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ORIGINAL PAPER

Body size and dietary risk factors for aggressive prostate cancer: a case–control study

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Abstract

Purpose Diet and body size may affect the risk of aggressive prostate cancer (APC), but current evidence is inconclusive.

Methods A case–control study was conducted in men under 75 years of age recruited from urology practices in Victoria, Australia; 1,254 with APC and 818 controls for whom the presence of prostate cancer had been excluded by biopsy. Dietary intakes were assessed using a validated food frequency questionnaire. Multivariable unconditional logistic regression estimated odds ratios and confidence intervals for hypothesized risk factors, adjusting for age, family history of prostate cancer, country of birth, socioeconomic status, smoking, and other dietary factors.

Results Positive associations with APC (odds ratio, 95% confidence intervals, highest vs. lowest category or quintile) were observed for body mass index (1.34, 1.02–1.78, $P_{trend}=0.04$), and trouser size (1.54, 1.17–2.04, $P_{trend}=0.001$). Intakes of milk and all dairy products were inversely associated with APC risk (0.71, 9.53–0.96, $P_{trend}=0.05$, and 0.64, 0.48–0.87, $P_{trend}=0.012$, respectively), but there was little evidence of an association with other dietary variables ($P_{trend}>0.05$).

Conclusions We confirmed previous evidence for a positive association between body size and risk of APC, and suggest that consumption of dairy products, and milk more specifically, is inversely associated with risk.

Keywords Aggressive prostate cancer · Body mass index · Diet · Nutrition · Case–control study

Introduction

Prostate cancer (PC) is the most common cancer diagnosed in Australian men, and the second most common in men worldwide [1, 2]. Many previous observational studies investigating PC have treated all PC as a single condition. More recent studies that have stratified on tumor aggressiveness report that the risk factors for aggressive and indolent disease might differ in both the strength and direction of association [3]. The substantially lower mortality rates compared with incidence [1, 2] suggests that most PC cases are not aggressive; hence, the importance of investigating and identifying modifiable risk factors specific to higher Gleason score and non-organ confined disease.

PC has few established risk factors, particularly those of a modifiable nature [4]. To date, advancing age and a positive family history of PC, as well as African American ethnicity, are the most well-established risk factors for development of the disease [5]. The World Cancer Research Fund (WCRF) has identified body fatness (defined by BMI, waist circumference, or waist-hip ratio) to be a probable risk factor for advanced PC, although no conclusion could be drawn in relation to overall PC risk [4]. The relationship between BMI and PC may vary in direction depending on age and cancer aggressiveness. Positive associations have been reported with APC for older men, while inversely related to low-grade PC risk for younger men [6–8]. In other studies, inverse associations have been observed for all PC with BMI at all ages [9].

Dietary factors and specific nutrients have been frequently investigated for their potential roles in carcinogenesis. Those that have been reported to be associated with decreased PC or APC risk include intakes of lycopene, found in high levels in tomatoes [10, 11], fruits and vegetables [12, 13], cruciferous vegetables such as broccoli, cabbage, and cauliflower [14, 15], allium vegetables including onion, leek, and garlic

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[16, 17], as well as fish [18, 19]. On the other hand, high intakes of processed meat [20, 21], dairy products [22, 23], and calcium [24, 25] have been reported to be associated with increased risk of PC, APC, and PC-specific mortality. Although some studies have reported associations between these factors and adverse PC outcomes, others have observed no associations [4, 14, 18, 23, 26–33], and few have focused on APC specifically. Thus, additional studies with the clinically important APC as the outcome of interest are needed. Our aim was to assess associations of body size and dietary risk factors with risk of APC.

Materials and methods

Study design

We conducted a case–control study of APC in Victoria, Australia, initiated in 2011, designed to examine associations between lifestyle factors, including diet, and the risk of APC. Dietary data were collected using a validated, self-administrated 127-item food frequency questionnaire (FFQ). Information on demographics, body size history, smoking, and other health conditions was also collected. Informed consent was obtained from all participants and the study was approved by the Cancer Council Victoria Human Research Ethics Committee (#0910).

Case and control definition and recruitment

Eligible cases were men, identified from the Victorian Cancer Registry (VCR), who had been diagnosed (between 1st January 2010 and 30th June 2014) before age 75 years with APC defined as a Gleason sum 7 (4 + 3 only), Gleason sum 8–10, and/or TNM stage T3 or T4, and metastatic PC [4]. Men had to be aged less than 75 years at recruitment as we have found in previous studies that beyond this age the response rate and quality of data provided tend to diminish rapidly. Additionally, our main interest is in the prevention of years of life lost to APC in younger men. Age 75 years is the conventional reference age for calculating potential years of life lost (PYLL) in developed countries and cases above this age do not contribute to PYLL estimates.

Eligible controls were men aged less than 75 years at recruitment, identified from the same urology clinics as cases, who had undergone the same urological examination procedures as cases (transrectal ultrasound-guided biopsy) and had a PSA level above the following age-specific limits ($\geq$ 2 ng/ml for men aged < 49 years; $\geq$ 3 ng/ml for men aged 50–59 years; $\geq$ 4 ng/ml for men aged 60–69 years; and $\geq$ 5.5 ng/ml for men aged 70–74 years), but a negative biopsy.

Eligible cases and controls had to be able to complete self-administered questionnaires in English.

Due to low frequencies of non-Caucasian participants, 3.3% and 4.5% for cases and controls, respectively, they were excluded from the analysis. Study participants with missing covariate data were also excluded.

Dietary intakes measurement

The FFQ assessed the frequency of intakes (from never to three or more times per day) of 127 items, including foods and beverages, in the year before last, which were all converted to daily averages based on standard portion sizes from repeated 24-h recalls as previously described [34]. Nutrient intakes were calculated using NUTTAB 2010 [35] and AUSNUT 2007 [36] databases and the US Department of Agriculture carotenoid database [37].

Covariate measurement

Age in years was defined at the completion of the questionnaire. Self-reported height and weight were used to calculate BMI. Men were asked about trouser size as a measure of waist circumference and abdominal obesity and reported this in several different units, including centimeters (cm), inches, descriptive sizes (S/M/L etc.), as well as some additional information in text format. All observations on trouser size were converted into cm. Descriptive sizes were converted into corresponding values in cm using standard Australian sizes (XS = 77 cm, S = 82 cm, M = 87 cm, L = 92 cm, XL = 97 cm, XXL = 102 cm, XXXL = 107 cm). Socioeconomic status was defined by the socioeconomic indexes for area (SEIFA) index of socioeconomic advantage and disadvantage produced by the Australian Bureau of Statistics based on census characteristics [38]. Regular cigarette smoking for more than one year was categorized as never, current, or former (Table 1).

Statistical analysis

Directed acyclic graphs (DAGs) were used to determine which variables to include in the models. The DAG for the overall diet and APC (Fig. 1) identified the following variables for inclusion: age, smoking status, country of birth and socioeconomic status (both strong determinants of PSA testing), and BMI or trouser size. Although family history of PC is an established risk factor for APC but not necessarily associated with diet, and thus should not be adjusted for according to the DAG, we decided to include this variable in our models.

Odds ratios (OR) and confidence intervals (CI) were estimated using multivariable unconditional logistic regression. A first model adjusted for age (continuous), family history of

Table 1 Characteristics of the study sample, $n = 2{,}072$

	Cases ($n = 1{,}254$)	Controls ($n = 818$)
Age at questionnaire (years), median	67	63
First-degree family history, *n* (%)		
Yes	305 (24)	127 (16)
No	949 (76)	691 (84)
Country of birth, *n* (%)		
Australia	943 (75)	622 (76)
Other	311 (25)	196 (24)
Body mass index (kg/m^2), mean (sd)	27.5 (4.4)	27.1 (3.7)
Body mass index (kg/m^2), *n* (%)		
< 25	342 (27)	246 (30)
25–30	620 (49)	411 (50)
> 30	263 (21)	145 (18)
Missing	29 (2.3)	16 (2.0)
Socioeconomic status, *n* (%)		
1st quintile (most disadvantaged)	143 (11)	68 (8.3)
2nd quintile	200 (16)	118 (14)
3rd quintile	252 (20)	134 (16)
4th quintile	287 (23)	191 (23)
5th quintile (least disadvantage)	372 (30)	307 (38)
Trouser size (cm), mean (sd)	92.2 (9.3)	90.6 (8.6)
Trouser size, *n* (%)		
< 90 cm	511 (41)	411 (50)
90–100 cm	515 (41)	301 (37)
> 100 cm	228 (18)	106 (13)
Cigarette smoking, *n* (%)		
Never	606 (48)	479 (59)
Former	568 (45)	302 (37)
Current	80 (6.4)	37 (4.5)
Dietary/nutrient intakes, means (sd)		
Fruit (g/day)	191 (130)	186 (128)
Vegetables (g/day)	193 (112)	185 (107)
Processed meat (g/day)	13.0 (14.6)	13.1 (14.3)
Total meat (g/day)	147 (70)	142 (64)
Fish (g/day)	36 (29)	37 (27)
Dairy (g/day)	348 (227)	368 (221)
Fresh tomatoes (g/day)	25 (22)	24 (20)
Tomato-based foods (g/day)	38 (44)	38 (49)
Total tomatoes (g/day)	63 (52)	62 (54)
Allium vegetables (g/day)	6.1 (6.1)	5.9 (5.9)
Cruciferous vegetables (g/day)	21 (21)	19 (21)
Lycopene (mcg/day)	7201 (6135)	7347 (7273)
Vitamin E (mg/day)	12 (4.1)	12 (4.1)
Vitamin D (mcg/day)	3.6 (1.6)	3.6 (1.4)
Vitamin C (mg/day)	106 (56)	103 (54)
Zinc (mg/day)	12 (3.5)	12 (3.5)
Calcium (mg/day)	853 (322)	882 (331)
Magnesium (mg/day)	400 (122)	406 (122)
Phosphorus (mg/day)	1551 (465)	1568 (460)
Long chain omega 3 fatty acids (mg/day)	375 (245)	379 (231)

Sd standard deviation, *g/d* grams/day, *mcg* micrograms, *mg* milligrams

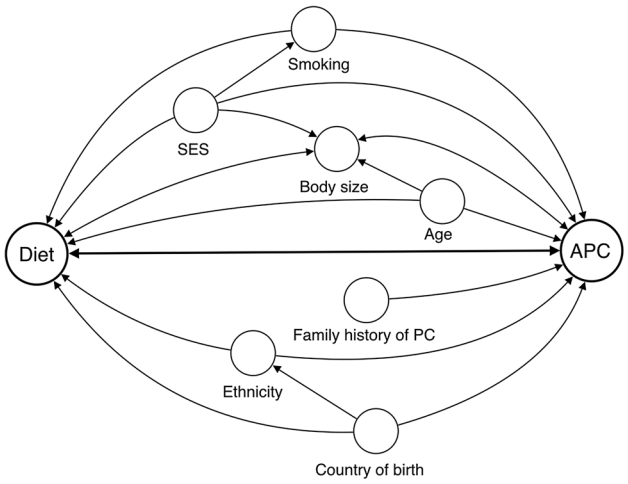

Fig. 1 Directed acyclic graph for the overall diet and APC

PC (yes/no), country of birth, socioeconomic status (in quintiles), smoking status (never, current, or former), as well as quintiles of intakes of fruit, vegetables, fish, and processed meat. A second model additionally adjusted for trouser size (categorical: < 90 cm, 90–100 cm, or > 100 cm). To estimate linear trends, each dietary or nutrient intake variable was fitted as a pseudocontinuous covariate using the median value in each quintile.

In the second model, we tested whether BMI or trouser size was a better fit using Akaike's information criterion (AIC) and Bayesian information criterion (BIC). The AIC and BIC values were similar, but we chose to include trouser size (as a categorical variable) in Model 2 as the values were slightly lower for this model (data not shown), and there were 45 study participants with missing data on BMI but not trouser size.

A combined dairy product variable included intakes of butter, butter-margarine blend, cream/sour cream, full-cream milk, reduced fat milk, skim milk, flavored milk, ice cream, yogurt, ricotta/cottage cheese, and other cheese. Spearman's correlation was used to test the correlation between the variables for quintiles of intakes of dairy products and calcium. Total milk intake was analyzed separately. We also compared levels of intake of full-cream milk (</≥ median) with no consumption, to investigate whether a potential association would differ according to milk fat content, as has been previously suggested [23].

Effect modification was assessed using the likelihood ratio test for two-way interaction terms between age and BMI and between age and trouser size. Age was dichotomised at < 65/≥ 65 years, consistent with the literature that suggests an age–BMI interaction [6, 7], as well as being close to the median ages of cases and controls (Table 1). All analyses were performed using Stata 14.2 (College Station, TX, USA).

Results

Figure 2 shows the recruitment of study participants. Study participants that were excluded due to missing covariate data included 223 cases and 126 controls. The number of non-Caucasians excluded were 47 cases and 42 controls. The final sample ($n = 2{,}072$) included 1,254 cases and 818 controls.

Characteristics of the study sample are presented in Table 1. Most study participants were born in Australia. Cases tended to be older and more likely to have a first-degree family history of PC compared with controls. They were also more likely to live in a more socioeconomically disadvantaged area and to be current or former smokers. BMI was similar between cases and controls, while trouser size tended to be greater for cases (Table 1). The average time between diagnosis and questionnaire completion was 352 days (mean). The 25%, 50%, and 75% percentiles were 259, 352, and 475 days, respectively.

The ORs and corresponding 95% CIs for APC risk for BMI and trouser size are presented in Table 2. A BMI > 30 kg/m^2 compared with a BMI < 25 kg/m^2 was positively associated with APC risk (OR = 1.34, 95% CI 1.02–1.78). Additionally, a trouser size between 90-100 cm or > 100 cm compared with one < 90 cm was associated with increased APC risk (OR = 1.28, 95% CI 1.05–1.58 and OR = 1.54, 95% CI 1.17–2.04, respectively). No evidence of interaction with age was found for BMI or trouser size ($P_{\text{interaction}} = 0.93$ and $P_{\text{interaction}} = 0.13$, respectively) (data not shown).

Table 3 shows ORs and corresponding 95% CIs for APC risk for quintiles of dietary intakes. Food and nutrient intakes showed little association with APC. The exception was dairy product intake. For the highest intake (Q5) compared with the lowest (Q1) intake of dairy products, the adjusted OR was 0.64, 95% CI 0.48–0.87, $P_{\text{trend}} = 0.012$ (Model 1). A weak inverse association was observed for overall milk intake (Q5 vs. Q1 OR = 0.72, 95% CI 0.54–0.98, $P_{\text{trend}} = 0.058$) (Model 1), which was slightly more pronounced in Model 2 (Q5 vs. Q1 OR = 0.71, 95% CI 0.53–0.96, $P_{\text{trend}} = 0.051$).

There was weak evidence that calcium intake was inversely associated with APC risk in Model 1 (Q5 vs. Q1 OR = 0.72, 95% CI 0.52–0.98, $P_{\text{trend}} = 0.06$ and in Model 2 (Q5 vs. Q1 OR = 0.71, 95% CI 0.52–0.98, $P_{\text{trend}} = 0.06$). When Model 1 was additionally adjusted for dairy intake the risk estimate was attenuated and no longer close to significant (Q5 vs. Q1 OR = 1.07, 95% CI 0.75–1.51, $P_{\text{trend}} = 0.60$) (data not shown). When testing Spearman correlation between quintiles of intakes of dairy products and calcium, the rho was 0.82, indicating a strong correlation.

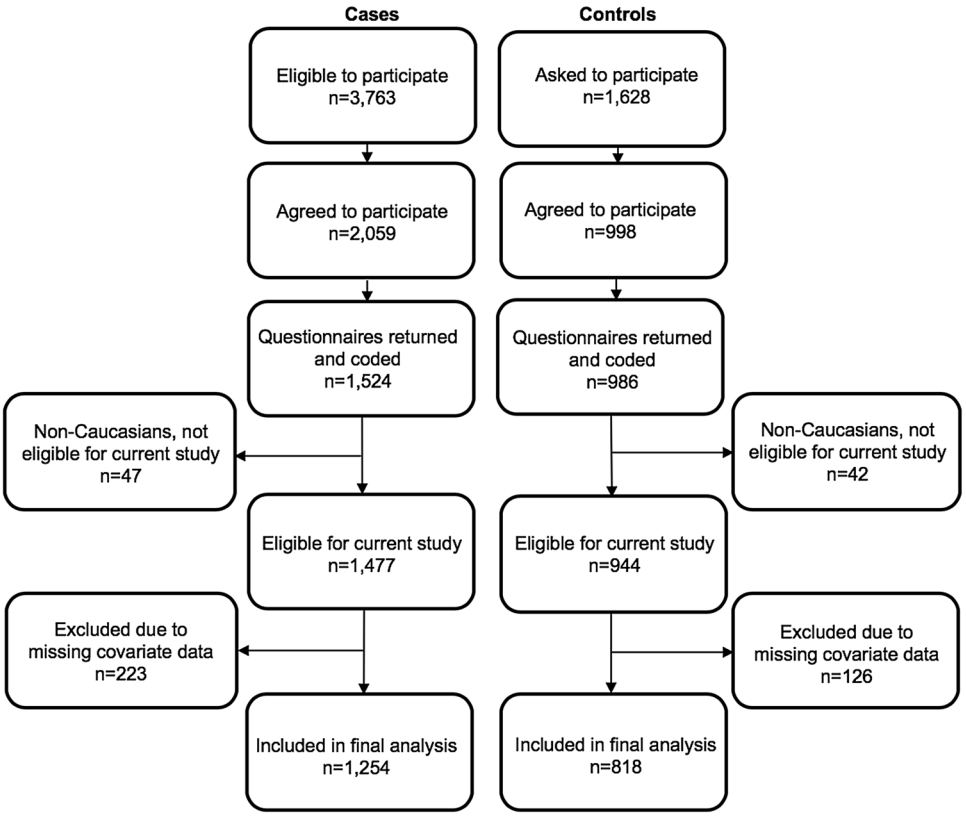

Fig. 2 Study participant recruitment flow-chart

Table 2 The risk of aggressive prostate cancer associated with BMI ($n=2,027$) and trouser size ($n=2,072$)

Cases/controls, *n*		Model 1[a] OR (95% CI)	P_{trend}[b]
1,225/802	BMI (per 5 kg/m^2)	1.14 (1.01–1.28)	0.04
342/246	BMI (< 25 kg/m^2)		
620/411	25–30 kg/m^2	1.07 (0.86–1.33)	
263/145	> 30 kg/m^2	1.34 (1.02–1.78)	
1,254/818	Trouser size (per 10 cm)	1.17 (1.05–1.30)	0.001
511/411	Trouser size (< 90 cm)		
515/301	90–100 cm	1.28 (1.05–1.58)	
228/106	> 100 cm	1.54 (1.17–2.04)	

OR odds ratios, *CI* confidence interval

[a]Adjusted for age, family history of PC, socioeconomic status, country of birth, smoking status, and quintiles of intakes of foods (fruits, vegetables, fish, and processed meat)

[b]P_{trend} obtained from using the median value in each quintile as a pseudocontinuous variable

When comparing men who had high and low intakes of full-cream milk, ≥ 257 g/day and < 257 day/g, respectively, with non-full-cream milk consumers, no associations were observed (Table 4).

Discussion

This case–control study investigating associations between risk of APC and body size and dietary factors found that BMI and trouser size were positively associated with APC risk while dairy product intake was inversely associated, and this latter association was little changed after additional adjustment for trouser size. We found no evidence that BMI or trouser size were more strongly associated with risk of APC for men aged 65 years or older.

Although the positive associations for both BMI and trouser size with risk of APC supported the stated hypothesis and are consistent with the conclusions of the WCRF in 2018 that body size was probably associated with APC [4], hypothesized interactions between age and BMI or trouser size were not confirmed. Previous studies have suggested

Table 3 The risk of aggressive prostate cancer associated with quintiles of food and nutrient intakes

Cases/controls, *n*	Quintile (Q) [median g/day]	Model 1[a] OR (95% CI)	P_{trend}[c]	Model 2[b] OR (95% CI)	P_{trend}[c]
252/169	Fruit (g/day) ref Q1 [58.8]				
244/177	Q2 [103.5]	0.88 (0.66–1.18)		0.88 (0.66–1.18)	
239/158	Q3 [156.3]	0.98 (0.73–1.32)		0.98 (0.73–1.33)	
259/160	Q4 [231.6]	1.07 (0.79–1.44)		1.09 (0.80–1.47)	
260/154	Q5 [361.1]	1.14 (0.83–1.55)	0.17	1.15 (0.84–1.57)	0.14
236/166	Vegetables (g/day) ref Q1 [69.6]				
257/165	Q2 [119.9]	1.11 (0.82–1.49)		1.08 (0.80–1.46)	
243/176	Q3 [167.9]	0.96 (0.71–1.30)		0.95 (0.70–1.28)	
249/162	Q4 [229.9]	1.03 (0.76–1.39)		1.02 (0.75–1.38)	
269/149	Q5 [329.4]	1.12 (0.82–1.53)	0.59	1.12 (0.82–1.53)	0.57
319/198	Processed meat (g/day) ref Q1 [1.2]				
271/159	Q2 [4.2]	1.07 (0.81–1.42)		1.06 (0.80–1.40)	
203/152	Q3 [8.4]	0.89 (0.67–1.19)		0.86 (0.64–1.15)	
371/258	Q4 [16.8]	0.96 (0.75–1.24)		0.94 (0.73–1.21)	
90/50	Q5 [46.7]	1.16 (0.77–1.76)	0.65	1.14 (0.76–1.73)	0.71
261/154	Fish (g/day) ref Q1 [10.5]				
255/170	Q2 [19.2]	0.90 (0.67–1.21)		0.89 (0.66–1.20)	
248/171	Q3 [28.5]	0.87 (0.65–1.17)		0.86 (0.64–1.16)	
260/152	Q4 [42.2]	1.02 (0.75–1.37)		1.02 (0.76–1.39)	
230/171	Q5 [74.6]	0.85 (0.63–1.16)	0.51	0.86 (0.63–1.17)	0.56
272/139	Dairy products (g/day) ref Q1 [92.2]				
240/162	Q2 [194.6]	0.72 (0.53–0.98)		0.73 (0.54–0.98)	
257/164	Q3 [302.2]	0.77 (0.57–1.05)		0.77 (0.57–1.05)	
246/173	Q4 [527.2]	0.71 (0.52–0.95)		0.71 (0.53–0.96)	
239/180	Q5 [639.2]	0.64 (0.48–0.87)	0.012	0.63 (0.47–0.86)	0.009
268/151	Milk (g/day) ref Q1 [64.4]				
379/232	Q2 [129.9]	0.88 (0.67–1.15)		0.87 (0.66–1.14)	
219/152	Q3 [259.8]	0.79 (0.58–1.07)		0.78 (0.57–1.06)	
169/109	Q4 [515.0]	0.82 (0.59–1.14)		0.81 (0.58–0.96)	
219/174	Q5 [519.5]	0.72 (0.54–0.98)	0.058	0.71 (0.53–0.96)	0.051
243/161	Fresh tomatoes (g/day) ref Q1 [3.9]				
242/175	Q2 [10.8]	0.82 (0.61–1.10)		0.81 (0.60–1.09)	
256/165	Q3 [19.2]	0.90 (0.66–1.23)		0.90 (0.66–1.23)	
254/161	Q4 [30.2]	0.92 (0.67–1.27)		0.93 (0.68–1.28)	
259/156	Q5 [50.4]	0.85 (0.61–1.18)	0.60	0.86 (0.61–1.20)	0.70
241/169	Tomato-based foods (g/day) ref Q1 [5.6]				
258/156	Q2 [14.3]	1.32 (0.98–1.78)		1.33 (1.00–1.80)	
248/166	Q3 [24.1]	1.25 (0.93–1.68)		1.24 (0.92–1.67)	
255/160	Q4 [40.3]	1.31 (0.96–1.78)		1.31 (0.96–1.78)	
252/167	Q5 [83.9]	1.28 (0.93–1.77)	0.38	1.27 (0.92–1.76)	0.42
238/169	Total tomatoes (g/day) ref Q1 [17.6]				
248/171	Q2 [33.9]	1.12 (0.82–1.52)		1.12 (0.82–1.53)	
261/155	Q3 [49.7]	1.20 (0.87–1.66)		1.19 (0.85–1.64)	
255/155	Q4 [70.5]	1.32 (0.94–1.86)		1.34 (0.95–1.89)	
252/168	Q5 [119.6]	1.07 (0.74–1.53)	0.93	1.07 (0.74–1.54)	0.90
254/158	Allium veg (g/day) ref Q1 [0.6]				
240/176	Q2 [2.1]	0.92 (0.68–1.23)		0.91 (0.67–1.22)	
253/172	Q3 [4.2]	1.02 (0.75–1.37)		1.01 (0.75–1.37)	
257/160	Q4 [7.5]	1.04 (0.76–1.42)		1.03 (0.75–1.42)	
250/152	Q5 [14.5]	0.91 (0.65–1.27)	0.69	0.91 (0.65–1.27)	0.72

Table 3 (continued)

Cases/controls, *n*	Quintile (Q) [median g/day]	Model 1[a] OR (95% CI)	P_{trend}[c]	Model 2[b] OR (95% CI)	P_{trend}[c]
238/171	Cruciferous veg (g/day) ref Q1 [2.7]				
239/177	Q2 [7.4]	1.00 (0.74–1.34)		0.99 (0.74–1.34)	
252/161	Q3 [13.2]	1.21 (0.88–1.65)		1.22 (0.89–1.66)	
247/168	Q4 [23.2]	1.11 (0.79–1.55)		1.10 (0.79–1.54)	
278/141	Q5 [44.5]	1.37 (0.95–1.97)	0.08	1.36 (0.94–1.96)	0.10
246/167	Lycopene (mcg/day) ref Q1 [2116]				
269/145	Q2 [3903]	1.35 (1.00–1.83)		1.33 (0.98–1.81)	
237/181	Q3 [5618]	1.04 (0.77–1.42)		1.03 (0.75–1.40)	
249/163	Q4 [8006]	1.16 (0.84–1.60)		1.16 (0.84–1.59)	
253/162	Q5 [14,036]	1.20 (0.85–1.69)	0.59	1.17 (0.83–1.65)	0.65
256/151	Calcium (mg/day) ref Q1 [456]				
256/157	Q2 [666]	0.89 (0.66–1.20)		0.89 (0.65–1.20)	
247/171	Q3 [832]	0.78 (0.58–1.06)		0.77 (0.57–1.05)	
262/161	Q4 [1013]	0.89 (0.65–1.21)		0.90 (0.66–1.22)	
233/178	Q5 [1308]	0.72 (0.52–0.98)	0.06	0.71 (0.52–0.98)	0.06

OR odds ratios, *CI* confidence interval, *veg* vegetables

[a]Adjusted for age, family history of PC, socioeconomic status, country of birth, smoking status, and quintiles of intakes of foods (fruits, vegetables, fish, and processed meat)

[b]Additionally adjusted for trouser size;

[c]P_{trend} obtained from using the median value in each quintile as a pseudocontinuous variable

Table 4 The risk of aggressive prostate cancer associated with full-cream milk intake

	Non-full-cream milk drinkers[c]	Low full-cream milk intake (< 257 g/day)	High full-cream milk intake (≥ 257 g/day)
Cases, *n*	846	154	254
Controls, *n*	555	102	161
OR (95% CI) Model 1[a]	1 (ref)	0.96 (0.72–1.28)	0.95 (0.74–1.21)
OR (95% CI) Model 2[b]	1 (ref)	0.97 (0.72–1.29)	0.95 (0.75–1.22)

OR odds ratios, *CI* confidence interval

[a]Adjusted for age, family history of PC, socioeconomic status, country of birth, smoking status, and quintiles of intakes of foods (fruits, vegetables, fish, and processed meat)

[b]Additionally adjusted for trouser size

[c]Non-full-cream milk drinkers include men who reported no milk intake and usual consumption of reduced fat or skimmed milk

that a high BMI might be protective against low-grade disease, possibly more so for younger men, and positively associated with APC risk for older men [6–8], but evidence for this potential interaction remains inconclusive. Our study included for cases, 490 and 328 men aged ≤ 65 and > 65 years, respectively. For controls, 513 and 741 men were aged ≤ 65 and > 65, respectively. The distribution of men across age groups in both cases and controls should increase the likelihood of observing a potential interaction, thus strengthening our findings. One study reported that BMI was inversely associated with total PC and non-APC, but not APC, for men aged less than 65 years [6]. In another study, a protective effect on risk of all PC, APC, and non-APC, of high (≥ 30 kg/m^2) compared with low (< 25 kg/m^2) BMI in men aged less than 60 years was detected, as well as a statistically significant interaction between BMI and age ($P_{interaction} < 0.001$) [7]. The Prostate Cancer Prevention Trial reported that the inverse and positive associations of BMI with risk of low-grade and high-grade PC, respectively, were stronger for men aged 65 years and above compared with younger men [8].

No associations were found between intakes of tomatoes or lycopene and APC. Previous studies have been inconsistent, and few studies have investigated the association with APC. One recent study reported high dietary intakes of lycopene to be inversely associated with APC (OR = 0.55, 95% CI 0.34–0.89, $P_{trend} = 0.02$) [10], and potential mechanisms, mostly connected to the inhibition of angiogenesis

[39, 40] exist. The most recent meta-analysis on lycopene from WCRF (2018) downgraded the evidence for an inverse association with PC risk from 'a strong association with reduced risk' to 'no conclusion possible' [4].

Many plausible mechanisms for a potential protective effect of fruits and vegetables exist, involving the effects of various nutrients and phytochemicals, which together facilitate a vast array of potentially anticarcinogenic molecular pathways, including cell cycle regulation, activation of enzymes, and immunomodulatory effects [41, 42]. Thus, we hypothesized that fruit and vegetable consumption would be associated with decreased risk of APC but observed no associations; adding to an accumulating body of evidence against any strong link between fruit and vegetable intake and PC or APC.

An inverse association with APC was observed when comparing top with bottom quartiles of intake of leafy vegetables (OR = 0.66, 95% CI 0.46–0.96, P_{trend} = 0.02), as well as of carotenoid-rich vegetables (OR = 0.71, 95% CI 0.48–1.04, P_{trend} = 0.04) in a large case–control study [13]. In contrast, a large analysis of 15 prospective cohort studies including 52,680 PC cases observed no significant associations between fruit and vegetable consumption and any PC outcome, including APC [26]. Another prospective analysis of four cohorts, including EPIC-Norfolk and EPIC-Oxford, observed no significant associations for APC with fruit or vegetable intakes [27].

Cruciferous vegetables are rich in sulforaphane and 3,3′-diindolylmethane (DIM), which are considered anticarcinogenic [43, 44]. Some studies, [14, 45, 46], have indicated an inverse association between APC and cruciferous vegetable consumption, yet this was not confirmed by our study. Consistent with our findings other studies have reported no association [28–30].

We found no evidence for an association between allium vegetable intake and APC. To date, few studies have explored the specific relationship between allium vegetables and APC, and to our knowledge, no study has identified an association with APC risk. A systematic review and meta-analysis including 132,192 subjects found a significantly reduced risk of total PC for allium vegetable intake (OR = 0.80, 95% CI 0.70–0.92, p = 0.012), but the analysis was not stratified by stage or grade [16].

In our current study, intake of processed meat was not associated with risk of APC. Although a few studies have observed at least suggestive results [20, 21], evidence relating processed meat consumption to APC risk is scarce. A recent review and meta-analysis of 19 prospective cohort studies found no significant relationship with processed meat for either total PC or APC [31]. The rationale for a relationship between processed meat and APC risk is based on the associations with other types of cancer [47, 48], as well as biological plausibility. The most thoroughly investigated potential carcinogenic mechanisms linked to processed meat involve *N*-nitroso compounds, heme iron, polycyclic aromatic hydrocarbons, nitrates and nitrites, and heterocyclic amines [49].

We found no association between APC and fish consumption in our study. The relationship of fish intake with PC has been previously investigated, but few studies have addressed the association with APC specifically. There are several mechanisms by which fish intake could potentially be linked to reduced APC risk, often involving n-3 PUFAs, which fatty fish is rich in. Evidence exists on several levels; not only from epidemiological [50–52], but also from animal [53–55] and molecular [56, 57], studies. In vitro investigations of the effects of n-3 or n-6 PUFAs on macrophages observed beneficial effects of n-3 PUFAs in prostate carcinogenesis [53].

We observed an inverse association between consumption of dairy products and risk of APC, and a weak inverse association for overall milk intake. It was potentially of interest to determine whether these associations differed according to the level of fat in dairy foods. Because we did not specifically collect information on this other than for milk, we investigated whether full-cream milk intake was associated with APC risk and found no evidence of association. The few prospective investigations previously conducted reported contrasting evidence: some early studies reported positive associations with total PC [58, 59], others have reported no associations [27, 32]. When investigating different types of dairy products, whole-milk intake was associated with increased risk of several PC outcomes including APC. For example, Steck et al. recently conducted a case-only study investigating 2,060 PC cases, comparing highly aggressive cancers (APC) with all other PC cases [23]. A significant positive association for APC was seen for whole-fat compared with non-whole-fat milk intake, while no significant associations were observed for intakes of total or any other subgroup of dairy products with risk of APC [23]. Total dairy product intake has been investigated in relation to total PC risk by several studies. A systematic review and meta-analysis of prospective studies identified significant associations with increased PC risk for intakes of total dairy, milk, cheese, and low-fat and skim milk, but an inverse association was seen for whole milk [22]. On the other hand, there are studies that have found no associations for dairy product intake and PC risk [27, 60–62]. The 2018 annual report from WCRF/AICR on cancer prevention and survival concluded there was suggestive evidence for dairy products and increased risk of PC [63].

Calcium is an important nutrient obtained from dairy products. We observed a suggestive weak inverse association between calcium intake and APC risk. This was attenuated when additionally adjusting for intake of dairy products, and there was a high correlation between the intakes of dairy

products and calcium, indicating that dairy was an important source of calcium, and that they are not independent. In contrast to these findings, Giovannucci et al. found that a high calcium intake was associated with increased risk of APC (advanced and aggressive), but not with total or non-advanced PC [24]. Rodriguez et al. observed a positive association between high total (including supplementary) and dietary calcium intakes and total PC and advanced PC, but they did not examine PC aggressiveness due to small numbers [61]. Others reported positive associations for calcium intake with risk of non-APC [64] and APC [25]. Steck et al. reported no clear associations between dietary or supplemental calcium intake and APC [23].

One of the main strengths of the present study is that a relatively large sample size was obtained ($n = 2{,}072$). Information on a variety of potential confounders such as age, family history of PC, BMI, trouser size, socioeconomic status, country of birth, and smoking status, was available in the analysis. In our study, the controls were clinically assessed as not having PC, using the contemporary gold standard method for PC diagnosis (transrectal ultrasound-guided biopsy), compared with most other studies where men just had not been diagnosed with PC. It is also a strength that all men had undergone PSA testing, eliminating potential bias, since PSA testing is associated with other risk factors such as age, family history of PC, body size, as well as lifestyle and health-behaviors [65].

There are a few limitations of this study that should be considered. Cases were slightly older than controls, and although age was adjusted for in our analyses, this might have affected our results. Participants were asked to estimate food intakes in the year before last, in contrast to the last year. This was done to increase the likelihood of capturing the dietary habits of cases prior to APC diagnosis, as lifestyle factors such as diet may be altered after a cancer diagnosis. Although the relatively close proximity of the time of dietary exposure to completion of the questionnaire is beneficial in terms of minimizing recall bias, the dietary data relate to recent intakes and do not reflect lifetime dietary habits or dietary changes over time. As most tumors are characterized by relatively slow initiation and growth, commonly spanning many years, the reported dietary data may not reflect diet at the time of tumor initiation or progression into an aggressive subtype. Additionally, the general assessment of dietary intakes in epidemiological studies, often through methods of self-report, involves sources of error including subjects' inability to accurately estimate their intakes and the inherent limitations in the methods and databases that are used to convert the recorded diet into daily averages of foods and nutrients. Although men were asked to report on diet from the year before last, the reported body size reflected current measurements and may have been affected by diagnosis in cases.

Another limitation was the lack of information on physical activity levels, which may be a confounder of associations between diet and APC. Research has suggested an inverse association between physical activity, especially that of vigorous nature, and risk of APC [66]. On the other hand, the WCRF/AICR reports the evidence linking physical activity and all PC outcomes as limited [4]. Thus, its non-availability is unlikely to have materially affected our results.

In conclusion, we have confirmed the positive association between body size, particularly abdominal obesity, and APC risk. Consistent with most of the literature, no associations were observed for any dietary factors, except for consumption of dairy products, and milk more specifically, which in contrast to our hypothesis was found to be significantly inversely associated with APC risk. Mechanisms for this association remain unclear. Given the importance of elucidating potential modifiable risk factors for APC, future research calls for repeated observational studies with large study samples to further investigate, and thus increase our understanding of which factors, including body size and diet, may affect APC risk.

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Compliance with ethical standards

Conflict of interest NP is currently employed by Janssen-Cilag Pty Ltd. The company had no role in producing this manuscript.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Cancer Council Victoria Human Research Ethics Committee, #910) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. Australian Institute of Health and Welfare (2019) Cancer in Australia 2019. Cancer series no. 199. Cat. No. CAN 123. Canberra: AIHW
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries: Global Cancer Statistics 2018. CA Cancer J Clin 68(6):394–424. https://doi.org/10.3322/caac.21492
3. Giovannucci E, Liu Y, Platz EA, Stampfer MJ, Willett WC (2007) Risk factors for prostate cancer incidence and progression in the health professionals follow-up study. Int J Cancer 121(7):1571–1578
4. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet,

nutrition, physical activity and prostate cancer. https://dietandcancerreport.org
5. Leitzmann M, Rohrmann S (2012) Risk factors for the onset of prostatic cancer: age, location, and behavioral correlates. Clin Epidemiol. 4:1–11. https://doi.org/10.2147/CLEP.S16747
6. Möller E, Wilson KM, Batista JL, Mucci LA, Bälter K, Giovannucci E (2016) Body size across the life course and prostate cancer in the Health Professionals Follow-up Study: Body size and prostate cancer. Int J Cancer. 138(4):853–865. https://doi.org/10.1002/ijc.29842
7. Giovannucci E, Rimm EB, Liu Y, Leitzmann M, Wu K, Stampfer MJ, et al (2003) Body mass index and risk of prostate cancer in U.S. health professionals. JNCI J Natl Cancer Inst. 95(16):1240–1244
8. Gong Z, Neuhouser ML, Goodman PJ, Albanes D, Chi C, Hsing AW et al (2006) Obesity, diabetes, and risk of prostate cancer: results from the prostate cancer prevention trial. Cancer Epidemiol Biomark Prev 15(10):1977–1983
9. Kelly SP, Lennon H, Sperrin M, Matthews C, Freedman ND, Albanes D et al (2018) Body mass index trajectories across adulthood and smoking in relation to prostate cancer risks: the NIH-AARP Diet and Health Study. Int J Epidemiol. https://doi.org/10.1093/ije/dyy/219
10. Antwi SO, Steck SE, Su LJ, Hebert JR, Zhang H, Craft NE et al (2016) Carotenoid intake and adipose tissue carotenoid levels in relation to prostate cancer aggressiveness among African-American and European-American men in the North Carolina-Louisiana prostate cancer project (PCaP): carotenoids and prostate cancer aggressiveness. Prostate 76(12):1053–1066. https://doi.org/10.1002/pros.23189
11. Giovannucci E, Rimm EB, Liu Y, Stampfer MJ, Willett WC (2002) A prospective study of tomato products, lycopene, and prostate cancer risk. J Natl Cancer Inst 94(5):391–398
12. Perez-Cornago A, Travis RC, Appleby PN, Tsilidis KK, Tjønneland A, Olsen A et al (2017) Fruit and vegetable intake and prostate cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC): fruit, vegetable intake and prostate cancer risk. Int J Cancer 141(2):287–297. https://doi.org/10.1002/ijc.30741
13. Hardin J, Cheng I, Witte JS (2011) Impact of consumption of vegetable, fruit, grain, and high glycemic index foods on aggressive prostate cancer risk. Nutr Cancer 63(6):860–872. https://doi.org/10.1080/01635581.2011.582224
14. Kirsh VA, Peters U, Mayne ST, Subar AF, Chatterjee N, Johnson CC et al (2007) Prospective study of fruit and vegetable intake and risk of prostate cancer. JNCI J Natl Cancer Inst 99(15):1200–1209
15. Liu B, Mao Q, Cao M, Xie L (2012) Cruciferous vegetables intake and risk of prostate cancer: a meta-analysis: cruciferous vegetables and prostate cancer. Int J Urol 19(2):134–141. https://doi.org/10.1111/j.1442-2042.2011.02906.x
16. Zhou X-F, Ding Z-S, Liu N-B (2013) Allium vegetables and risk of prostate cancer: evidence from 132,192 subjects. Asian Pac J Cancer Prev 14(7):4131–4134
17. Hsing AW, Chokkalingam AP, Gao YT, Madigan MP, Deng J, Gridley G et al (2002) Allium vegetables and risk of prostate cancer: a population-based study. J Natl Cancer Inst 94(21):1648–1651
18. Lovegrove C, Ahmed K, Challacombe B, Khan MS, Popert R, Dasgupta P (2015) Systematic review of prostate cancer risk and association with consumption of fish and fish-oils: analysis of 495,321 participants. Int J Clin Pract 69(1):87–105. https://doi.org/10.1111/ijcp.12514
19. Augustsson K, Michaud DS, Rimm EB, Leitzmann MF, Stampfer MJ, Willett WC et al (2003) A prospective study of intake of fish and marine fatty acids and prostate cancer. Cancer Epidemiol Biomark Prev 12(1):64–67
20. Wu K, Spiegelman D, Hou T, Albanes D, Allen NE, Berndt SI et al (2016) 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: meat, seafood, eggs and prostate cancer. Int J Cancer 138(10):2368–2382. https://doi.org/10.1002/ijc.29973
21. Wilson KM, Mucci LA, Drake BF, Preston MA, Stampfer MJ, Giovannucci E et al (2016) Meat, fish, poultry, and egg intake at diagnosis and risk of prostate cancer progression. Cancer Prev Res (Phila) 9(12):933–941
22. Aune D, Navarro Rosenblatt DA, Chan DS, Vieira AR, Vieira R, Greenwood DC et al (2015) Dairy products, calcium, and prostate cancer risk: a systematic review and meta-analysis of cohort studies. Am J Clin Nutr 101(1):87–117. https://doi.org/10.3945/ajcn.113.067157
23. Steck SE, Omofuma OO, Su LJ, Maise AA, Woloszynska-Read A, Johnson CS et al (2018) Calcium, magnesium, and whole-milk intakes and high-aggressive prostate cancer in the North Carolina-Louisiana Prostate Cancer Project (PCaP). Am J Clin Nutr 107(5):799–807. https://doi.org/10.1093/ajcn/nqy037
24. Giovannucci E, Liu Y, Stampfer MJ, Willett WC (2006) A prospective study of calcium intake and incident and fatal prostate cancer. Cancer Epidemiol Biomark Prev 15(2):203–210
25. Batai K, Murphy AB, Ruden M, Newsome J, Shah E, Dixon MA et al (2017) Race and BMI modify associations of calcium and vitamin D intake with prostate cancer. BMC Cancer 17(1):64. https://doi.org/10.1186/s12885-017-3060-8
26. Petimar J, Wilson KM, Wu K, Wang M, Albanes D, van den Brandt PA et al (2017) A pooled analysis of 15 prospective cohort studies on the association between fruit, vegetable, and mature bean consumption and risk of prostate cancer. Cancer Epidemiol Biomark Prev 26(8):1276–1287. https://doi.org/10.1158/1055-9965.EPI-16-1006
27. Lane JA, Oliver SE, Appleby PN, Lentjes MAH, Emmett P, Kuh D et al (2017) Prostate cancer risk related to foods, food groups, macronutrients and micronutrients derived from the UK Dietary Cohort Consortium food diaries. Eur J Clin Nutr 71(2):274–283. https://doi.org/10.1038/ejcn.2016.162
28. Key TJ, Allen N, Appleby P, Overvad K, Tjønneland A, Miller A et al (2004) Fruits and vegetables and prostate cancer: no association among 1,104 cases in a prospective study of 130,544 men in the European Prospective Investigation into Cancer and Nutrition (EPIC): fruits and vegetables and prostate cancer. Int J Cancer 109(1):119–124
29. Stram DO, Hankin JH, Wilkens LR, Park S, Henderson BE, Nomura AM et al (2006) Prostate cancer incidence and intake of fruits, vegetables and related micronutrients: the multiethnic cohort study (United States). Cancer Causes Control 17:1193–1207
30. Takachi R, Inoue M, Sawanda N, Iwasaki M, Sasazuki S, Ishihara J et al (2010) Fruits and vegetables in relation to prostate cancer in Japanese men: the Japan Public Health Center-Based Prospective Study. Nutr Cancer 62(1):30–39. https://doi.org/10.1080/01635580903191502
31. Bylsma LC, Alexander DD (2015) A review and meta-analysis of prospective studies of red and processed meat, meat cooking methods, heme iron, heterocyclic amines and prostate cancer. Nutr J 14:125. https://doi.org/10.1186/s12937-015-0111-3
32. Rohrmann S, Platz EA, Kavanaugh CJ, Thuita L, Hoffman SC, Helzlsouer KJ (2007) Meat and dairy consumption and subsequent risk of prostate cancer in a US cohort study. Cancer Causes Control 18(1):41–50
33. Allen NE, Key TJ, Appleby PN, Travis RC, Roddam AW, Tjønneland A et al (2008) Animal foods, protein, calcium and prostate cancer risk: the European Prospective Investigation into Cancer and

Nutrition. Br J Cancer 98(9):1574–1581. https://doi.org/10.1038/sj.bjc.6604331
34. Bassett JK, English DR, Fahey MT, Forbes AB, Gurrin LC, Simpson JA et al (2016) Validity and calibration of the FFQ used in the Melbourne Collaborative Cohort Study. Public Health Nutr 19(13):2357–2368. https://doi.org/10.1017/S1368980016000690
35. Food Standards Australia New Zealand NUTTAB (2010) https://www.foodstandards.gov.au/science/monitoringnutrients/nutrientables/nuttab/Pages/NUTTAB-2010-electronic-database-files.aspx. Accessed Aug 2013
36. Food Standards Australia New Zealand AUSNUT (2007) https://www.foodstandards.gov.au/science/monitoringnutrients/ausnut/Pages/ausnut2007.aspx. Accessed Aug 2013
37. US Department of Agriculture, Agricultural Research Service (2013) USDA National Nutrient Database for Standard Reference, Release 26. Nutrient Data Laboratory Home Page. https://www.ars.usda.gov/ba/bhnrc/ndl. Accessed Aug 2013
38. Australian Bureau of Statistics (2011) Census of population and housing: Socio-Economic Indexes for Areas (SEIFA), Australia, 2011. https://www.abs.gov.au/ausstats/abs@.nsf/mf/2033.0.55.001. Accessed 3 June 2016
39. Huang CS, Chuang CH, Lo TF, Hu ML (2013) Anti-angiogenic effects of lycopene through immunomodulation of cytokine secretion in human peripheral blood mononuclear cells. J Nutr Biochem 24(2):428–434. https://doi.org/10.1016/j.jnutbio.2012.01.003
40. Chen M-L, Lin Y-H, Yang C-M, Hu M-L (2012) Lycopene inhibits angiogenesis both in vitro and in vivo by inhibiting MMP-2/uPA system through VEGFR2-mediated PI3K-Akt and ERK/p38 signaling pathways. Mol Nutr Food Res 56(6):889–899. https://doi.org/10.1002/mnfr.201100683
41. Liu RH (3485S) Potential synergy of phytochemicals in cancer prevention: mechanism of action. J Nutr 134(12 Suppl):3479S–3485S. https://doi.org/10.1093/jn/134.12.3479S
42. Steinmetz KA, Potter JD (1991) Vegetables, fruit, and cancer. II. Mechanisms. Cancer Causes Control 2(6):427–442
43. Dashwood RH, Myzak MC, Ho E (2006) Dietary HDAC inhibitors: time to rethink weak ligands in cancer chemoprevention? Carcinogenesis 27(2):344–349
44. Vivar OI, Lin C-L, Firestone GL, Bjeldanes LF (2009) 3,3′-Diindolylmethane induces a G1 arrest in human prostate cancer cells irrespective of androgen receptor and p53 status. Biochem Pharmacol 78(5):469–476. https://doi.org/10.1016/j.bcp.2009.05.008
45. Kolonel LN, Hankin JH, Whittemore AS, Wu AH, Gallagher RP, Wilkens LR et al (2000) Vegetables, fruits, legumes and prostate cancer: a multiethnic case-control study. Cancer Epidemiol Biomark Prev 9(8):795–804
46. Cohen JH, Kristal AR, Stanford JL (2000) Fruit and vegetable intakes and prostate cancer risk. J Natl Cancer Inst 92(1):61–68
47. World Cancer Research Fund/American Institute for Cancer Research (2011) Continuous update project report. Food, nutrition, physical activity, and the prevention of colorectal cancer
48. Bouvard V, Loomis D, Guyton KZ, Grosse Y, Ghissassi FE, Benbrahim-Tallaa L et al (2015) Carcinogenicity of consumption of red and processed meat. Lancet Oncol 16(16):1599–1600. https://doi.org/10.1016/S1470-2045(15)00444-1
49. Diallo A, Deschasaux M, Latino-Martel P, Hercberg S, Galan P, Fassier P et al (2018) Red and processed meat intake and cancer risk: results from the prospective NutriNet-Santé cohort study: red and processed meat intake and cancer risk. Int J Cancer 142(2):230–237. https://doi.org/10.1002/ijc.31046
50. Fradet V, Cheng I, Casey G, Witte JS (2009) Dietary omega-3 fatty acids, cyclooxygenase-2 genetic variation, and aggressive prostate cancer risk. Clin Cancer Res 15(7):2559–2566. https://doi.org/10.1158/1078-0432.CCR-08-2503
51. Pelser C, Mondul AM, Hollenbeck AR, Park Y (2013) Dietary fat, fatty acids, and risk of prostate cancer in the NIH-AARP diet and health study. Cancer Epidemiol Biomark Prev 22(4):697–707. https://doi.org/10.1158/1055-9965.EPI-12-1196-T
52. Leitzmann MF, Stampfer MJ, Michaud DS, Augustsson K, Colditz GC, Willett WC et al (2004) Dietary intake of n-3 and n-6 fatty acids and the risk of prostate cancer. Am J Clin Nutr 80(1):204–216
53. Liang P, Henning SM, Schokrpur S, Wu L, Doan N, Said J et al (2016) Effect of dietary omega-3 fatty acids on tumor-associated macrophages and prostate cancer progression: fish oil and tumor-associated macrophages. Prostate 76(14):1293–1302. https://doi.org/10.1002/pros.23218
54. Saw CL, Wu TY, Paredes-Gonzalez X, Khor TO, Pung D, Kong AN (2011) Pharmacodynamics of fish oil: protective effects against prostate cancer in TRAMP mice fed with a high fat western diet. Asian Pac J Cancer Prev 12(12):3331–3334
55. Lloyd JC, Masko EM, Wu C, Keenan MM, Pilla DM, Aronson WJ et al (2013) Fish oil slows prostate cancer xenograft growth relative to other dietary fats and is associated with decreased mitochondrial and insulin pathway gene expression. Prostate Cancer Prostatic Dis 16(4):285–291. https://doi.org/10.1038/pcan.2013.19
56. Meng H, Shen Y, Shen J, Zhou F, Shen S, Das UN (2013) Effect of n-3 and n-6 unsaturated fatty acids on prostate cancer (PC-3) and prostate epithelial (RWPE-1) cells in vitro. Lipids Health Dis 12(1):160. https://doi.org/10.1186/1476-511X-12-160
57. Liu Z, Hopkins MM, Zhang Z, Quisenberry CB, Fix LC, Galvan BM et al (2015) Omega-3 fatty acids and other FFA4 agonists inhibit growth factor signaling in human prostate cancer cells. J Pharmacol Exp Ther 352(2):380–394. https://doi.org/10.1124/jpet.114.218974
58. Chan JM, Stampfer MJ, Ma J, Gann PH, Gaziano JM, Giovannucci EL (2001) Dairy products, calcium, and prostate cancer risk in the Physicians' Health Study. Am J Clin Nutr 74(4):549–554
59. Michaud DS, Augustsson K, Rimm EB, Stampfer MJ, Willett WC, Giovannucci E (2001) A prospective study on intake of animal products and risk of prostate cancer. Cancer Causes Control 12(6):557–567
60. Hodge AM, English DR, McCredie MRE, Severi G, Boyle P, Hopper JL et al (2004) Foods, nutrients and prostate cancer. Cancer Causes Control 15(1):11–20
61. Rodriguez C, McCullough ML, Mondul AM, Jacobs EJ, Fakhrabadi-Shokoohi D, Giovannucci EL et al (2003) Calcium, dairy products, and risk of prostate cancer in a prospective cohort of United States men. Cancer Epidemiol Prev Biomark 12(7):597–603
62. Koh KA, Sesso HD, Paffenbarger RS, Lee I-M (2006) Dairy products, calcium and prostate cancer risk. Br J Cancer 95(11):1582–1585
63. World Cancer Research Fund/American Institute for Cancer Research (2018) Meat, fish and dairy products and the risk of cancer: continuous update project expert report 2018. https://dietandcancerreport.org
64. Ahn J, Albanes D, Peters U, Schatzkin A, Lim U, Freedman M et al (2007) Dairy products, calcium intake, and risk of prostate cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. Cancer Epidemiol Biomark Prev 16(12):2623–2630
65. Littlejohns TJ, Travis RC, Key TJ, Allen NE (2016) Lifestyle factors and prostate-specific antigen (PSA) testing in UK Biobank: implications for epidemiological research. Cancer Epidemiol 45:40–46. https://doi.org/10.1016/j.canep.2016.09.010
66. Pernar CH, Ebot EM, Wilson KM, Mucci LA (2018) The epidemiology of prostate cancer. Cold Spring Harb Perspect Med. https://doi.org/10.1101/cshperspect.a030361

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