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Associations between unprocessed red and processed meat, poultry, seafood and egg intake and the risk of prostate cancer: A pooled analysis of 15 prospective cohort studies

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Associations between unprocessed red and processed meat, poultry, seafood and egg intake and the risk of prostate cancer: a pooled analysis of 15 prospective cohort studies

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Novelty and Impact of Paper (word count: 75)

In this consortium of 15 cohorts including studies that had not published on these associations previously, we harmonized the primary data of each cohort and examined associations between meat and egg intake and nine prostate cancer outcomes. The analyses included over 50,000 cases and detected some associations that differed by outcome and geographical region (North America vs. other continents). Exploration of these differences may further elucidate the relationship between these foods and prostate cancer outcomes.

Abstract (word count: 249)

Reports relating meat intake to prostate cancer risk are inconsistent. Associations between these dietary factors and prostate cancer were examined in a consortium of 15 cohort studies. During follow-up, 52,683 incident prostate cancer cases, including 4,924 advanced cases, were identified among 842, 149 men. Cox proportional hazard models were used to calculate study-specific relative risks (RR) and then pooled using random effects models. Results do not support a substantial effect of total red, unprocessed red and processed meat for all prostate cancer outcomes, except for a modest positive association for tumors identified as advanced stage at diagnosis (advanced(r)). For seafood, no substantial effect was observed for prostate cancer regardless of stage or grade. Poultry intake was inversely associated with risk of advanced and fatal cancers (pooled multivariable RR [MVRR], 95% confidence interval, comparing ≥45 vs. <5 g/d: advanced 0.83, 0.70-0.99; trend test p-value 0.29), fatal, 0.69, 0.59-0.82, trend test p-value 0.16). Participants who ate ≥25 vs <5 g/d of eggs (1 egg ~ 50 g) had a significant 14% increased risk of advanced and fatal cancers (MVRR: advanced 1.14, 1.01-1.28, trend test p-value 0.01; fatal 1.14, 1.00-1.30, trend test p-value 0.01). When associations were analyzed separately by geographical region (North America vs. other continents), positive associations between unprocessed red meat and egg intake, and inverse associations between poultry intake and advanced, advanced(r) and fatal cancers were limited to North American studies. However, differences were only statistically significant for eggs. Observed differences in associations by geographical region warrant further investigation.

Manuscript (word count: 3,916)

Introduction

Epidemiological evidence linking meat intake to prostate cancer risk has been inconsistent [1, 2]. One reason for the inconsistencies between studies may be that prostate cancer is a heterogeneous disease and risk factors for indolent prostate cancers differ from those for fatal cancers, while the majority of prostate cancer studies on meat consumption have focused on total prostate cancer. However, in terms of cancer prevention, identification of modifiable risk factors associated with prostate cancers that have lethal potential is more relevant. Furthermore, risk factors that enhance progression of prostate cancers may be independent from those that affect grade, i.e. differentiation of prostate cancer [3].

We conducted a pooled analysis of the associations between meat and egg intake and prostate cancer risk overall and separately by stage and grade using primary data from 15 cohort studies. Ten of these studies had previously published their results regarding at least one of the dietary factors evaluated and prostate cancer risk [4-16]. We also examined associations between egg intake and prostate cancer, because eggs are another major source of animal protein and recent evidence suggests that higher egg intake may increase risk of lethal prostate cancer [16, 17]

Methods

Study Population

The Pooling Project of Prospective Studies of Diet and Cancer (DCPP) is a consortium established to examine associations between dietary factors and cancer risk [18]. Fifteen cohorts

from North America, Europe, Australia and Asia were included in this pooled analysis (Table 1) [4, 5, 7-13, 19-23]. Each study met the following predefined inclusion criteria: a) at least one publication on any diet and cancer association, b) assessment of long-term diet, c) validation of the dietary assessment method or a closely related dietary instrument and d) at least 50 incident cases of prostate cancer [18]. The Netherlands Cohort Study was analyzed as a case-cohort study because in that study questionnaires were only processed for cases and a random sample of the cohort [18, 24]. Each study was approved by its respective Institutional Review Board.

Ascertainment of Cases

We included primary incident prostate cancer cases. Only deaths where the underlying cause of death was prostate cancer were considered as fatal cases. Advanced cancers were defined as tumors with stage T4, N1, M1 or fatal tumors. In order to account for cases that were initially diagnosed as localized cancers or cases with missing stage data at time of diagnosis, who died during follow-up, a second advanced outcome was defined ("advanced restricted"). The definition of "advanced restricted" (from now on referred to as advanced(r)) includes cases known to be advanced at diagnosis i.e. T4, N1, M1 or fatal cases after exclusion of fatal cases who were initially diagnosed as localized cases or those with missing stage information at diagnosis. Fatal cases, initially diagnosed as localized are likely cases with undetected micro-metastases at diagnosis. High-grade cancers were defined as having Gleason score ≥8 or being poorly differentiated /undifferentiated (for more detail please refer to the Appendix).

For the Prostate Cancer Prevention Trial (PCPT) [23] only cases diagnosed through a biopsy performed because of an elevated prostate-specific antigen (PSA) or suspicious digital rectal exam ("for cause") were included. Further, only participants in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) assigned to the screened arm were included in this study [5].

Dietary Assessment

Each study provided their primary dietary data, which were collected using baseline self-administered food frequency questionnaires (FFQs) [18] or interviewer-administered quantitative dietary questionnaires at some centers in the European Prospective Investigation into Cancer and Nutrition (EPIC) study [25]. The validity of intakes of food groups was not assessed by most cohorts [18]; but cohort-specific correlations comparing the intake estimates by the FFQs vs. multiple dietary records or 24-hour recalls for total fat, saturated fat, total protein or cholesterol (nutrients related to meat and/or egg intake) were generally greater than 0.40 [18, 23, 25-31].

For more detail details regarding how the unprocessed red meat (from now on referred to as red meat), processed meat, poultry, seafood and egg food groups were defined, refer to footnote in Table 2. For three studies, the Japan Public Health Center-Based Study Cohort 1 and 2 and our largest cohort, the NIH AARP Diet and Health Study with over 18,889 cases, we were unable to distinguish total shellfish from total fish intake. Thus, results are presented for shellfish and fish intake combined (referred to as seafood). However, four studies (Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, CLUE II: Campaign Against Cancer and Heart Disease, Cancer Prevention Study-II Nutrition Cohort and Netherlands Cohort Study) did not assess shellfish intake therefore seafood intake represents fish intake for those studies.

Assessment of Non-dietary Risk Factors

All studies provided information on age, height and weight at baseline. Most studies assessed smoking habits, physical activity, education, marital status and multivitamin use. Missing information was coded using an indicator variable for the missing category for all measured variables in a study.

Statistical Analysis

Participants with a history of cancer (except for non-melanoma skin cancer), with energy intakes beyond 3 standard deviations from the study-specific $\log_e$-transformed mean energy intake, or with missing information on the exposure evaluated were excluded from our analyses. Participants contributed person years of follow-up from the date of the baseline questionnaire to the date of diagnosis of prostate cancer, death (for all fatal cases including those with available date of diagnosis) and loss to follow-up, if available, or administrative end of follow-up, whichever came first. Intakes of meat and eggs were modeled as categorical variables using absolute intake cutoffs. The absolute intake cutoffs were defined *a priori* and were selected to maximize inclusion of data from individual studies in each intake category and to represent increments of generally accepted serving sizes of each item.

We used a two-stage analytic approach to calculate pooled relative risks [18]. First, we estimated study-specific relative risks (RR) and 95% confidence intervals (CI) between our exposure variables and risk of prostate cancer using the Cox proportional hazard model [32]. We adjusted for age and calendar time by stratifying by age at baseline (in years), year of questionnaire

return, and center (only EPIC), and treated months since entry into the study until the minimum date of diagnosis of prostate cancer, death (for all fatal cases) or end of study as the time scale [18]. In addition, we adjusted for known or suspected risk factors for prostate cancer either by including these variables in the multivariable model or, for studies with less than 200 cases, by using the propensity score method [33-35] (for more detail on covariates included in the final multivariable model, see Table 3). Because pooled multivariable and age-adjusted RRs were similar, only pooled multivariable RRs (MVRR) are presented. Trend tests were conducted by including the median value of each exposure category as a continuous variable in the models. The second stage of the analysis includes calculating pooled RRs employing the random-effects model with studies weighted by the sum of the inverse of the variance and the estimated between-studies variance components [36, 37]. The Q-statistic [36, 38] and the I^2 statistic [39] were used to test for heterogeneity in the study-specific results. Before we examined associations between the main exposures as continuous variables and risk of prostate cancer, we tested whether associations were non-linear using non-parametric regression analyses [40-42]. For these analyses, we created one dataset including data from all studies and excluded participants in the top 1% of the exposure being examined. All models were stratified by age, year of questionnaire return and study and included all other covariates. A likelihood ratio test was employed to compare the model with both the linear and the cubic spline terms selected using a stepwise regression procedure with the model only including the linear term. We only examined an exposure as a continuous variable if these analyses showed a linear relationship between the exposure and the examined outcome.

To examine possible effect modification of associations between the main exposure variables and risk of prostate cancer by age at diagnosis, follow-up time and body mass index (BMI), we used mixed effects meta-regr88ession models [43].

A contrast test was employed to compare associations for prostate cancers by stage and grade [44]. A two-sided p-value of 0.05 was considered statistically significant.

Results

During follow-up ranging from 9 to a maximum of 22 years across studies, 52,683 incident prostate cancer cases (stage: 38,445 localized, 4,924 advanced which included 3,199 fatal; grade: 37,530 low and 9,746 high) were identified (Table 1). The proportion of advanced and fatal cases varied considerably across studies, ranging from 2%-37% for advanced and 1%-21% for fatal cases. There was also considerable variation across studies with regard to meat and egg intake; differences in the study-specific median intakes ranged from 5-fold for poultry to 43-fold for processed meat (Table 2).

Note: In terms of magnitude of associations, we only discuss RRs of at least 1.10 or equal to or below 0.90 (10% difference in risk, when comparing highest vs. lowest category of intake).

Associations between intakes of meat and eggs and total prostate cancer risk were similar to those for localized prostate cancer (Table 3). Higher intake of unprocessed red or processed meat was not associated with a substantially increased risk of total, advanced, low or high-grade cancers. After excluding fatal cases initially diagnosed as localized and those with

missing stage at diagnosis from the definition of advanced cases, participants in the highest red and processed meat intake categories had a 17%-19% increased risk of advanced (i.e. advanced(r)) cancers than those in the lowest category. There was statistically significant heterogeneity between studies in the MVRRs for unprocessed red meat intake and advanced and fatal cancers (heterogeneity test for highest category p-value=0.03) with study-specific RRs ranging from 0.33 to 1.51. Differences in geographical region (i.e. North-America vs. other continents, Table 4), age at diagnosis (<65 years vs. >=65 years), or follow-up time (<5 years or >=5 years) did not explain the heterogeneity (all tests for interaction p-value >=0.20).

Poultry intake was associated with a statistically significantly higher risk of localized and low grade cancers but was associated with a statistically significantly lower risk of advanced and fatal cancers (highest vs. lowest category: MVRR: advanced 0.83, 95% CI 0.70-0.99, heterogeneity test for highest category p-value 0.16; fatal 0.69, 95% CI 0.59-0.82, heterogeneity test for highest category p-value 0.47).

Seafood intake was not significantly associated with risk of prostate cancer regardless of stage or grade. However, there was evidence for heterogeneity between studies in the MVRRs for seafood intake and localized (heterogeneity test for highest category p-value 0.06) and low grade cancers (heterogeneity test for highest category p-value 0.04). Heterogeneity due to differences by region was observed for the association with localized tumors (interaction test p-value = 0.03) with an 8% increase in risk being observed in the North American studies and a nonsignificant 10% decrease in risk being observed in studies from other continents. Among the studies that assessed fish intake separately from shellfish intake, associations between

total fish intake and risk of advanced (advanced, 11 studies, advanced(r), 8 studies) and fatal prostate (9 studies) cancers were similar to those observed for seafood intake (highest vs. lowest category (cutoffs same as for seafood): MVRR, 95% CI: advanced 0.96, 0.83-1.12, trend test p-value 0.83; advanced(r) 1.08, 0.89-1.30, trend test p-value 0.30; fatal 0.89, 0.74-1.07, trend test p-value 0.46).

Participants in the highest category of egg intake (≥25 g/d, 1 egg ~50g) had a 14% increased risk of advanced and fatal cancers when compared with participants in the lowest category (<5g/day) (MVRR: advanced 1.14, 95% CI 1.01-1.28, heterogeneity test for highest category p-value= 0.24; fatal 1.14, 95% CI 1.00-1.30, heterogeneity test for highest category p-value= 0.33).

Despite an absence of statistical heterogeneity for the overall pooled estimate, we (*post-hoc)* examined associations between meat and egg intake and risk of advanced, advanced (r) and fatal cancers separately by geographical region as there was a suggestion that study-specific MVRRs may differ by region for some exposures (Table 4). When associations were analyzed separately by geographical region (North America vs. other Continents) red meat and egg intake were positively associated and poultry intake inversely associated with risk of advanced, advanced(r) and fatal cancers in North American studies only. However, only the difference in the results for egg intake and advanced, advanced (r) and fatal cancers were statistically significant (all tests for interaction highest category p-value <=0.02). Associations for processed meat and seafood intake did not appear to differ by geographical region.

All participants in the PLCO trial [5] and the PCPT trial [23] who were included in this study have been screened, i.e. underwent Prostate Specific Antigen (PSA) testing prior to study entry. Therefore, associations between our exposures and advanced or fatal cancers were also examined after excluding PLCO from the analysis (PCPT was already excluded in our advanced/fatal analysis due to limited number of cases), but results were essentially unchanged (data not shown).

Associations between poultry and egg intake and risk of advanced, advanced(r) and fatal cancers remained similar after mutual adjustment for processed, unprocessed red meat, poultry (for egg intake only), seafood and egg (for poultry intake only) intake as well as after adding dietary components from meat or egg intake, i.e. saturated fat, cholesterol, total iron and protein intake separately to the models (data not shown).

Associations between red meat, processed meat, poultry, seafood and egg intake and risk of localized, advanced, fatal, and low and high-grade prostate cancers did not vary by age at diagnosis (<65 vs. ≥65 years), follow-up time (<5 vs. ≥5 years) or BMI (<25 vs. ≥25 kg/m^2, data not shown)

Discussion

Our results do not support a substantial effect of red and processed meat for all prostate cancer outcomes, except for a modest positive association for tumors identified as advanced at diagnosis. For processed meat and seafood consumption, no substantial association was observed for prostate cancer regardless of stage or grade. Higher poultry intake was

associated with a modestly lower risk of advanced and fatal cancers. Higher egg intake was associated with a modestly higher risk of advanced and fatal cancers and not associated with risk of localized, low-grade, or high-grade tumors. In addition, our results also suggested differences by geographical region.

Red and Processed Meat

Epidemiological evidence relating red meat and processed meat intake to prostate cancer risk has been inconsistent [2, 45, 46]. Differences in the definition of the prostate cancer outcome variables and limited statistical power to examine metastatic or fatal cancers may, at least in part, explain some of the inconsistencies in results between studies. In our study, we also observed different associations with red and processed meat intake for the two advanced outcomes where modest positive associations were observed only for tumors identified as advanced at diagnosis [advanced (r) tumors]. Another possible explanation for the inconsistencies in study results is the varied definition of red and processed meat. For example, some studies examined unprocessed red meat and processed meat separately whereas other studies examined unprocessed red and processed meats in combination [2, 46], but the type of meat consumed may influence exposure to potential carcinogens. For example, nitrite and nitrate, which can be converted to carcinogenic N-nitroso compounds, are commonly added to processed meats as preservatives [47, 48] (for a general discussion on inconsistencies in study results also refer to Strengths and Limitations).

Poultry and Seafood

In our study, higher poultry intake modestly reduced risk of advanced and fatal prostate cancer. The biological mechanisms underlying our findings on poultry intake and risk of fatal cancer are unclear. In the CaPSURE™ study, men with a higher intake of poultry with skin after diagnosis had increased prostate cancer progression [49], but no association was observed for consumption of poultry without skin. These findings may possibly be due to higher heterocyclic amine content or overall meat derived mutagenicity (compounds associated with certain cooking methods), in chicken eaten with skin versus without skin [50]. In the California Collaborative Prostate Cancer Study, higher intake of baked poultry, but not grilled, broiled or high-temperature cooked poultry, was associated with lower risk of advanced cancers[51].

Consuming fish may lower risk of prostate cancer, because fish contains high amounts of omega-3 polyunsaturated fatty acids (PUFA) which have anti-inflammatory properties.[52]A recent meta-analysis [52] observed a statistically significant 73% lower risk of prostate cancer mortality comparing the highest vs. lowest categories of fish intake. However, the results were based on only 4 cohort studies and there was significant heterogeneity in the results between studies (test for heterogeneity p-value = 0.001). None of the aforementioned 4 cohort studies [53-56] were included in this analysis, because they did not meet our inclusion criteria (for more detail on inclusion criteria please see above under methods). We did not examine associations separately for intakes of dark meat fish, which contain higher amounts of omega-3s than white meat fish [57], or individual omega-3s because these data generally were not available in the studies that contributed to this analysis.

Eggs

In our study, higher egg intake was significantly associated with a modestly higher risk of advanced and fatal prostate cancer. Four prospective studies [11, 16, 54, 58], of which two [11, 16] were included in this analysis, have reported on the association between egg intake and risk of advanced or fatal cancers, but results were inconsistent. While in the Lutheran Brotherhood Cohort Study no association between egg intake and risk of fatal cancers was found [54], another study among Seventh-day Adventists observed a 60% higher risk of fatal prostate cancers among participants who ate eggs at least 3 days per week compared to less than 1 day per week, but the association was not statistically significant (trend test p-value = 0.09) [58]. The aforementioned two cohort studies were not included in our analysis because both studies did not meet our inclusion criteria (Lutheran Brotherhood Cohort Study: lack of validated dietary instrument; the Seventh-day Adventists Study: less than 50 incident cases of prostate cancer). In the CaPSURE™ study, higher egg intake was associated with a 2-fold increase in risk of prostate cancer progression (RR for highest vs. lowest quartile = 2.07, 95% CI 1.16-3.70) [49].

The biological mechanisms underlying these positive associations are unknown, but eggs contain considerable amounts of choline [59]. Choline is crucial for cell membrane synthesis and in prostate cancer cell lines choline kinase, which is involved in the conversion of choline to phosphatidylcholine, is overexpressed compared with normal prostate cell lines [59, 60]. Positive associations between plasma choline [61] and choline intake [17] also have been reported, although the association was statistically significant only in the study on choline intake. [62-65]

Associations by Geographical Region

In our study, positive associations between unprocessed red meat and egg intake and advanced, advanced(r) and fatal cancers were generally observed in North American studies, but not in studies from other continents. However, the heterogeneity observed by region was only statistically significant for egg intake. Unlike in Europe and Australia (regions represented in our pooled analysis), in North America, starting in the mid-90s PSA tests have been increasingly used to screen for prostate cancers which results in cancers being detected at an earlier stage [66] and we observed that some cancers in our study, that were initially diagnosed with a stage of T1 or T2, N0, M0 and thus would be considered "localized" tumors, progressed over time likely due to undetected micro-metastases and became lethal. It is conceivable that in North America, men with an unhealthy lifestyle may be less likely to undergo PSA screening than those with a healthy lifestyle and therefore may be diagnosed at more advanced stages [67]. Differences in PSA screening may also, at least in part, explain the stronger positive associations we observed for red meat intake with advanced(r) vs. advanced tumors. One way to examine whether PSA screening affected our observed associations is to examine associations separately for cases diagnosed in the "pre and post" PSA eras or to exclude participants with a history of PSA screening. However, we were not able to conduct these analyses, because the majority of the North American studies started after or around the PSA era (post PSA), we did not have a sufficient number of cases in the "pre-PSA" stratum (i.e. cases diagnosed before 1992). Furthermore, information on history of PSA screening was not available for the majority our studies. Besides differences in prostate cancer screening practices, other explanations such as differences in characteristics of study population or diet assessment may also account for some of the observed differences by geographical region. Further, even though at this point purely speculative, it is also possible that other factors that

may differ by geographical region such as meat processing, farming practices, nutrient or preservative content in animal feeds or culinary preference, may at least in part be responsible for our observed associations. In North America, eggs are often consumed with processed meats such as bacon or sausages. However, in our study observed associations between egg intake and advanced, advanced(r) and fatal cancers remained similar after mutual adjustment for processed, unprocessed red meat, poultry and seafood intake (data not shown).

Strengths

Besides its prospective design, which minimizes recall and selection bias, other strengths of this study include its large sample size allowing us to examine associations with more statistical power than the individual studies. Also, the wide variation in meat and egg intake across studies enabled us to examine a wider range of intake than in individual studies. Further, we analyzed the primary data from each study and created harmonized exposure and outcome variables, thereby reducing heterogeneity among studies caused by differences in definitions of these variables. Another advantage of this study is the uniform definition of prostate cancer. Previous individual studies have defined “advanced” or “aggressive” cancers inconsistently [3]. Some studies used different stage cutoffs (e.g. extension beyond prostate (T3N0M0) [12] vs. distant metastases (N1 or M1) [9]), while other studies used a combination of stage and grade to define “aggressive” prostate cancers [8, 22]. However, some risk factors that may lead to progression may be different from those related to high-grade cancers [3].

Limitations

Our study also has some limitations. First, associations were examined using only baseline intake data, thus we could not account for changes in intake over time. Secondly, our definitions of specific meat groups may only roughly approximate the true exposure of interest, including compounds associated with cooking methods [68, 69] or intakes of nitrite/nitrate [47]. In animal studies, PhIP (2-amino-1-methyl-6-phenylimidazo [4,5-b] pyridine), the major heterocyclic amine found in human diet [70], has been found to increase the rates of prostate cancer in rats [71]. However, results from cohort studies that have examined associations between cooking methods or meat-related mutagens and prostate cancer risk in detail are inconclusive [5, 12, 51, 72-76]. We did not examine intake of meat mutagens, because only a few studies in our analyses had collected detailed information on cooking methods. Thirdly, we cannot exclude the possibility that our findings may reflect associations with certain lifestyle factors related to meat or egg intake. However, we adjusted for known and potential lifestyle related risk factors for prostate cancer and our age-adjusted and multivariable adjusted models yielded similar results.

In conclusion, our results do not support a substantial association between red and processed meat and all prostate cancer outcomes except for a modest positive association for tumors identified as advanced tumors at diagnosis. For seafood, no substantial association was observed for prostate cancer regardless of stage or grade. Higher poultry intake was associated with a modest lower risk, while higher egg intake was associated with a modest higher risk of fatal cancers. Observed differences in associations by geographical region warrant further investigation.

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Table 1. Characteristics of the Studies included in the Pooled Analysis of Meat and Prostate Cancer

Study	Country	Follow-up	Baseline cohort size	Age range, years	Total cases	Localized	Advanced (Percent[1])	Advanced (restricted) (Percent[1])	Fatal (Percent)	Low grade	High grade (Percent[2])
Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Finland	1985-2002	26,987	49-70	1316	828	354(37)	243(19)	270(21)	825	223(21)
Beta-Carotene and Retinol Efficacy Trial	USA	1985-2005	10,474	44-75	736	442	68(11)	45(8)	38(6)	555	79(12)
Campaign Against Cancer and Heart Disease	USA	1989-2009	5,926	18-90	461	250	54(14)	25(6)	46(12)	296	133(31)
Cancer Prevention Study-II Nutrition Cohort	USA	1992-2005	65,923	42-93	6943	5785	458(7)	282(4)	283(4)	5433	1238(19)
Cohort of Swedish Men	Sweden	1998-2008	45,338	45-79	3014	1853	538(18)	398(14)	310(11)	1726	365(17)
European Investigation into Cancer and Nutrition	Europe	1991-2006	142,195	20-97	2727	1337	345(17)	175(9)	248(12)	1325	298(18)
Health Professionals' Follow-Up Study	USA	1986-2008	47,781	32-79	5536	3879	669(13)	321(6)	532(10)	4094	571(12)
The Japan Public Health Center-Based Study Cohort 1	Japan	1990-2004	20,161	40-59	135	78	20(19)	16(15)	5(5)	90	34(27)
The Japan Public Health Center-Based Study Cohort 2	Japan	1993-2004	24,116	40-69	167	84	38(27)	32(23)	12(9)	92	46(33)
Melbourne Collaborative Cohort Study	Australia	1990-2006	14,824	27-72	910	737	76(9)	11(1)	70(8)	668	218(25)
Multiethnic Cohort Study	USA	1993-2004	84,297	45-78	5583	4597	512(10)	367(7)	283(5)	3668	1575(30)
The Netherlands Cohort Study	Netherlands	1986-2007	58,279	54-70	2416	1263	749(33)	557(24)	460(20)	1746	500(22)
The NIH-AARP Diet and Health Study	USA	1995-2006	250,065	50-71	18889	13946	886(5)	540(3)	554(3)	13744	3964(22)
Prostate Cancer Prevention Trial	USA	1994-2003	15,620	55-86	853	792	13(2)	8(1)	7(1)	684	107(14)
The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	USA	1993-2008	30,163	55-75	2997	2574	144(5)	90(3)	81(3)	2584	395(13)

Total			842,149		52683	38445	4924	3110	3199	37530	9746

"Localized": defined as cancers with information on stage but are not defined as "periprostatic", i.e. cancers confined within the prostate; "Advanced": defined as cancers with extension to or fixation to adjacent structures other than seminal vesicles, i.e. T4, N1, M1 or fatal; "Advanced (restricted)": same as "advanced" but excluding localized cases and cases with missing stage, who died of prostate cancer during follow-up; "Low grade": Gleason score <8 or well/moderately differentiated; "High grade": Gleason score >=8 or poorly differentiated/undifferentiated

[1]Percentages calculated using total number of cases with non-missing data on stage, therefore numbers do not add to 100%; advanced: includes all fatal cancers as an outcome, advanced (restricted) : same as advanced but excludes cases diagnosed with incident localized cancer or incident cancer but with missing stage data, who died of prostate cancer during follow-up (n=1,814)

[2]Percentages calculated using total number of cases with non-missing data on grade, therefore numbers do not add up to 100%

Table 2. Median intake of dietary factors by studies (10th-90th percentile)[1]

Study	Unprocessed red meat (g/d)	Processed meat (g/d)	Poultry (g/d)	Seafood (g/d)[2]	Eggs (g/d)
Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	65.1 (35.9 - 113)	60.2 (22.2 - 142)	7.95 (0.00 - 30.4)	32.5 (11.4 - 74.5)	44.6 (18.1 - 96.9)
Beta-Carotene and Retinol Efficacy Trial	44.9 (15.8 - 106)	16.1 (2.79 - 51.4)	13.5 (3.40 - 39.2)	17.6 (2.31 - 46.4)	13.3 (0.00 - 46.7)
CLUE II Campaign Against Cancer and Heart Disease	37.1 (8.6 - 93.6)	17.9 (1.65 - 57.2)	15.4 (3.47 - 41.8)	11.1 (0.00 - 30.7)	12.5 (0.00 - 46.7)
Cancer Prevention Study-II Nutrition Cohort	44.2 (12.8 - 103)	13.1 (0.00 - 45.6)	20.57 (6.00 - 50.0)	17.1 (3.34 - 45.3)	8.36 (0.00 - 28.6)
Cohort of Swedish Men	55.7 (23.3 - 88.9)	32.8 (10.2 - 66.1)	8.87 (7.60 - 25.0)	30.4 (12.7 - 61.6)	15.3 (4.80 - 36.2)
European Investigation into Cancer and Nutrition	49.6 (8.55 - 114)	31.8 (2.40 - 88.3)	15.7 (0.37 - 49.5)	27.8 (4.10 - 78.2)	15.3 (3.50 - 42.5)
Health Professionals' Follow-Up Study	56.4 (18.1 - 134)	6.80 (0.00 - 22.6)	39.2 (19.6 - 79.8)	32.6 (9.00 - 84.4)	7.00 (0.00 - 40.0)
The Japan Public Health Center-Based Study Cohort 1	21.0 (10.3 - 35.3)	4.71 (0.00 - 11.0)	10.7 (0.00 - 25.0)	41.4 (21.4 - 104)	25.0 (10.7 - 50.0)
The Japan Public Health Center-Based Study Cohort 2	10.3 (3.4 - 24.0)	1.40 (0.00 - 4.28)	9.42 (3.10 - 22.0)	53.0 (14.4 - 115)	25.0 (3.50 - 50.0)
Melbourne Collaborative Cohort Study	109 (39.2 - 235)	21.4 (2.80 - 58.7)	24.0 (8.40 - 66.0)	23.5 (8.40 - 61.0)	17.5 (0.00 - 49.4)
Multiethnic Cohort Study	55.0 (12.0 - 146)	14.6 (2.90 - 46.3)	36.3 (11.3 - 101)	18.4 (3.58 - 54.4)	11.5 (2.88 - 39.1)
The Netherlands Cohort Study	63.8 (31.6 - 107)	15.3 (2.90 - 42.0)	10.6 (0.00 - 18.2)	11.5 (0.00 - 33.9)	14.2 (7.10 - 28.5)
The NIH-AARP Diet and Health Study	38.7 (9.0 - 102)	16.7 (3.7 - 53.1)	24.4 (5.81 - 77.6)	14.7 (3.74 - 48.7)	10.7 (0.00 - 25.0)
Prostate Cancer Prevention Trial	40.7 (7.92 - 116)	8.29 (0.53 - 33.5)	29.8 (6.87 - 93.1)	24.2 (3.57 - 72.3)	7.36 (0.00 - 47.3)
The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	56.0 (16.7 - 143)	15.5 (3.25 - 51.1)	18.1 (4.10 - 60.7)	21.7 (5.60 - 66.4)	12.1 (1.40 - 42.5)

[1]Definition of meat and fish variables: unprocessed red meat included all unprocessed red meats such as beef, pork, lamb and veal but excluding organs; processed meat included all processed meats such as sausages, hot dogs, bacon, ham and luncheon meats; unprocessed poultry included unprocessed meats from birds such as chicken and turkey; seafood included fish and shellfish but excluding fish organs or roe.

[2]In the Japan Public Health Center-Based Study Cohort 1 and 2 fish intake was measured with shellfish on the FFQ, fish intake was only assessed separately for dry fish, small fish and fish paste intake. In the NIH-AARP Diet and Health Study one question combined shellfish and other fish on the FFQ, fish intake was only assessed separately for tuna and fried fish. Four studies (Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, Campaign Against Cancer and Heart Disease, Cancer Prevention Study-II Nutrition Cohort and the Netherlands Cohort Study) did not assess shellfish intake therefore seafood intake represents fish intake.

Table 3. Multivariate Pooled Relative Risks (RR)[1] and 95% Confidence Intervals (95% CI) for Meat and Egg Consumption and Prostate Cancer Risk

	Categories (g/d)[2]								
Total Red Meat	**<20**	**20-<40**	**40-<80**	**80-<120**	**≥120**	**P-value, test of trend**	**P-value, test of between-studies heterogeneity, highest category**	**I^2, highest category**	**P-value, test of common effects, highest category**
Total	0.96 (0.92-0.99)	1.00	0.97 (0.93-1.02)	1.00 (0.97-1.03)[3,4]	0.99 (0.94-1.03)[3,4]	0.19	0.23	24%	
By stage									
Localized	0.96 (0.92-0.99)	1.00	0.99 (0.95-1.03)	1.00 (0.97-1.04)[3,4]	1.00 (0.96-1.04)[3,4]	0.20	0.74	0%	
Advanced [5]	0.96 (0.85-1.09)	1.00	1.01 (0.92-1.11)	0.99 (0.88-1.10)	1.04 (0.89-1.21)	0.63	0.17	29%	0.61[10]
Advanced (restricted)[6]	0.93 (0.79-1.11)	1.00	1.05 (0.92-1.19)	1.05 (0.91-1.21)	1.18 (1.01-1.38)	0.26	0.89	0%	0.05[11]
Fatal [7]	1.03 (0.88-1.21)[15]	1.00	0.97 (0.86-1.10)	0.98 (0.85-1.14)	1.00 (0.81-1.24)	0.59	0.08	43%	0.96[12]
By grade									
Low	0.95 (0.92-0.99)	1.00	0.99 (0.96-1.03)	1.01 (0.97-1.04)[3,4]	1.01 (0.97-1.06)[3,4]	0.05	0.67	0%	
High[8]	0.94 (0.87-1.01)[15]	1.00	0.96 (0.90-1.02)	0.97 (0.90-1.04)	0.93 (0.86-1.01)	0.57	0.56	0%	0.07[13]
Unprocessed Red Meat	**<20**	**20-<40**	**40-<60**	**60-<100**	**≥100**				
Total	1.00	1.02 (0.98-1.06)	1.02 (0.99-1.05)	1.02 (0.99-1.06)[4]	1.02 (0.98-1.06)[3,4]	0.93	0.43	2%	
By stage									
Localized	1.00	1.01 (0.97-1.07)	1.02 (0.99-1.06)	1.03 (0.99-1.07)[4]	1.02 (0.97-1.06)[3,4]	0.51	0.53	0%	
Advanced [5]	1.00	1.02 (0.91-1.14)	1.00 (0.88-1.14)	0.97 (0.83-1.13)	1.02 (0.83-1.24)	0.56	0.03	52%	>0.99[10]
Advanced (restricted)[6]	1.00	1.02 (0.89-1.16)	1.11 (0.96-1.27)	1.05 (0.91-1.21)	1.19 (1.01-1.40)	0.07	0.47	0%	0.07[11]
Fatal [7]	1.00	0.94 (0.81-1.09)	0.95 (0.83-1.08)	0.93 (0.79-1.11)	0.99 (0.78-1.26)	0.66	0.03	53%	0.83[12]
By grade									
Low	1.00	1.01 (0.96-1.08)	1.02 (0.99-1.06)	1.03 (0.99-1.07)[4]	1.03 (0.99-1.08)[3,4]	0.30	0.67	0%	
High[8]	1.00	1.00 (0.90-1.11)	0.99 (0.91-1.08)	1.01 (0.92-1.11)	0.93 (0.81-1.06)	0.58	0.09	42%	0.14[13]
Processed Meat[9]	**<5**	**5-<10**	**10-<20**	**20-<40**	**≥40**				
Total	1.00	1.03 (1.00-1.06)	1.03 (0.99-1.07)	1.03 (0.98-1.08)	1.04 (1.01-1.08)	0.29	0.61	0%	
By stage									

Localized	1.00	1.03 (0.99-1.06)	1.03 (0.99-1.06)	1.03 (0.99-1.08)	1.04 (1.00-1.09)	0.11	0.77	0%	
Advanced [5]	1.00	1.06 (0.95-1.18)	1.17 (1.06-1.30)	1.02 (0.91-1.15)	1.09 (0.95-1.26)	0.55	0.39	7%	0.55[10]
Advanced (restricted)[6]	1.00	1.06 (0.93-1.22)	1.16 (1.02-1.32)	1.04 (0.90-1.20)	1.17 (0.99-1.39)	0.10	0.94	0%	0.21[11]
Fatal [7]	1.00	1.06 (0.93-1.20)	1.15 (1.02-1.30)	1.05 (0.92-1.21)	1.04 (0.88-1.24)	0.63	0.51	0%	>0.99[12]
By grade									
Low	1.00	1.04 (1.00-1.08)	1.04 (1.00-1.08)	1.04 (1.00-1.08)	1.06 (1.01-1.10)	0.17	0.87	0%	
High[8]	1.00	1.03 (0.96-1.10)	1.03 (0.97-1.10)	0.98 (0.91-1.05)	1.01 (0.90-1.14)	0.75	0.20	29%	0.54[13]

Poultry	**<5**	**5-<15**	**15-<25**	**25-<45**	**≥45**				
Total	1.00	1.01 (0.97-1.05)	1.03 (0.97-1.10)[3]	1.01 (0.95-1.07)	1.05 (1.00-1.09)[4]	0.33	0.55	0%	
By stage									
Localized	1.00	1.03 (0.97-1.09)	1.07 (1.00-1.14)[3]	1.04 (0.97-1.11)	1.07 (1.02-1.13)[4]	0.26	0.75	0%	
Advanced [5]	1.00	0.91 (0.82-1.00)	0.84 (0.75-0.94)	0.79 (0.69-0.90)	0.83 (0.70-0.99)	0.29	0.16	30%	0.007[10]
Advanced (restricted)[6]	1.00	0.98 (0.86-1.11)	0.86 (0.75-1.00)	0.83 (0.70-0.99)	0.97 (0.79-1.19)	0.44	0.28	19%	0.37[11]
Fatal [7]	1.00	0.83 (0.72-0.96)	0.79 (0.65-0.95)	0.72 (0.62-0.85)	0.69 (0.59-0.82)	0.16	0.47	0%	<0.001[12]
By grade									
Low	1.00	1.02 (0.97-1.08)	1.04 (0.97-1.11)[3]	1.03 (0.95-1.11)	1.06 (1.01-1.12)[4]	0.66	0.78	0%	
High[8]	1.00	0.97 (0.90-1.06)	1.00 (0.92-1.09)	0.96 (0.88-1.06)	1.00 (0.91-1.10)	0.33	0.71	0%	0.28[13]

Seafood	**<5**	**5-<10**	**10-<20**	**20-<40**	**≥40**				
Total	1.00	1.05 (1.00-1.11)[3]	1.05 (1.01-1.08)	1.05 (1.02-1.09)	1.04 (0.98-1.09)	0.67	0.22	25%	
By stage									
Localized[14]	1.00	1.04 (1.00-1.08)[3]	1.06 (1.01-1.11)	1.07 (1.03-1.11)	1.04 (0.97-1.12)	0.38	0.06	46%	
Advanced [5]	1.00	1.07 (0.95-1.21)	0.98 (0.88-1.08)	0.97 (0.87-1.09)	0.94 (0.82-1.07)	0.73	0.73	0%	0.16[10]
Advanced (restricted)[6]	1.00	1.09 (0.93-1.27)	1.02 (0.90-1.17)	1.01 (0.83-1.22)	1.04 (0.88-1.22)	0.59	0.73	0%	0.98[11]
Fatal [7]	1.00	1.05 (0.90-1.22)	0.90 (0.77-1.04)	0.93 (0.80-1.10)	0.87 (0.72-1.06)	0.40	0.24	24%	0.10[12]
By grade									
Low[14]	1.00	1.07 (1.01-1.13)[3]	1.07 (1.02-1.12)	1.06 (1.02-1.10)	1.02 (0.94-1.09)	0.38	0.04	49%	
High[8]	1.00	1.01 (0.94-1.09)	1.00 (0.93-1.07)	1.04 (0.95-1.14)	1.03 (0.95-1.12)	0.17	0.77	0%	0.80[13]

Eggs	**<5**	**5-<25**	**≥25**						
Total	1.00	1.01 (0.99-1.03)	0.99 (0.96-1.02)			0.65	0.97	0%	
By stage									

Localized	1.00	1.01 (0.98-1.03)	0.97 (0.94-1.00)	0.09	0.90	0%	
Advanced [5]	1.00	1.05 (0.98-1.14)	1.14 (1.01-1.28)	0.01	0.24	23%	0.009[10]
Advanced (restricted)[6]	1.00	1.06 (0.95-1.18)	1.07 (0.89-1.29)	0.35	0.06	50%	0.02[11]
Fatal [7]	1.00	1.02 (0.93-1.13)	1.14 (1.00-1.30)	0.01	0.33	13%	0.02[12]
By grade							
Low	1.00	0.99 (0.97-1.02)	0.97 (0.94-1.00)	0.06	0.80	0%	
High[8]	1.00	1.08 (1.00-1.17)	1.06 (0.98-1.15)	0.07	0.31	18%	0.03[13]

"Localized": defined as cancers with information on stage but are not defined as "periprostatic", i.e. cancers confined within the prostate; "Advanced": defined as cancers with extension to or fixation to adjacent structures other than seminal vesicles, i.e. T4, N1, M1 or fatal; "Advanced (restricted)": same as "advanced" but excluding localized cases and cases with missing stage, who died of prostate cancer during follow-up; "Low grade": Gleason score <8 or well/moderately differentiated; "High grade": Gleason score >=8 or poorly differentiated/undifferentiated

[1]All models multivariate were adjusted for marital status (married (reference (ref)), never married, widowed, divorced), race (Caucasian (ref), African-American, Asian, Hispanic, other), education (<high school (ref), high school, >high school), body mass index (BMI, kg/m^2) (<23 (ref), 23-<25, 25-<30, ≥30), height (meter) (<1.70 (ref), 1.70-<1.75, 1.75-<1.80, 1.80-<1.85, ≥1.85), alcohol (g/day) (0 (ref), >0-<5, 5-<15,15-<30, ≥30), total energy intake (kcal/d, as continuous variable), smoking status (never (ref), past smoker <15 pack years, past smoker ≥15 pack years, current smoker <40 pack years, current smoker ≥40 pack years), prostate cancer family history (no (ref), yes), physical activity (low (ref), medium, high), history of diabetes (no (ref), yes), multivitamin use (no (ref), yes). Age in years and year of questionnaire return were included as stratification variables.

[2] Grams vs. ounces: 5 g/day = 0.18 ounces/day ; 10g/day=0.35 ounces/day; 25 g/day = 0.88 ounces/day; 40 g/day=1.41 ounces/day; 100 g/day=3.52 ounces/day; 120g/day= 4.23 ounces/day; 1 egg about 50g (1.76 ounces); 25g/day about half an egg per day

[3]The Japan Public Health Center Study 1 was excluded from this category because this study did not have any cases in this category. The participants in this study who were in this category and were not cases were included in the next highest category.

[4]The Japan Public Health Center Study 2 was excluded from this category because this study did not have any cases in this category. The participants in this study who were in this category and were not cases were included in the next highest category.

[5]The Japan Public Health Center Study 1, the Japan Public Health Center Study 2 and the Prostate Cancer Prevention Trial were excluded from these analyses because these studies had less than 50 advanced prostate cancer cases.

[6]The Beta-Carotene Retinol Efficacy Trial, Campaign Against Cancer and Heart Disease, Japan Public Health Center Study 1, the Japan Public Health Center Study 2, Melbourne Collaborative Cohort Study, and the Prostate Cancer Prevention Trial were excluded from these analyses because these studies had less than 50 advanced (restricted) prostate cancer cases. For egg intake: the Alpha-Tocopherol Beta-Carotene Prevention Study was excluded from this analysis because this study did not have any cases in the reference group.

[7]The Beta-Carotene Retinol Efficacy Trial, Campaign Against Cancer and Heart Disease, Japan Public Health Center Study 1, the Japan Public Health Center Study 2 and the Prostate Cancer Prevention Trial were excluded from these analyses because these studies had less than 50 fatal prostate cancer cases.

[8]The Japan Public Health Center Study 1 and 2 were excluded from the analyses of high grade cancers because these studies had <50 high grade cancer cases.

[9]The Japan Public Health Center Study 1 and 2 were excluded from the analyses of processed meat consumption due to low consumption.

[10]Test for common effects : localized vs. advanced cancers

[11]Test for common effects : localized vs. advanced (restricted) cancers

[12]Test for common effects : localized vs. fatal cancers

[13]Test for common effects : low grade vs. high grade cancers

[14]The Japan Public Health Center Study 2 was excluded from the analyses of localized cancers because this study had no cases in the reference group.

Table 4: Multivariate Pooled Relative Risks (RR)[1] and 95% Confidence Intervals (95% CI) for Meat and Egg Consumption and Prostate Cancer Risk by Geographic Region

	Categories (g/d)[2]					P-value for test of trend	P-value for test of between-studies heterogeneity, highest category	P-value for test of interaction, highest category
Unprocessed red meat	**<20**	**20-<40**	**40-<60**	**60-<100**	**≥100**			
Advanced[3]								
North America	1.00	1.07 (0.96-1.20)	1.07 (0.94-1.22)	1.08 (0.96-1.23)	1.19 (1.02-1.39)	0.01	0.37	0.70
Other Continents	1.00	0.86 (0.64-1.16)	0.85 (0.60-1.22)	0.76 (0.52-1.11)	0.82 (0.54-1.26)	0.25	0.02	
Advanced (restricted)[4]								
North America	1.00	1.05 (0.90-1.22)	1.15 (0.98-1.36)	1.10 (0.93-1.30)	1.30 (1.07-1.57)	0.01	0.78	0.49
Other Continents	1.00	0.93 (0.73-1.19)	1.01 (0.78-1.29)	0.95 (0.74-1.22)	0.96 (0.70-1.33)	0.82	0.35	
Fatal[5]								
North America	1.00	1.01 (0.87-1.16)	1.00 (0.85-1.17)	1.03 (0.88-1.21)	1.12 (0.85-1.46)	0.18	0.11	0.20
Other Continents	1.00	0.82 (0.59-1.14)	0.84 (0.62-1.13)	0.78 (0.53-1.14)	0.84 (0.54-1.29)	0.37	0.09	
Processed meat	**<5**	**5-<10**	**10-<20**	**20-<40**	**≥40**			
Advanced[3]								
North America	1.00	1.05 (0.92-1.20)	1.19 (1.06-1.33)	0.95 (0.84-1.08)	1.07 (0.86-1.34)	0.93	0.17	0.08
Other Continents	1.00	1.12 (0.88-1.42)	1.13 (0.92-1.40)	1.24 (1.00-1.53)	1.12 (0.87-1.45)	0.55	0.62	
Advanced (restricted)[4]								
North America	1.00	1.02 (0.87-1.19)	1.16 (0.98-1.37)	0.95 (0.81-1.13)	1.16 (0.95-1.42)	0.18	0.76	0.36
Other Continents	1.00	1.24 (0.93-1.65)	1.18 (0.91-1.54)	1.29 (0.99-1.69)	1.20 (0.87-1.65)	0.40	0.78	
Fatal[5]								
North America	1.00	1.05 (0.91-1.22)	1.16 (1.00-1.36)	0.97 (0.83-1.14)	1.02 (0.76-1.36)	0.99	0.19	0.61
Other Continents	1.00	1.07 (0.81-1.42)	1.13 (0.88-1.46)	1.29 (1.00-1.67)	1.11 (0.82-1.51)	0.56	0.78	
Poultry	**<5**	**5-<15**	**15-<25**	**25-<45**	**≥45**			
Advanced[3]								
North America	1.00	0.86 (0.74-1.01)	0.78 (0.67-0.92)	0.75 (0.64-0.88)	0.77 (0.59-1.00)	0.42	0.10	0.79
Other Continents	1.00	0.94 (0.82-1.07)	0.89 (0.76-1.04)	0.86 (0.69-1.06)	0.92 (0.73-1.17)	0.56	0.52	
Advanced (restricted)[4]								
North America	1.00	1.01 (0.81-1.25)	0.87 (0.70-1.09)	0.83 (0.66-1.04)	0.89 (0.69-1.15)	0.51	0.33	0.55
Other Continents	1.00	0.96 (0.83-1.12)	0.86 (0.71-1.03)	0.84 (0.63-1.10)	1.12 (0.79-1.58)	0.71	0.25	

Fatal[5]								
North America	1.00	0.71 (0.58-0.86)	0.65 (0.53-0.79)	0.65 (0.53-0.80)	0.63 (0.51-0.78)	0.23	0.38	0.10
Other Continents	1.00	0.94 (0.81-1.10)	0.97 (0.81-1.16)	0.87 (0.67-1.13)	0.85 (0.63-1.14)	0.54	0.78	
Seafood	**<5**	**5-<10**	**10-<20**	**20-<40**	**≥40**			
Advanced[3]								
North America	1.00	1.06 (0.92-1.22)	1.00 (0.88-1.15)	0.91 (0.79-1.04)	0.89 (0.76-1.04)	0.11	0.48	0.72
Other Continents	1.00	1.10 (0.86-1.40)	0.93 (0.78-1.11)	1.13 (0.93-1.37)	1.04 (0.82-1.31)	0.12	0.88	
Advanced (restricted)[4]								
North America	1.00	1.08 (0.90-1.30)	1.01 (0.85-1.20)	0.91 (0.72-1.17)	0.97 (0.79-1.19)	0.52	0.59	0.34
Other Continents	1.00	1.10 (0.82-1.49)	1.04 (0.85-1.28)	1.21 (0.96-1.52)	1.18 (0.89-1.55)	0.04	0.73	
Fatal[5]								
North America	1.00	1.03 (0.85-1.24)	0.94 (0.76-1.17)	0.84 (0.71-1.00)	0.81 (0.61-1.08)	0.05	0.13	0.11
Other Continents	1.00	1.15 (0.85-1.56)	0.86 (0.69-1.07)	1.10 (0.85-1.42)	1.02 (0.77-1.35	0.26	0.73	
Eggs	**<5**	**5-<25**	**≥25**					
Advanced[3]								
North America	1.00	1.13 (1.03-1.24)	1.27 (1.14-1.42)			<0.001	0.60	0.003
Other Continents	1.00	0.88 (0.76-1.02)	0.92 (0.77-1.11)			0.88	0.96	
Advanced (restricted)[4]								
North America	1.00	1.15 (1.02-1.30)	1.23 (1.02-1.48)			0.03	0.23	<0.001
Other Continents	1.00	0.84 (0.66-1.08)	0.84 (0.67-1.05)			0.23	0.99	
Fatal[5]								
North America	1.00	1.10 (0.98-1.23)	1.26 (1.10-1.45)			0.006	0.50	0.02
Other Continents	1.00	0.83 (0.65-1.06)	0.88 (0.73-1.07)			0.80	0.91	

"Localized": defined as cancers with information on stage but are not defined as "periprostatic", i.e. cancers confined within the prostate; "Advanced": defined as cancers with extension to or fixation to adjacent structures other than seminal vesicles, i.e. T4, N1, M1 or fatal; "Advanced (restricted)": same as "advanced" but excluding localized cases and cases with missing stage, who died of prostate cancer during follow-up; "Low grade": Gleason score <8 or well/moderately differentiated; "High grade": Gleason score >=8 or poorly differentiated/undifferentiated

[1]All models multivariate were adjusted for marital status (married (reference (ref)), never married, widowed, divorced), race (Caucasian (ref), African-American, Asian, Hispanic, other), education (<high school (ref), high school, >high school), body mass index (BMI, kg/m^2) (<23 (ref), 23-<25, 25-<30, ≥30), height (meter) (<1.70 (ref), 1.70-<1.75, 1.75-<1.80, 1.80-<1.85, ≥1.85), alcohol (g/day) (0 (ref), >0-<5, 5-<15,15-<30, ≥30), total energy intake (kcal/d, as continuous variable), smoking status (never (ref), past smoker <15 pack years, past smoker ≥15 pack years, current smoker <40 pack years, current smoker ≥40 pack years), prostate cancer family history (no (ref), yes), physical activity (low (ref), medium, high), history of diabetes (no (ref), yes), multivitamin use (no (ref), yes). Age in years and year of questionnaire return were included as stratification variables

[2] Grams vs. ounces: 5 g/day = 0.18 ounces/day ; 10g/day=0.35 ounces/day; 25 g/day = 0.88 ounces/day; 40 g/day=1.41 ounces/day; 100 g/day=3.52 ounces/day; 120g/day= 4.23 ounces/day; 1 egg about 50g (1.76 ounces); 25g/day about half an egg per day

[3]The Japan Public Health Center Study 1, the Japan Public Health Center Study 2, and the Prostate Cancer Prevention Trial were excluded from these analyses

because these studies had less than 50 advanced prostate cancer cases.
[4]The Beta-Carotene Retinol Efficacy Trial, Campaign Against Cancer and Heart Disease, the Japan Public Health Center Study 1, the Japan Public Health Center Study 2, the Prostate Cancer Prevention Trial and the Melbourne Collaborative Cohort Study were excluded from these analyses because these studies had less than 50 advanced (restricted) prostate cancer cases. For egg intake: the Alpha-Tocopherol Beta-Carotene Prevention Study was also excluded from this analysis because this study did not have any cases in the reference group for egg intake.
[5]The Beta-Carotene Retinol Efficacy Trial, Campaign Against Cancer and Heart Disease, the Japan Public Health Center Study 1, the Japan Public Health Center Study 2, and the Prostate Cancer Prevention Trial were excluded from these analyses because these studies had less than 50 fatal prostate cancer cases.