostatic biopsies. Matching criteria within each study were participant age ( $\pm 3$  years from diary commencement) and month of diary completion ( $\pm 3$  months). As these studies commenced prior to the consortium there were some differences in matching for age ( $\pm 6$  months for EPIC-Oxford and  $\pm 5$  years for ProtecT) and for diary completion date ( $\pm 6$  months EPIC-Oxford).

### **Measurement of food and nutrient intake**

Seven-day food diaries (five-day in NSHD) were completed at recruitment (EPIC-Norfolk and ProtecT) or approximately six months later (EPIC-Oxford) or at second follow-up (Whitehall II) or when participants were 43 years old (NSHD). Participants were asked to

record all food and drinks consumed at times specified (e.g. breakfast, lunch) with photographs of food items to aid estimation of portion sizes. Information from food diaries was coded to derive nutrient intakes based on national food composition tables contemporaneous with diary completion dates as described previously (13). The food groups were defined by the consortium: red meat, processed meat, poultry, white and oily fish and included disaggregation of dishes containing constituent foods (20). EPIC-Norfolk, EPIC-Oxford, Whitehall II and 1,107 ProtecT diaries were coded with the Data Into Nutrients for Epidemiological Research (DINER) data entry and DINERMO processing software (21) whilst NSHD and 1,208 of the ProtecT diaries (coded before joining the consortium but case/control pairs coded with the same software) used the Diet In Data Out (DIDO) programme (22). Some NSHD (100) and ProtecT (99) diaries were processed with DIDO and DINER and there was good agreement for total energy, carbohydrate, fat, calcium, total sugars and starch intakes. The DIDO programme gave lower values for alcohol intake than DINER which we hypothesised reflected UK alcohol measures having increasing over time so the DIDO estimates were retained as they were determined contemporaneously to diary completion.

## **Statistical methods**

The pre-specified consortium analysis plan for all cancers defined the selection and categorisation of dietary exposures and confounders with lycopene and selenium added to the prostate plan based on AICR/WCRF guidelines for prostate cancer prevention (5). Analyses used all available data, including diaries with incomplete days. Conditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (95% CI) for prostate cancer risk according to quintiles of intake of 37 dietary variables (quintiles calculated on intakes combined across studies for all participants) with the p value for trend test being of principal interest. There was a high proportion of non-consumers of oily fish (first and second quintiles were combined) and yoghurt (first three combined), whilst five cut-



points were used for alcohol consumption (<1, 1-9, 10-19, 20-39, 40 and above g/d). To test for trends in prostate cancer risk across the distribution of intakes we calculated the ORs (95% CI) for a one standard deviation increase in nutrient intake with the p value being obtained by comparing the ratio of the logarithm of the OR and its standard error to the normal distribution.

As age is a risk factor for prostate cancer, age was utilised as a continuous variable in the regression models. Additional adjustment was made for other potential confounders, i.e. total energy intake (quintiles), body mass index (BMI: <22.5, 22.5-24.9, 25.0-27.4, 27.5-29.9, 30.0 and above, unknown kgm<sup>-2</sup>), smoking status (never, previous, current, unknown), marital status (married or cohabiting, single including divorced and separated, unknown), self-reported diabetes at recruitment (no, yes, unknown) and a residential area-based measure of material deprivation (quartiles of Townsend Score) (23). Unknown values were categorised as missing (BMI 6%; smoking 5%; marital status 1%; diabetes 8%; socioeconomic measure 3%), except for energy. Prostate cancer risk was also assessed for the cohort studies combined (i.e. predominantly clinically-diagnosed disease) and for PSA-detected disease ( ProtecT study, akin to screening) and reported as a one standard deviation in dietary intake. Disease-diet associations were also examined and reported in the same way for localised and advanced prostate cancer. Analyses were performed using Stata version 10 (24).

## RESULTS

### Study and participant characteristics

In total, 1 717 men diagnosed with prostate cancer were compared with 3 528 matched controls without prostate cancer (Table 1). There were 1 277 cases of localised prostate cancer (74.4%) and 226 advanced cases (13.2%). Table 2 summarises the clinical and socio-demographics of participants by prostate cancer status. Participants had a mean age of 62 years, were on average slightly overweight (BMI 26.3 kg/m<sup>2</sup>) and over 85% were married or cohabiting.

### Dietary intake and overall prostate cancer risk

The unadjusted intakes of dietary factors for cases and controls are shown in Table 3 combined for the five studies (Table 3). There were some modest differences in consumption between cases and controls; namely oily fish, red meat and protein (each 2% more in cases), energy (1.5% less), cheese (3% less), yoghurt (12% more), alcohol (4% more), fruit and vegetables (1% less), vitamin C (2% more), calcium (1% more), retinol (1% less) and selenium (4% more). The adjusted risk estimates for overall prostate cancer incidence showed no strong linear trends across the distributions of the 37 dietary factors (Table 4).

### **Dietary intake and risk of prostate cancer by detection method and disease stage**

The risk of prostate cancer detected clinically or by PSA is shown in Table 5 in relation to dietary intakes. None of the foods and nutrients showed a major influence on prostate cancer risk for either cancer detection method. Vitamin D might increase the risk of PSA-detected disease (6%) and reduce the risk of clinically-detected disease (8%), whilst fruit and vegetables might reduce the risk of PSA-detected disease (7%) and increase the risk of clinically-detected disease (6%) but these findings require confirmation given the number of associations investigated overall.

The risk of prostate cancer across food and nutrient groups (Table 6) shows that most food or nutrients did not show substantial heterogeneity by disease stage. Cheese consumption reduced the risk of localised disease by 10% with no effect on advanced disease. Higher energy intake appeared to increase the risk of advanced disease by 23%, but not localised disease. These findings require confirmation in other studies given the large numbers of comparisons being made overall.

## DISCUSSION

Prostate cancer risk was not strongly associated with 37 dietary components in middle-aged and older men in this comprehensive analysis based on food diaries (records). There was weak evidence of a heterogeneity of risk for Vitamin D and for fruit and vegetables between clinically and screen-detected disease, a reduced risk of localised disease with cheese and possibly an increased risk of advanced cancer with high energy intake. The main strengths of this study are its size and diversity through pooling over 1 700 prostate cancer cases from five predominantly population-based UK studies with adjustment for clinical and demographic confounders. Dietary records were completed prior to men's knowledge of disease status in the prospective cohorts thus removing recall bias or prior to ProtecT biopsies (definitive diagnosis). Novel comparisons of clinically and screen-detected prostate cancer risk were possible and by disease stage.

This evaluation of prostate cancer risk and dietary factors is also one of few to examine intakes derived from food diaries rather than FFQs. Biomarker validation studies have shown that food diaries are more accurate than FFQs for estimating some nutrients and prospective data collection is less liable to differential recall than FFQs (26-27). Pooling five studies may have potentially introduced non-differential errors in nutrient intakes across the studies but the consortium provided training, protocols and data checking software to enhance consistency. We collected data on entire cohorts and utilised a nested matched case-control analysis to accommodate the resources required for diary coding but this reduced power to identify weak associations compared with a complete cohort analysis.

Limitations of these analyses include the inability to adjust for individual social class which potentially created a confounder in the cohort studies as prostate cancer testing is more frequent in affluent individuals (27). Prostate cancer screening history was unavailable for the cohorts although PSA testing rates are probably low as there is no formal UK screening programme (UK figures are 4-6% (19, 28) and less than 15% had received a prior test in the ProtecT study (17). A limitation which could attenuate diet and prostate cancer associations is that some controls will have undiagnosed disease (based on autopsy data (29)) although all ProtecT controls had a PSA or biopsy result so reducing misattribution bias. Clinical stage was missing for NHSD and Whitehall studies which reduced power to examine differences by stage although they contributed the fewest cases. Some differences (e.g. diary duration) could not be rectified in the analysis as these studies were established before the diet consortium and some confounders relevant to prostate cancer were not collected in all studies, e.g. family history of cancer, or were measured in ways that did not allow pooling (e.g. physical activity). We utilised standardised dietary coding systems which increased exposure quantification consistency although heterogeneity in measurement duration could have also potentially modified any associations. ProtecT study participants were predominately white (ethnicity was not recorded otherwise) so potentially limiting the wider generalisability to populations at elevated risk of disease.

A recent meta-analysis of dietary factors and supplements and prostate cancer risk has concluded that the intake of red and well-done meat, fat and milk should be limited whilst lycopene, green tea and potentially soy-containing products may be preventative (6). These dietary components were not associated in this study with clinically or screen-detected disease or by disease stage (green tea and soy products were not evaluated). However, recent evidence that ProtecT participants who consumed at least 10 portions of tomatoes weekly showed an 18% reduced risk of developing prostate cancer supports the meta-

analyses recommendations (30). Previously, the European EPIC consortium found an increased prostate cancer risk with the highest quartiles of dairy protein (31) but no association with dietary fat (mostly using FFQs) (32). Data from the US Health Professionals study based on clinically-detected cases found no association between calcium intake and localised prostate cancer (measured with FFQs) but a positive association with advanced disease (33). Conversely, calcium intake was related to an increased risk of localised disease with screen-detected cases in the US PLCO trial (34). The finding of a potential protective association of cheese with localised disease requires further exploration and it counters meta-analysis recommendations.

The evidence for a link between obesity and fatal prostate cancer (4) is strengthening and energy intake, which was shown to potentially increased the risk of advanced disease by 23% in this study, might be on that causal pathway. An association between energy intake and advanced disease was shown in a meta-analysis for studies with disease stage with a combined odds ratio of 1.6 for advanced disease (35).

The finding of a heterogeneity of the association of vitamin D with clinically or screen-detected disease requires further investigation. The precision of estimates of foods consumed irregularly such as oily fish, a good source of vitamin D, may be lower in food diaries than questionnaires. Vitamin D levels are also related to sunlight exposure making serological assessments more comprehensive. In the ProtecT study, lower circulating levels of vitamin D were associated with a greater risk of aggressive prostate cancer (higher grade or stage) (36) which would be more prevalent in clinically-detected cases, but the recent meta-analysis does not support Vitamin D supplementation, except for deficiency (6).

There was no association of overall diet (assessed using FFQs) and screen-detected prostate cancer in the US PCPT trial and in a Swedish study (37-38). Food diary data from 133 prostate cancer cases also revealed no association with diet and prostate cancer but a reduction with a Mediterranean diet rich in monounsaturated fatty acids and vegetables/fruits and low in red meats (39). A recent meta-analysis of adherence to a Mediterranean diet and overall cancer risk showed a 4% risk reduction for prostate cancer incidence and 10 % reduction for overall cancer mortality (40).

The natural history of prostate cancer remains poorly understood, including the time points when dietary and environmental factors may influence disease development or progression (38). This study measured dietary intake prior to diagnosis and found no major associations with prostate cancer risk yet migrant studies and international variation in prostate cancer incidence suggest that dietary or other environmental components contribute to disease risk. More recent evidence highlights a role of dietary factors in disease progression, e.g. fat intake and prostate cancer mortality (41). Future studies will need to extend measurement of dietary intake across the life course, consider intermediary influences such as the insulin growth factor axis and examine the role of obesity which increases the risk of aggressive prostate cancer and subsequent disease progression and mortality (42).

## **Conclusions**

In summary, this large study revealed no strong evidence that prostate cancer risk is associated with dietary intake measured prior to diagnosis in middle-aged and older men.

Possible associations of Vitamin D, cheese and energy intake with disease risk require further investigation.



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**TABLE 1** Characteristics of the Dietary Cohort Consortium studies

Study <sup>1</sup>	Participants	Diary completion (years)	Final follow-up date	Follow-up duration (years)	Prostate cancer cases (n)	Clinical stage (n, advanced/localised/unknown)	Controls (n)	Age at diary completion (years)
EPIC-Norfolk	Population	1993-1998	31/12/2009	7.3 (3.2) <sup>2</sup>	439	105/251/83	1,752	64.8 (7.7) <sup>2</sup>
EPIC-Oxford	Population and vegetarians	1993-1999	31/12/2007	6.6 (2.7)	125	22/73/30	125	64.6 (8.0)
NSHD	Born 1946	1989-1990	31/12/2008	13.3 (3.3)	15	0/0/15	60	43.5 (0.2)
ProtecT	Population	2003-2009	29/04/2009	0.2 (0.3)	1,054	99/953/2	1,261	62.9 (4.7)
Whitehall II	Civil servants	1991-1993	29/11/2005	9.0 (2.9)	84	0/0/84	330	54.8 (4.8)

<sup>1</sup>EPIC: European Prospective Investigation into Cancer and Nutrition; NSHD: National Survey of Health and Development; ProtecT: Prostate testing for cancer and Treatment.

<sup>2</sup>Mean (SD) in years.

**TABLE 2** Baseline characteristics of prostate cancer cases and controls pooled across five studies

<b>Characteristic</b>	<b>Controls<sup>1</sup> (n = 3 528)</b>	<b>Cases (n = 1 717)</b>
Age at diary completion (years)	62.7 (7.5)	63.0 (6.5)
Height (m)*	1.75 (0.07)	1.75 (0.07)
Weight (kg)*	80.7 (11.6)	80.8 (11.7)
Body mass index, n (kg/m <sup>2</sup> ) (SD)*	26.4 (3.3)	26.3 (3.3)
<22.5 (%)	334 (9.9)	171 (10.8)
22.5-24.9	822 (24.5)	428 (27.1)
25.0-27.4	1 100 (32.7)	487 (30.8)
27.5-29.9	643 (19.1)	291 (18.4)
≥30.0	462 (13.7)	203 (12.8)
Smoking status, n (%)*		
Never	1 116 (33.1)	605 (37.7)
Former	1 873 (55.5)	821 (51.2)
Current	383 (11.4)	177 (11.0)
Marital status, n (%)*		
Married or cohabiting	3 030 (86.4)	1 500 (88.0)
Unmarried	478 (13.6)	205 (12.0)
Diabetes, n (%)*		
No diabetes	3 121 (94.4)	1 462 (95.1)
Diabetes (self-reported)	185 (5.6)	76 (4.9)
Townsend material deprivation score, n (%)*		
Low (richest)	817 (24.6)	403 (25.5)
Medium-low	864 (26.0)	370 (23.4)
Medium-high	837 (25.2)	383 (24.3)
High (poorest)	802 (24.2)	422 (26.7)

<sup>1</sup>Values are unadjusted means (SD except where indicated) combined for five studies.

\*Unknown categories not presented.

**TABLE 3** Consumption of food groups, foods, macronutrients and micronutrients pooled across five studies

<b>Dietary intake and units<sup>1</sup></b>		<b>Controls (n = 3 258)</b>	<b>Prostate cancer cases (n = 1 717)</b>
<b>Protein<sup>2</sup></b>			
	Red meat	41.6 (31.3)	42.3 (31.2)
	Processed meat	27.8 (22.0)	27.6 (21.2)
	Red and processed meat	69.4 (39.8)	70.0 (39.8)
	Poultry	25.7 (24.8)	26.0 (25.6)
	White fish	15.9 (17.2)	15.3 (17.7)
	Oily fish	14.7 (21.2)	15.6 (22.8)
	Milk	207 (143)	205 (146)
	Cheese	17.4 (17.2)	16.0 (17.2)
	Yogurt	24.1 (43.2)	26.9 (47.0)
<b>Total energy intake (MJ/d) <sup>3</sup></b>		9.12 (2.11)	8.98 (2.07)
<b>Macronutrients<sup>2</sup></b>			
	Protein	15.4 (2.6)	15.7 (2.7)
	Protein from dairy products	2.6 (1.3)	2.6 (1.4)
	Carbohydrate	45.6 (6.7)	45.2 (6.9)
	Total fat consumption	33.2 (5.4)	32.9 (5.5)
	Saturated fat consumption	12.4 (3.0)	12.1 (3.1)
	Monounsaturated fat consumption	11.5 (2.1)	11.4 (2.1)
	Polyunsaturated fat consumption	6.2 (1.7)	6.1 (1.8)
	n-6 fatty acids*	5.3 (1.8)	5.2 (1.7)
	n-3 fatty acids*	0.69 (0.26)	0.71 (0.30)
	Ratio n-6:n-3*	8.4 (3.7)	8.2 (3.8)
<b>Alcohol consumption<sup>2</sup></b>		18.4 (21.4)	19.2 (21.9)
<b>Fruit and vegetables<sup>2</sup></b>		313 (174)	310 (169)
<b>Dietary fibre<sup>2</sup></b>		15.9 (6.0)	15.6 (6.0)
<b>Micronutrients</b>			
	Retinol µg/d	700 (1072)	656 (1020)
	Carotene µg/d*	2 675 (1556)	2 773 (1597)
	Lycopene µg/d*	1 485 (1983)	1 481 (1968)
	Vitamin B6 mg/d	2.25 (0.66)	2.31 (0.68)
	Folate µg/d	293 (90)	295 (89)
	Vitamin B12 µg/d	5.68 (3.97)	5.64 (3.96)

Vitamin C mg/d	87.7 (51.6)	89.2 (55.0)
Vitamin D µg/d	3.82 (2.76)	3.88 (2.80)
Vitamin E mg/d	11.0 (4.9)	10.8 (5.0)
Calcium mg/d	896 (283)	887 (283)
Iron mg/d	13.1 (4.0)	13.0 (3.9)
Magnesium mg/d	322 (91)	323 (90)
Selenium µg/d	71.0 (31.4)	73.8 (40.1)
Zinc mg/d	9.52 (2.53)	9.52 (2.55)

<sup>1</sup>Values are unadjusted means or percentages (SD), <sup>2</sup>g/d, <sup>3</sup>percentage of total energy intake in MJ/d, \*unknown for some participants.



**TABLE 4** Odds ratios for prostate cancer diagnosis by food groups, foods and nutrient consumption

Food group, food or nutrient	Food or nutrient intake (increasing quintiles except where indicated)					P value for trend <sup>2</sup>
	1 (referent)	2	3	4	5	
Red meat (g/d)						
Cut-point		14.6	30.4	45.4	65.3	
Cases/Controls	345/688	330/735	331/718	355/694	356/693	
Odds ratio (95% CI)	1.00	0.90 (0.74-1.09)	0.93 (0.77-1.14)	1.02 (0.84-1.24)	0.99 (0.81-1.21)	0.99
Processed meat (g/d)						
Cut-point		8.6	18.9	29.3	43.7	
Cases/Controls	333/716	342/710	347/699	340/709	355/694	
Odds ratio (95% CI)	1.00	1.06 (0.87-1.29)	1.10 (0.91-1.34)	1.11 (0.91-1.35)	1.14 (0.93-1.39)	0.98
Red and processed meat (g/d)						
Cut-point		37.2	56.8	75.9	99.7	
Cases/Controls	344/705	341/708	321/728	349/700	362/687	
Odds ratio (95% CI)	1.00	1.03 (0.84-1.26)	0.95 (0.78-1.16)	1.07 (0.88-1.31)	1.05 (0.86-1.29)	0.99
Poultry (g/d)						
Cut-point		0.2	15.3	27.1	43.2	
Cases/Controls	388/718	312/687	323/716	339/713	355/694	
Odds ratio (95% CI)	1.00	0.86 (0.71-1.05)	0.87 (0.72-1.06)	0.89 (0.74-1.08)	0.95 (0.79-1.15)	0.78
White fish (g/d)						
Cut-point		0.2	9.3	16.5	27.1	
Cases/Controls	626/1224	86/161	351/708	286/690	368/745	
Odds ratio (95% CI)	1.00	1.04 (0.77-1.40)	1.02 (0.86-1.21)	0.92 (0.77-1.10)	1.10 (0.93-1.31)	0.54
Oily fish (g/d) <sup>3</sup>						
Cut-point		-	0.2	12.9	28.6	
Cases/Controls	788/1603	-	213/511	350/728	366/686	
Odds ratio (95% CI)	1.00	-	0.89 (0.73-1.08)	0.93 (0.79-1.10)	1.00 (0.85-1.18)	0.83
Milk (g/d)						
Cut-point		89	154	216	308	
Cases/Controls	349/699	343/707	350/699	340/709	335/714	
Odds ratio (95% CI)	1.00	1.05 (0.87-1.28)	1.05 (0.86-1.27)	1.04 (0.86-1.27)	1.04 (0.85-1.28)	0.33
Cheese (g/d)						
Cut-point		2.6	9.9	16.5	28.4	
Cases/Controls	372/674	364/687	340/710	326/733	315/724	
Odds ratio (95% CI)	1.00	1.04 (0.86-1.26)	0.95 (0.78-1.15)	0.89 (0.73-1.08)	0.95 (0.77-1.16)	0.25



Cut-point		4.8	5.6	6.4	7.4	
Cases/Controls	367/682	333/716	343/706	347/702	327/722	
Odds ratio (95% CI)	1.00	0.93 (0.77-1.13)	1.04 (0.85-1.26)	1.02 (0.84-1.24)	0.98 (0.80-1.19)	0.78
n-6 fatty acids (% energy)*						
Cut-point		4.0	4.7	5.4	6.5	
Cases/Controls	235/593	232/596	254/573	239/589	216/611	
Odds ratio (95% CI)	1.00	0.91 (0.72-1.14)	1.04 (0.82-1.31)	0.98 (0.78-1.24)	0.86 (0.68-1.09)	0.42
n-3 fatty acids (% energy)*						
Cut-point		0.51	0.60	0.71	0.86	
Cases/Controls	246/582	213/615	234/593	231/597	252/575	
Odds ratio (95% CI)	1.00	0.80 (0.64-1.01)	0.91 (0.72-1.14)	0.85 (0.68-1.07)	0.91 (0.72-1.14)	0.72
Ratio n-6:n-3*						
Cut-point		5.5	6.8	8.3	10.7	
Cases/Controls	243/585	263/565	228/599	223/605	219/608	
Odds ratio (95% CI)	1.00	1.15 (0.92-1.44)	0.99 (0.79-1.24)	0.93 (0.74-1.17)	0.94 (0.74-1.18)	0.75
Alcohol (g/d) <sup>5</sup>						
Cut-point		1.0	10.0	20.0	40.0	
Cases/controls	362/780	389/871	348/623	374/790	244/464	
Odds ratio (95% CI)	1.00	0.98 (0.81-1.18)	1.07 (0.88-1.30)	0.93 (0.77-1.12)	1.02 (0.82-1.28)	0.93
Dietary fibre (g/d)						
Cut-point		10.9	13.6	16.3	20.1	
Cases/controls	360/689	335/714	342/707	351/698	329/720	
Odds ratio (95% CI)	1.00	0.93 (0.76-1.13)	0.89 (0.73-1.10)	0.98 (0.80-1.21)	0.90 (0.72-1.12)	0.34
Retinol (µg/d)						
Cut-point		234	325	439	654	
Cases/controls	359/690	351/698	337/712	334/715	336/713	
Odds ratio (95% CI)	1.00	0.98 (0.81-1.19)	0.94 (0.77-1.15)	1.00 (0.81-1.24)	1.07 (0.86-1.33)	0.51
Carotene (µg/d)*						
Cut-point		1470	2139	2796	3696	
Cases/controls	234/593	230/599	223/604	237/591	252/575	
Odds ratio (95% CI)	1.00	0.96 (0.76-1.20)	0.88 (0.69-1.11)	0.95 (0.75-1.20)	0.96 (0.76-1.22)	0.84
Lycopene (µg/d)*						
Cut-point		350	775	1303	2140	
Cases/controls	217/596	236/577	258/554	237/576	213/599	
Odds ratio (95% CI)	1.00	1.10 (0.88-1.38)	1.17 (0.94-1.47)	1.02 (0.81-1.28)	0.85 (0.67-1.07)	0.28
Vitamin B-6 (mg/d)						
Cut-point		1.72	2.04	2.34	2.76	

Cases/controls	306/743	339/710	347/713	338/700	387/662	
Odds ratio (95% CI)	1.00	1.12 (0.91-1.37)	1.16 (0.94-1.42)	1.09 (0.88-1.35)	1.26 (1.00-1.58)	0.20
Folate (µg/d)						
Cut-point		218	261	304	362	
Cases/controls	336/713	338/711	327/722	369/680	347/702	
Odds ratio (95% CI)	1.00	1.00 (0.82-1.21)	1.03 (0.84-1.26)	1.21 (0.98-1.49)	1.04 (0.83-1.30)	0.69
Vitamin B-12 (µg/d)						
Cut-point		3.18	4.17	5.24	7.15	
Cases/controls	338/711	345/704	340/709	356/693	338/711	
Odds ratio (95% CI)	1.00	1.02 (0.84-1.24)	0.99 (0.81-1.21)	1.04 (0.85-1.27)	1.03 (0.83-1.26)	0.42
Vitamin C (mg/d)						
Cut-point		45.6	65.0	88.6	125.2	
Cases/controls	346/703	343/706	333/716	331/718	364/685	
Odds ratio (95% CI)	1.00	1.06 (0.87-1.28)	0.95 (0.78-1.16)	0.99 (0.81-1.21)	1.05 (0.86-1.29)	0.63
Vitamin D (µg/d)						
Cut-point		1.85	2.73	3.76	5.26	
Cases/controls	334/715	346/703	340/709	347/702	350/699	
Odds ratio (95% CI)	1.00	1.13 (0.93-1.37)	1.09 (0.90-1.34)	1.06 (0.87-1.30)	1.09 (0.88-1.33)	0.84
Vitamin E (mg/d)						
Cut-point		7.1	9.0	11.1	14.1	
Cases/controls	381/668	336/713	325/724	334/715	341/708	
Odds ratio (95% CI)	1.00	0.90 (0.74-1.09)	0.89 (0.73-1.09)	0.90 (0.73-1.11)	1.02 (0.81-1.27)	0.55
Calcium (mg/d)						
Cut-point		659	798	928	1112	
Cases/controls	362/687	337/712	328/721	366/683	324/725	
Odds ratio (95% CI)	1.00	0.98 (0.80-1.19)	0.96 (0.78-1.17)	1.20 (0.97-1.49)	1.00 (0.79-1.28)	0.53
Iron (mg/d)						
Cut-point		9.9	11.7	13.6	15.9	
Cases/controls	366/683	335/714	334/715	348/702	334/714	
Odds ratio (95% CI)	1.00	0.92 (0.75-1.12)	0.92 (0.75-1.14)	1.01 (0.81-1.26)	0.97 (0.76-1.24)	0.97
Magnesium (mg/d)						
Cut-point		248	292	334	390	
Cases/controls	339/710	358/691	316/733	352/697	352/697	
Odds ratio (95% CI)	1.00	1.10 (0.90-1.34)	0.90 (0.73-1.11)	0.99 (0.80-1.24)	1.02 (0.79-1.31)	0.63
Selenium (µg/d)						
Cut-point		49.3	61.0	73.2	89.1	
Cases/controls	319/730	316/733	376/673	335/714	371/678	

Odds ratio (95% CI)	1.00	0.93 (0.76-1.14)	1.19 (0.98-1.46)	0.93 (0.76-1.15)	0.95 (0.76-1.19)	0.95
Zinc (mg/d)						
Cut-point		7.4	8.7	9.8	11.4	
Cases/controls	347/702	327/722	369/681	341/707	333/716	
Odds ratio (95% CI)	1.00	0.94 (0.77-1.15)	1.07 (0.87-1.32)	0.93 (0.74-1.15)	0.89 (0.70-1.14)	0.77

<sup>1</sup>Conditional logistic regression adjusted for age, BMI, socioeconomic, smoking and marital status, diabetes and energy intake.

<sup>2</sup>P values relate to tests for trend obtained for continuous intake variable.

<sup>3</sup>First and second quintiles (and third<sup>4</sup>) combined due to large proportion of non-consumers.

<sup>5</sup>Alcohol intake in five categories (<1, 1-9, 10-19, 20-39, ≥40 g/d).

\* Unknown for some participants.

**TABLE 5** Odds ratios for prostate cancer diagnosis with dietary intake by cancer detection method

<b>Food or nutrient intake (one SD) <sup>1</sup></b>	<b>All studies N = 1 717/3 258<sup>2</sup></b>	<b>Clinically- detected (4 studies) N = 663/2 267<sup>2</sup></b>	<b>PSA-detected ( ProtecT study) N = 1 054/1 261<sup>2</sup></b>	<b>P value for heterogeneity<sup>3</sup></b>
Red meat (31.3 g/d)	1.00 (0.94-1.07)	0.96 (0.87-1.06)	1.04 (0.95-1.13)	0.25
Processed meat (21.8 g/d)	1.00 (0.94-1.07)	0.98 (0.89-1.08)	1.02 (0.94-1.11)	0.55
Red and processed meat (39.8 g/d)	1.00 (0.94-1.07)	0.96 (0.86-1.06)	1.04 (0.96-1.14)	0.20
Poultry (25.1 g/d)	1.01 (0.95-1.07)	1.05 (0.96-1.15)	0.98 (0.90-1.06)	0.27
White fish (17.4 g/d)	1.02 (0.96-1.08)	1.02 (0.93-1.11)	1.02 (0.93-1.11)	0.99
Oily fish (21.7 g/d)	1.01 (0.95-1.07)	0.94 (0.86-1.03)	1.06 (0.97-1.15)	0.08
Milk (144 g/d)	1.03 (0.97-1.10)	1.06 (0.97-1.16)	1.00 (0.91-1.10)	0.37
Cheese (17.2 g/d)	0.96 (0.90-1.03)	0.96 (0.87-1.05)	0.96 (0.88-1.06)	0.93
Yogurt (44.5 g/d)	0.98 (0.93-1.04)	0.96 (0.87-1.07)	0.99 (0.92-1.07)	0.64
Fruit and vegetables (172 g/d)	0.99 (0.92-1.05)	1.06 (0.97-1.16)	0.93 (0.85-1.03)	0.06
Energy intake (2.10 MJ/d)	1.01 (0.95-1.08)	1.06 (0.96-1.16)	0.98 (0.89-1.07)	0.22
Protein (2.7 % energy)	1.01 (0.95-1.09)	1.03 (0.92-1.16)	1.01 (0.92-1.10)	0.74
Protein from dairy products (1.3 % energy)	1.00 (0.94-1.06)	1.03 (0.94-1.13)	0.97 (0.89-1.06)	0.38
Carbohydrate (6.8 % energy)	0.98 (0.92-1.05)	1.03 (0.93-1.13)	0.95 (0.87-1.04)	0.26
Total fat consumption (5.4 % energy)	1.01 (0.95-1.07)	0.99 (0.90-1.09)	1.02 (0.94-1.11)	0.61
Saturated fat consumption (3.0 % energy)	1.00 (0.94-1.06)	0.98 (0.89-1.08)	1.01 (0.92-1.09)	0.73
Monounsaturated fat consumption (2.1 % energy)	1.01 (0.95-1.08)	1.01 (0.92-1.11)	1.02 (0.94-1.11)	0.88

Polyunsaturated fat consumption (1.7 % energy)	1.01 (0.95-1.07)	0.98 (0.90-1.08)	1.03 (0.95-1.13)	0.42
n-6 fatty acids (1.8 % energy)*	0.97 (0.90-1.05)	0.98 (0.89-1.08)	0.95 (0.83-1.10)	0.77
n-3 fatty acids (0.27 % energy)*	1.01 (0.94-1.09)	1.02 (0.92-1.13)	1.01 (0.91-1.13)	0.88
Ratio n-6:n-3 (3.7)*	0.99 (0.92-1.06)	0.97 (0.89-1.06)	1.02 (0.90-1.16)	0.55
Alcohol consumption (21.6 g/d)	1.00 (0.93-1.06)	0.97 (0.88-1.07)	1.02 (0.93-1.11)	0.49
Dietary fibre (6.0 g/d)	0.97 (0.90-1.04)	1.04 (0.94-1.14)	0.92 (0.83-1.02)	0.09
Retinol (1055 µg/d)	1.02 (0.96-1.09)	1.04 (0.96-1.12)	1.00 (0.90-1.12)	0.62
Carotene (1568 µg/d)*	1.01 (0.94-1.08)	1.05 (0.96-1.15)	0.94 (0.82-1.07)	0.17
Lycopene (1978 µg/d)*	0.96 (0.89-1.03)	0.94 (0.84-1.05)	0.97 (0.88-1.07)	0.68
Vitamin B6 (0.67 mg/d)	1.05 (0.98-1.13)	1.09 (0.98-1.21)	1.04 (0.94-1.15)	0.54
Folate (90 µg/d)	1.01 (0.94-1.09)	1.05 (0.95-1.16)	1.00 (0.90-1.10)	0.46
Vitamin B12 (3.97 µg/d)	1.03 (0.96-1.09)	1.06 (0.98-1.15)	0.99 (0.89-1.09)	0.28
Vitamin C (52.8 mg/d)	1.02 (0.95-1.08)	1.02 (0.92-1.12)	1.02 (0.94-1.11)	0.91
Vitamin D (2.77 µg/d)	1.01 (0.95-1.07)	0.92 (0.83-1.03)	1.06 (0.98-1.15)	0.04
Vitamin E (4.9 mg/d)	1.02 (0.95-1.10)	1.01 (0.91-1.11)	1.05 (0.94-1.18)	0.55
Calcium (283 mg/d)	1.03 (0.95-1.11)	1.05 (0.94-1.18)	0.99 (0.88-1.11)	0.46
Iron (3.9 mg/d)	1.00 (0.93-1.08)	1.00 (0.89-1.12)	1.02 (0.92-1.15)	0.75
Magnesium (91 mg/d)	0.98 (0.90-1.06)	1.02 (0.91-1.14)	0.96 (0.85-1.08)	0.48
Selenium (34.5 µg/d)	1.00 (0.94-1.07)	0.95 (0.85-1.07)	1.04 (0.96-1.13)	0.22
Zinc (2.53 mg/d)	0.99 (0.91-1.07)	1.03 (0.92-1.15)	0.96 (0.85-1.08)	0.39

<sup>1</sup> Conditional logistic regression adjusted for age, BMI, socioeconomic, smoking and marital status, diabetes and energy intake

<sup>2</sup> Number of cases and controls.

<sup>3</sup> Test of heterogeneity of trends between cohort studies (mostly clinically-detected disease) and ProtecT (PSA-detected disease).

\* Unknown for some participants.



**TABLE 6** Odds ratios for prostate cancer with dietary intake by disease stage

<b>Food or nutrient intake (one standard deviation)<sup>1</sup></b>	<b>Localised and advanced stage* N = 1 503/2 418<sup>2</sup></b>	<b>Localised stage N = 1 277/1 952<sup>2</sup></b>	<b>Advanced stage N= 226/466<sup>2</sup></b>	<b>P value for heterogeneity by disease stage<sup>3</sup></b>
Red meat (31.3 g/d)	1.01 (0.94-1.09)	1.04 (0.96-1.13)	0.83 (0.66-1.04)	0.06
Processed meat (21.8 g/d)	1.00 (0.93-1.08)	1.01 (0.93-1.09)	0.99 (0.80-1.24)	0.92
Red and processed meat (39.8 g/d)	1.01 (0.93-1.09)	1.04 (0.96-1.13)	0.85 (0.67-1.07)	0.11
Poultry (25.1 g/d)	0.99 (0.92-1.06)	0.99 (0.91-1.07)	0.99 (0.81-1.21)	0.96
White fish (17.4 g/d)	1.00 (0.93-1.08)	0.99 (0.92-1.08)	1.10 (0.90-1.35)	0.37
Oily fish (21.7 g/d)	1.02 (0.95-1.10)	1.02 (0.94-1.10)	1.06 (0.87-1.29)	0.71
Milk (144 g/d)	1.02 (0.95-1.11)	1.01 (0.93-1.10)	1.11 (0.92-1.35)	0.36
Cheese (17.2 g/d)	0.93 (0.86-1.01)	0.90 (0.83-0.99)	1.03 (0.84-1.26)	0.25
Yogurt (44.5 g/d)	0.96 (0.89-1.03)	0.96 (0.89-1.03)	1.01 (0.80-1.27)	0.65
Fruit and vegetables (172 g/d)	0.98 (0.91-1.06)	0.97 (0.89-1.05)	1.11 (0.90-1.36)	0.23
Energy intake (2.10 MJ/d)	1.03 (0.95-1.11)	1.00 (0.92-1.08)	1.23 (1.00-1.51)	0.07
Protein (2.7 % energy)	1.01 (0.93-1.09)	1.01 (0.92-1.11)	1.00 (0.79-1.27)	0.96
Protein from dairy products (1.3 % energy)	0.97 (0.90-1.04)	0.94 (0.87-1.02)	1.09 (0.88-1.34)	0.21
Carbohydrate (6.8 % energy)	0.98 (0.91-1.06)	0.98 (0.90-1.07)	1.04 (0.83-1.29)	0.64
Total fat consumption (5.4 % energy)	1.05 (0.97-1.13)	1.04 (0.96-1.13)	1.03 (0.84-1.27)	0.93
Saturated fat consumption (3.0 % energy)	1.04 (0.96-1.12)	1.02 (0.94-1.11)	1.08 (0.88-1.34)	0.62
Monounsaturated fat consumption (2.1 % energy)	1.04 (0.97-1.12)	1.05 (0.97-1.13)	0.99 (0.81-1.22)	0.64
Polyunsaturated fat consumption (1.7 % energy)	1.04 (0.96-1.11)	1.05 (0.97-1.14)	0.94 (0.77-1.16)	0.33
n-6 fatty acids (1.8 % energy)*	0.98 (0.89-1.07)	0.99 (0.90-1.10)	0.91 (0.73-1.13)	0.48

n-3 fatty acids (0.27 % energy)*	1.01 (0.93-1.10)	1.02 (0.93-1.12)	0.96 (0.75-1.22)	0.67
Ratio n-6:n-3 (3.7)*	1.01 (0.92-1.10)	1.01 (0.92-1.12)	0.97 (0.79-1.20)	0.70
Alcohol consumption (21.6 g/d)	0.97 (0.90-1.05)	0.97 (0.90-1.06)	0.93 (0.74-1.17)	0.72
Dietary fibre (6.0 g/d)	0.98 (0.90-1.06)	0.96 (0.88-1.05)	1.14 (0.91-1.43)	0.17
Retinol (1055 µg/d)	1.03 (0.95-1.11)	1.02 (0.93-1.11)	1.09 (0.91-1.29)	0.50
Carotene (1568 µg/d)*	1.02 (0.93-1.11)	1.00 (0.91-1.11)	1.06 (0.84-1.35)	0.66
Lycopene (1978 µg/d)*	0.98 (0.90-1.06)	0.98 (0.90-1.07)	0.93 (0.72-1.19)	0.67
Vitamin B6 (0.67 mg/d)	1.02 (0.94-1.11)	1.02 (0.93-1.12)	1.08 (0.84-1.38)	0.70
Folate (90 µg/d)	1.01 (0.93-1.10)	1.00 (0.92-1.10)	1.08 (0.85-1.38)	0.58
Vitamin B12 (3.97 µg/d)	1.04 (0.97-1.12)	1.04 (0.96-1.13)	1.05 (0.86-1.29)	0.93
Vitamin C (52.8 mg/d)	1.00 (0.92-1.08)	1.00 (0.92-1.09)	0.99 (0.79-1.24)	0.93
Vitamin D (2.77 µg/d)	1.02 (0.95-1.09)	1.03 (0.96-1.12)	0.94 (0.74-1.19)	0.44
Vitamin E (4.9 mg/d)	1.03 (0.94-1.13)	1.04 (0.94-1.15)	0.97 (0.78-1.21)	0.57
Calcium (283 mg/d)	0.97 (0.88-1.07)	0.96 (0.86-1.06)	1.06 (0.82-1.37)	0.47
Iron (3.9 mg/d)	0.99 (0.91-1.09)	1.02 (0.92-1.12)	0.87 (0.67-1.13)	0.28
Magnesium (91 mg/d)	0.97 (0.89-1.07)	0.96 (0.87-1.06)	1.08 (0.83-1.41)	0.42
Selenium (34.5 µg/d)	1.00 (0.93-1.08)	0.99 (0.90-1.08)	0.99 (0.83-1.17)	0.99
Zinc (2.53 mg/d)	1.00 (0.91-1.10)	1.01 (0.91-1.12)	0.96 (0.73-1.26)	0.75

<sup>1</sup> Conditional logistic regression adjusted for age, BMI, smoking, marital status, diabetes, socioeconomic status and energy intake.

<sup>2</sup> Number of cases and controls.

<sup>3</sup> Test of heterogeneity of trends between localised and advanced disease.

\* Unknown for some participants.