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Article

A Western Dietary Pattern Increases Prostate Cancer Risk: A Systematic Review and Meta-Analysis

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Abstract: Dietary patterns were recently applied to examine the relationship between eating habits and prostate cancer (PC) risk. While the associations between PC risk with glycemic index and Mediterranean score have been reviewed, no meta-analysis is currently available on dietary patterns defined by "a posteriori" methods. Search was carried out (PubMed, Web of Science) to identify studies reporting the relationship between dietary patterns and PC risk. Relevant dietary patterns were selected and the risk estimated were calculated by a random-effect model. Multivariable-adjusted odds ratios (ORs) for a 1st-percentile increase in dietary pattern score were combined by a dose response meta-analysis. 12 observational studies were included in the meta-analysis which identified "Healthy pattern" and "Western pattern". The Healthy pattern was not related to PC risk (OR=0.96; 95% CI: 0.88-1.04) while the Western pattern significantly increased it (OR=1.34; 95% CI: 1.08-1.65). In addition, a "Carbohydrate pattern", identified in four articles, was positively associated with a higher PC risk (OR=1.64; 95% CI: 1.35-2.00). A significant linear trend between the Western (p=0.011) and the Carbohydrate (p=0.005) pattern and the increment of PC risk was observed. The small numbers of studies included suggest that further investigations are necessary to support these findings.

Keywords: dietary pattern; prostate cancer; systematic review; meta-analysis

1. Introduction

Prostate cancer (PC) is the second most common cancer in men after lung, with more than 1.1 million new cases and over 307,000 deaths estimated in 2012 worldwide [1]. Almost 70% of the PC cases occur in more developed regions and its incidence varies more than 25-fold in different geographic areas. Incidence rates are higher in Northern and Western Europe compared to Central and Eastern countries. In Northern America PC incidence is about 10 time higher than Asia [1]. Although these regional differences could be due to both race (genetic factors) and screening programs for early diagnosis, several evidences suggest that environmental and dietary factors may also play an important role in the prostate carcinogenesis [2, 3].

Several epidemiological studies have explored the association of dietary habits on PC risk and meta-analysis have recently summarized the association of individual foods and nutrients with PC risk. Indeed, significant preventive effects have been found for the intake of allium vegetables [4], carrots and coffee [5,6], whereas inconsistent correlation has been observed between PC risk and consumption of tomato and lycopene [7,8], tea [9], fruit and vegetables [10], fiber [11], fat [12], red meat, processed meat and seafood [13]. On the other hand, dairy products, calcium and eggs seem to act as risk factors for PC [13,14]. In any case, as recently reported by World Cancer Research Fund International/American Institute for Cancer Research, the role of individual foods and nutrients on PC risk is still limited and controversial [15].

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Alternatively to study the individual foods and nutrients, more recently dietary patterns have been applied in nutritional epidemiology to examine the relationship between diet and chronic diseases [16,17]. This strategy allows to study the effects of overall dietary habits in a way more closely to the real conditions in which foods and nutrients are consumed in combination. Different statistical methods have been used to define dietary patterns. They can be distinguished in "a posteriori" methods such a factor analysis (FA), cluster analysis (CA), principal component analysis (PCA) and principal component factor analysis (PCFA), which generate patterns (i.e. western, prudent, healthy patterns) on the basis of available dietary data obtained directly from the studied population and in "a priori" approaches which derive dietary indices and/or scores (i.e. Glycemic index, Mediterranean score) on the basis of previous knowledge of the healthy or unhealthy effects of various diet constituents [18]. In the last few years, several epidemiological studies have used these methods to estimate the relationships between different dietary patterns and PC risk. However, while the association between both "Glycemic index" and "Mediterranean score" have been recently reviewed and estimated, to our knowledge, no meta-analysis is currently available considering the effect of dietary patterns defined by "a posteriori" methods on PC risk [19,20].

In this systematic review and meta-analysis we selected studies addressing the correlation between different dietary patterns defined using "a posteriori" methods and PC risk and provided a quantitative estimation of the association.

2. Materials and Methods

2.1. Literature search strategy and selection criteria

We carried out a comprehensive literature search, without restrictions, up to December 2015 through PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and Web of Science (http://wokinfo.com/) databases. The original articles on the association between dietary patterns and PC risk were identified using the following search key words: (neoplasm OR cancer OR "neoplastic disease") AND (prostate OR prostatic) AND ("dietary pattern" OR "eating pattern" OR "food pattern" OR "dietary habit" OR diet OR dietary) AND ("factor analysis" OR "principal component analysis" OR "cluster analysis" OR clustering OR "reduced rank regression" OR "diet diversity" OR "diet variety" OR quality OR index OR indices OR scores). Furthermore, the reference lists of included articles and recent significant reviews were manually examined to identify additional relevant publications. The standard procedure for conducting and reporting meta-analysis according to the guidelines from the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group were followed [21]. Although useful to have background information, reviews and pooled analyses were excluded. Potential identified articles were included if they met the following criteria: i) used a case-control or prospective study design; ii) evaluated the association between dietary patterns derived by "a posteriori" methods and PC risk; iii) presented odds ratio (OR), relative risk (RR) or hazard ratio (HR) estimates with 95% confidence intervals (CIs). When there were several publications from the same study, the publication with the largest number of cases was selected. For each potential study to be included, two investigators independently carried out the selection evaluation, data abstraction, and quality assessment; disagreements between evaluators concerning the selected studies were resolved by discussion or in consultation with a third author.

2.2. Data abstraction and quality assessment

From the selected studies we extracted the following information: study design, first author's last name, year of publication, geographical area and country, sample size (number of cases and controls; cohort size and incident cases) when possible, age, duration of follow-up for cohort studies, dietary assessment and dietary pattern identification methods (FA, CA, PCA and PCFA), characteristics of the dietary assessment method, name of the dietary pattern type and its characteristics, cutoff points of the different categories of adherence to the dietary pattern (dichotomy, tertile, quartile and quintile), risk estimates with 95% confidence intervals for the

different categories of adherence, p-value for trend and confounding factors adjustment. When multiple estimates were reported in the article, we abstracted those that adjusted for the most confounding factors. The study quality was assessed by a 9-star system based on the Newcastle–Ottawa Scale method [22]. Therefore, the full score was 9 and a total score ≥7 was used to indicate high-quality study. To avoid selection bias, no study was excluded because of these quality criteria.

2.3. Statistical analysis

The overall effect-size statistic estimated was the average of the logarithm of the observed odds ratio (approximated to RR when necessary) associated to the highest versus the lowest level of consumption. We used random effects model to calculate summary OR and 95% confidence intervals. A two-tailed $p<0.05$ was considered statistically significant. We restricted the analysis to the "a posteriori" dietary patterns. In addition, a dose-response meta-analysis was conducted to study trend across categories. The linear increase in PC risk per percentile increase in dietary pattern was estimated using the method proposed by Greenland and Longnecker [23], that accounts for the correlation between risk estimates for separate exposure levels depending on the same reference group, when possible. For studies with non-zero or different exposure dose as reference we adjusted the values following Liu et al. [24]. We estimated the distribution of cases or controls or person years in studies that did not report these but reported the total number of cases or controls or person years if the results were analyzed by quantiles dividing the total number of person years by the number of reported quantiles. The study specific trends were then combined according to the principles of multivariate random-effects meta-analysis. Two most common dietary patterns which had similar factor loading of principle components were identified. The first pattern, named "Healthy pattern" was characterized by high loading of vegetables and fruits, poultry, fish, and whole grains. The selected articles labeled it as "Healthy" [25,28,32], "Vegetable" [26,30,34,36], "Prudent" and "Vitamins and Fiber" [27,29,31,33,35]. The second pattern, named "Western pattern" had a high loading of red meat, processed meat, eggs and sweets. The included articles labeled it as "Traditional Western/Processed diet" [25], "Western" [26,27,29,32,35], "Organ meat and fast food" [28], "Meat" [30], "Animal Products" [31], "Traditional" [33], "Red meat-starch" and "Meat & Potatoes" [34,36]. In addition, a "Carbohydrate pattern", characterized by high loading of bread, pasta and rice was identified in four articles which labeled it as "Carbohydrate" [28,33], "Refined carbohydrate" and "Starch-rich" [30,31]. The chi-square based Cochran's Q statistic and the I^2 statistic were used to evaluate heterogeneity in results across studies (37). For the Q statistic, a p-value <0.1 was considered to be representative of statistically significant heterogeneity. The I^2 statistic yields results ranged from 0 to 100% (I^2=0-25%, no heterogeneity; I^2 = 25-50%, moderate heterogeneity; I^2=50-75%, large heterogeneity; and I^2=75-100%, extreme heterogeneity) [38]. Results of the meta-analysis may be biased if the probability of a study being published is dependent on its results. We used the methods of Begg and Mazumdar, and Egger et al. to detect publication bias [39,40]. Both methods test for funnel plot asymmetry, the former being based on the rank correlation between the effect estimates and their sampling variances, and the latter on a linear regression of a standard normal deviate on its precision. If a potential bias was detected, we further conducted a sensitivity analysis to assess the robustness of combined effect estimates and the possible influence of the bias and to have the bias corrected. We also conducted a sensitivity analysis to investigate the influence of a single study on the overall risk estimate by omitting one study in each turn. We considered the funnel plot to be asymmetrical if the intercept of Egger's regression line deviated from zero with a p-value of less than 0.05. Subgroup analysis were conducted for the case-control and cohort studies. The ProMeta Version 2.0 statistical program (Internovi) and packages dosresmeta 1.3.2. for R 3.1.2. was used for the analysis [41]. All reported p values are from two-sided statistical tests, and differences with $p \leq 0.05$ were considered significant.

3. Results

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3.1. Study selection

From the primary literature research through PubMed (n=571) and Web of Science (n=1160) databases and after removing duplicate (n=382), we identified 1349 records for title and abstract revision (Figure 1). Of the 1349 articles screened, 1316 were excluded because they were not observational epidemiological studies leaving 33 articles for full-text revision. Hand searching of reference lists of both selected articles and recent relevant reviews led to the identification of 1 additional item. Twenty-two papers were subsequently excluded because they did not met the inclusion criteria as follow: four studies were on adherence to Mediterranean diet, two considered the inflammatory index and seven considered glycemic index, three studies were on adherence to dietary recommendations, one considered the oxidative balance score, two were on benign prostatic hyperplasia, one considered food groups and not dietary patterns, one considered individual dietary score and two article show the results of the same study so we did not considered the one in the native languages. Therefore, at the end of the selection process, 12 studies met the inclusion criteria (Figure 1) and were enclosed for the identification of the different dietary patterns in the systematic review and meta-analysis [25-36].

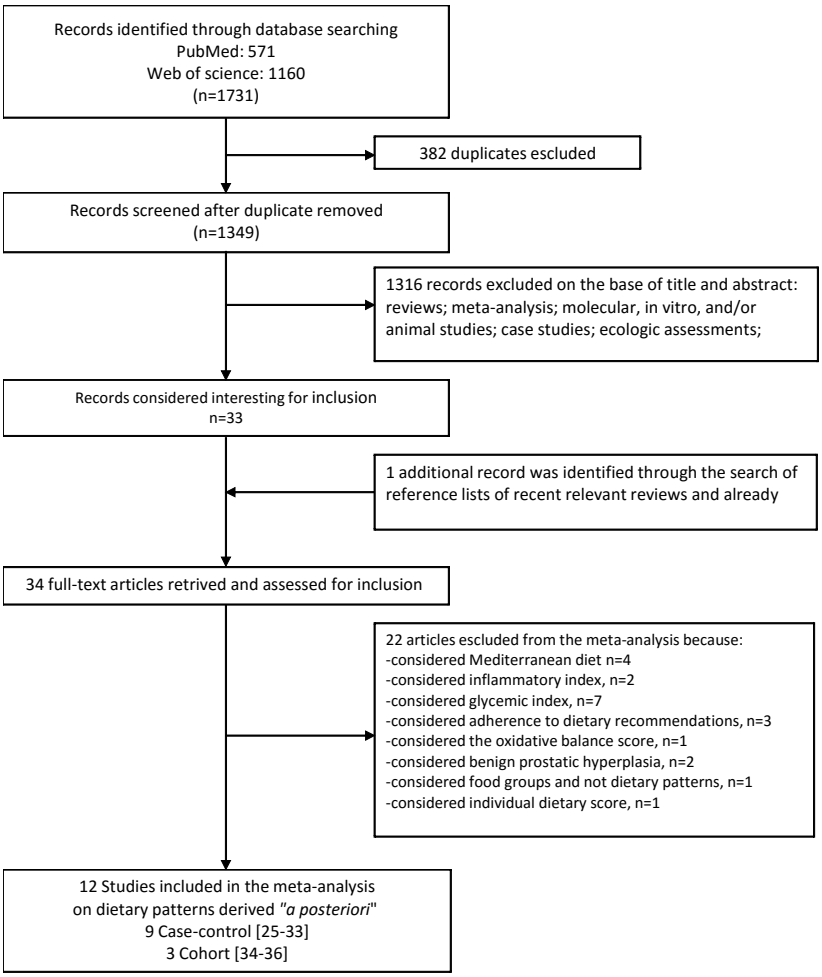

Figure 1. Flow diagram of systematic literature search on dietary patterns and prostate cancer risk.

3.2. Study characteristics and quality assessment

Of the 12 selected papers, 9 were case-control and 3 were cohort studies. General characteristics of case-control and cohort studies are shown in Table 1 and Table 2, respectively.

Table 1. Main characteristics of the case-control studies included in the systematic review and meta-analysis of dietary patterns and prostate cancer risk

Author, year Location	Case/control Age Period	Dietary pattern assessment and identification method	Dietary pattern type and characteristics	Pattern score	OR (95% CI)	*p* for trend	Confounding factor adjusted
Walker, 2005 [25] Canada	80/334 HB[1] 50-80 y (mean: 65.0 y cases; 63.6 y controls) (1997-1999)	67-item FFQ[2] (2 years before), SA[3] 34 food groups PCA[4] (in controls) Varimax rotation, EIG[5]>1.5 Loading >0.25 4 factors, VE[6] 10.51 %	***1. Healthy living***: vegetables, fruits, whole grains, fish and poultry	Tertile 1 Tertile 2 Tertile 3	1.00 (Ref.) 0.99 (0.55-1.78) 0.78 (0.42-1.45)	0.45	Age, physical activity a teen, current smoking a alcohol intake
			2. Traditional Western: red meats, processed meats, milk, sweets and hard liquor	Tertile 1 Tertile 2 Tertile 3	1.00 (Ref.) 1.00 (0.53-1.88) 1.43 (0.79-2.59)	0.22	
			3. Processed diet.: processed meats, red meats, organ meats, refined grains, onions and tomatoes, vegetable oils and juices, bottled water and soft drinks	Tertile 1 Tertile 2 Tertile 3	1.00 (Ref.) 2.11 (1.06-4.22) 2.75 (1.40-5.39)	0.003	
			4. Beverages: tap water, ''other'' beverages including soft drinks and fruit juices, potatoes, poultry and margarine / inversely associated with beer, liquor, wine and cream for coffee	Tertile 1 Tertile 2 Tertile 3	1.00 (Ref.) 0.68 (0.37-1.25) 0.84 (0.47-1.51)	0.54	
Ambrosini, 2008 [26] Australia	546/447 PB[7] 40-75 y	101-item FFQ (10 years before), SA PCA (in controls) Varimax rotation, EIG>1, scree plots Loading>0.3 3 factors, VE 29.2%	***1. Vegetable***: all vegetables listed in the FFQ (including fresh and tinned tomatoes) plus jam, honey, and apples	Quartile 1 Quartile 2 Quartile 3 Quartile 4	1.00 (Ref.) 1.03 (0.71-1.50) 1.26 (0.85-1.89) 1.13 (0.72-1.78)	0.46	Age, BMI[8], energy inta and paternal history of prostate cancer
			2. Western: full cream milk, white bread, cakes, potato crisps, French fries (chips), eggs, red and processed meats, hamburgers, fried or takeaway fish, and full alcohol beer	Quartile 1 Quartile 2 Quartile 3 Quartile 4	1.00 (Ref.) 1.42 (0.98-2.06) 1.32 (0.89-1.97) 1.82 (1.15-2.87)	0.02	
			3. Health-conscious: steamed and grilled fish, tinned fish, chicken, rice, pasta, legumes, and tofu; bean sprouts, nuts, yoghurt, ricotta cheese, red wine, and white wine	Quartile 1 Quartile 2 Quartile 3 Quartile 4	1.00 (Ref.) 1.24 (0.86-1.80) 1.02 (0.70-1.48) 1.06 (0.72-1.58)	0.97	
De Stefani, 2009 [27] Uruguay	345/2,532 HB (1996-2004)	64-item FFQ, IA[9] 17 food groups PCA (in controls) Varimax rotation, Loading>0.39 4 factors, VE 36.6%	***1. Prudent***: poultry, fish, fresh vegetables, cooked vegetables, and total fruits	Tertile 1 Tertile 2 Tertile 3	1.00 (Ref.) 1.01 (0.75-1.37) 1.05 (0.77-1.43)	0.76	Age, residence, urban/rural status, education, BMI, smoki status, years since
			2. Traditional: total grains, all tubers, desserts, and dairy foods	Tertile 1 Tertile 2 Tertile 3	1.00 (Ref.) 1.12 (0.80-1.55) 1.20 (0.81-1.78)	0.37	stopping, number of cigarettes/day among current smokers

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			3. Western: fried red meat, barbecue meat, processed meat and eggs	Tertile 1 Tertile 2 Tertile 3	1.00 (Ref.) 1.36 (1.01-1.81) 1.12 (0.81-1.56)	0.42	total energy intake and the dietary patterns
			4. Drinker: alcoholic beverages such as beer, wine and hard liquor	Tertile 1 Tertile 2 Tertile 3	1.00 (Ref.) 0.69 (0.51-0.92) 0.86 (0.64-1.17)	0.29	
Jackson, 2009 [28] Jamaica	204/204 HB (2004-2007)	FFQ, IA 33 food groups PCFA Varimax rotation, EIG>1 Loading>0.4 4 factors, VE 24.5%	***1. Healthy***: vegetables, fruits, peas and beans	Tertile 1 Tertile 2 Tertile 3	1.00 (Ref.) 0.72 (0.39-1.32) 0.84 (0.44-1.59)	Not reported	Age, family history of prostate cancer, educati BMI, smoking, alcohol and total energy intake
			2. Carbohydrate: white bread and refined cereals, poultry, rice/pasta, starchy roots and tubers	Tertile 1 Tertile 2 Tertile 3	1.00 (Ref.) 1.28 (0.70-2.43) 1.20 (0.58-2.48)		
			3. Sugary foods: sweet baked products non-diet drink	Tertile 1 Tertile 2 Tertile 3	1.00 (Ref.) 0.88 (0.49-1.62) 0.75 (0.40-1.38)		
			4. Organ meat and fast food: high fat dessert, organ meat, fast food and salty snacks	Tertile 1 Tertile 2 Tertile 3	1.00 (Ref.) 1.31 (0.73-2.33) 0.96 (0.53-1.76)		
De Stefani, 2010 [29] Uruguay	345/690 HB 45-89 y (1996-2004)	64-item FFQ, IA 21 food groups PCA Quartimax orthogonal Scree plot 5 factors, VE 38.4 %	***1. Prudent***: raw vegetables, citrus fruits, other fruits, and tea.	Quartile 1 Quartile 2 Quartile 3 Quartile 4	1.00 (Ref.) 0.96 (0.66-1.41) 0.96 (0.66-1.42) 0.82 (0.55-1.23)	0.40	Education, occupation, family history of prosta cancer among first-deg relatives, BMI, tobacc smoking, total energy
			2. Traditional: lamb, dairy foods, cooked vegetables, and all tubers	Quartile 1 Quartile 2 Quartile 3 Quartile 4	1.00 (Ref.) 1.62 (1.07-2.45) 1.87 (1.22-2.87) 1.85 (1.16-2.94)	0.01	intake and each pattern the others
			3. Substituter: poultry and fish and a negative loading for lamb consumption	Quartile 1 Quartile 2 Quartile 3 Quartile 4	1.00 (Ref.) 1.38 (0.94-2.02) 1.35 (0.91-2.01) 1.07 (0.70-1.65)	0.58	
			4. Drinker: mate, beer, wine, and hard liquor	Quartile 1 Quartile 2 Quartile 3 Quartile 4	1.00 (Ref.) 0.79 (0.54-1.16) 0.89 (0.61-1.32) 1.18 (0.78-1.78)	0.42	

			5. Western: beef, processed meat, boiled eggs, fried eggs, and total grains	Quartile 1 Quartile 2 Quartile 3 Quartile 4	1.00 (Ref.) 1.41 (0.92-2.17) 2.10 (1.35-3.25) 2.35 (1.44-3.85)	<0.0001	
Jackson, 2013 [30] Jamaica	243/275 HB 40-80 y (2005-2007)	FFQ 33 food groups PCA Varimax rotation EIG>1, scree plot 4 factors, VE 27.8%	***1.Vegetables & legumes (Healthy)***: Dark green leafy, yellow vegetable, nuts and seeds, other vegetables, peas and beans, ready-to-eat cereals, fruits	Tertile 1 Tertile 2 Tertile 3	1.00 (Ref.) 0.87 (0.49-1.55) 0.91 (0.50-1.67)	0.766	Age, family history of prostate cancer, educati BMI, smoking, physica activity, total energy intake
			2. Fast food: fast foods, alcoholic beverages, meal replacements, dairy dessert, fruit juice	Tertile 1 Tertile 2 Tertile 3	1.00 (Ref.) 1.12 (0.63-1.96) 0.66 (0.34-1.16)	0.162	
			3. Meat: processed meat, eggs, poultry, and starchy fruits, roots, and tubers	Tertile 1 Tertile 2 Tertile 3	1.00 (Ref.) 0.88 (0.50-1.57) 1.10 (0.62-1.96)	0.735	
			4. Refined Carbohydrate: rice and pasta, sugar sweetened beverages, sweet baked foods (refined carbohydrates), and poultry	Tertile 1 Tertile 2 Tertile 3	1.00 (Ref.) 1.65 (0.94-2.90) 2.02 (1.05-3.87)	0.029	
Rosato, 2014 [31] Italy	1,294/1,451 HB 46–74 y (median: 66 y cases; 63 y controls) (1991-2002)	78-items FFQ (2 years before), IA 28 selected nutrients/29 food groups PCFA Varimax rotation EIG≥1, scree plot Loading≥0.63 5 factors, VE 78,26 %	***1. Animal Products***: calcium, phosphorus, riboflavin, animal protein, saturated fatty acids, zinc, and cholesterol Milk and dairy products, eggs, red meat, cheese	Quintile 1 Quintile 3 Quintile 5	1.00 (Ref.) 1.35 (1.04–1.76) 1.51 (1.16–1.96)	0.02	Age, study center, education, BMI, tobacc alcohol drinking and family history of prostate cancer in first-degree relatives
			2. Vitamins and Fiber: vitamin C, total fiber, beta-carotene equivalents, total folate, and soluble carbohydrates Fruits, vegetables, legumes and olive oil	Quintile 1 Quintile 3 Quintile 5	1.00 (Ref.) 1.15 (0.90–1.48) 0.93 (0.72–1.21)	0.23	
			3. Starch-rich: starch, vegetable protein, and sodium Bread, pasta and rice	Quintile 1 Quintile 3 Quintile 5	1.00 (Ref.) 1.16 (0.89–1.49) 1.50 (1.16–1.93)	<0.001	
			4. VUFA[10]: linoleic acid, vitamin E, and linolenic acid Specified and unspecified seed oils, leafy vegetables and olive oil	Quintile 1 Quintile 3 Quintile 5	1.00 (Ref.) 1.21 (0.94–1.55) 1.16 (0.89–1.51)	0.41	
			5. AUFA[11]: polyunsaturated fatty acids and vitamin D Fish and offals	Quintile 1 Quintile 3 Quintile 5	1.00 (Ref.) 1.05 (0.81–1.36) 1.32 (1.02–1.70)	0.02	

Askari, 2014 [32] Iran	50/100 HB 40-78 y (cases) 43-71 y (controls)	125-item FFQ, IA PCA Varimax rotation Interpretability and scree plot EIG>1.9 2 factors	***1. Western diet***: sweets and desserts, organ meat, snacks, tea and coffee, French fries, salt, carbonated drinks, red or processed meat	Two categories (high 2nd median *vs* low 1st median)	4.00 (1.50-11.00)		Smoking, diabetes, ene intake
			2. Healthy diet: legumes, fish, dairy products, fruits and fruit juice, vegetables, boiled potatoes, whole cereal and egg		0.40 (0.20-1.00)		
Niclis, 2015 [33] Argentina	147/300 PB 48–89 y (cases) 46–89 y (controls)	125-item FFQ, IA 24 food groups PCA Varimax rotation Interpretability and scree plot EIG>1.0 Loading≥0.40 4 factors, VE 31,52 %	***1. Traditional***: fatty red meats, offal, processed meat, starchy vegetables, added sugars and sweets, candies, fats, and vegetable oils.	Quartile 1 Quartile 2 Quartile 3 Quartile 4	1.00 (Ref.) 1.60 (0.97-2.66) 1.73 (1.17-2.57) 2.54 (1.49-4.34)	0.048	Age, BMI, energy intal occupational exposure, family history of cance
			2. Prudent: nonstarchy vegetables, whole grains, and low loading for alcoholic drinks	Quartile 1 Quartile 2 Quartile 3 Quartile 4	1.00 (Ref.) 0.70 (0.39-1.26) 0.84 (0.54-1.31) 1.31 (0.49-3.51)	0.926	
			3. Carbohydrate: sodas/juices and bakery products	Quartile 1 Quartile 2 Quartile 3 Quartile 4	1.00 (Ref.) 1.76 (1.25-2.48) 2.67 (0.98-7.35) 2.10 (1.40-3.16)	0.069	
			4. Cheese: cheese and low loading for fish	Quartile 1 Quartile 2 Quartile 3 Quartile 4	1.00 (Ref.) 1.48 (0.69-3.20) 1.34 (0.84-2.16) 1.02 (0.54-1.93)	0.720	

[1]Hospital Based; [2]Food Frequency Questionnaire; [3]Self administered; [4]Principal Component Analysis; [5]Eigenvalues; [6]Variance Explained; [7]Population Based; [8]Body Mass Index; [9]Interviewer Administered; [10]Vegetable Unsaturated Fatty Acids; [11]Animal Unsaturated Fatty Acids

T*able 2*. Main characteristics of the cohort studies included in the systematic review and meta-analysis of dietary patterns and prostate cancer risk

Author, year Location	**Subjects Cohort Age Incident cases Follow-up (period)**	**Dietary pattern assessment and identification method**	**Dietary pattern type and characteristics**	**Pattern score**	**RR (95% CI)§**	***p* for trend**	**Confounding factor adjusted**
Tseng, 2004 [34] USA	3,779 25-74 y (mean 58 y) 136 cases mean follow-up 7.6 y (1982-1992)	105-item FFQ[1] PCA[2] (Varimax rotation, interpretability, EIG[3]>1.0, Scree plots) Loading >0.2 3 factors, VE[4] 10.8%	***1. Vegetable-fruit***: vegetables, fruits, fish, and shellfish	Tertile 1 Tertile 2 Tertile 3	1.00 (Ref.) 1.50 (0.9-2.3) 1.20 (0.7-2.0)	0.64	Age, race, poverty cens enumeration district, family income, region, residence, education, su
			2. Red meat-starch: red meats, potatoes, salty snacks, cheese, sweets, and desserts	Tertile 1 Tertile 2	1.00 (Ref.) 0.70 (0.5-1.2)	0.37	exposure, physical activity, smoking,

				Tertile 3	0.80 (0.4-1.4)		alcohol, energy intake
			3. Southern: beans, rice, and such traditionally Southern United States foods as cornbread, grits, sweet potatoes, and okra	Tertile 1 Tertile 2 Tertile 3	1.00 (Ref.) 0.90 (0.6-1.4) 0.60 (0.4-1.1)	0.08	
Wu, 2006 [35] USA	47,725 40-75 y 3002 cases follow-up 15 y (1986-2000)	131-item FFQ 40 food groups, FA[5] (Varimax rotation, interpretability, EIG>1.0, Scree test) Loading >0.3 2 factors, VE 17.4%	***1. Prudent***: fruits, vegetables, legumes, whole grains, fish, and poultry	Quintile 1 Quintile 3 Quintile 5	1.00 (Ref.) 1.10 (0.98-1.24) 0.95 (0.84-1.07)	0.37	Age, height, smoking, family history of prosta cancer, race, history of vasectomy, vigorous
			2. Western: red meat, processed meat, butter, eggs, refined grains and high-fat dairy	Quintile 1 Quintile 3 Quintile 5	1.00 (Ref.) 1.03 (0.92-1.16) 1.02 (0.91-1.15)	0.62	exercise, BMI[6], alcohol intake, total energy intake
Muller, 2009 [36] Australia	14,627 34-75 y 1018 cases Mean follow-up 13.6 y (1990-2007)	121-item FFQ FA (Varimax rotation, interpretability, EIG>2) Loading>0.3 4 factor, VE 67%	***1. Mediterranean***: some meats, vegetables, and fruits, and avoidance of cakes and sweet biscuits	Quartile 1 Quartile 2 Quartile 3 Quartile 4	1.00 (Ref.) 0.93 (0.79-1.11) 1.14 (0.95-1.37) 0.93 (0.74-1.18)	0.9	Age, total energy intake and ethnicity. Further adjustment for BMI,
			2. Vegetable: high intake of vegetables	Quartile 1 Quartile 2 Quartile 3 Quartile 4	1.00 (Ref.) 1.11 (0.90-1.36) 1.02 (0.83-1.27) 1.12 (0.90-1.40)	0.5	physical activity, smoking, alcohol intake and education did not chang estimated HRs or 95%
			3. Meat & Potatoes: high intake of meats and potato cooked in fat	Quartile 1 Quartile 2 Quartile 3 Quartile 4	1.00 (Ref.) 1.00 (0.84-1.20) 1.04 (0.87-1.24) 0.87 (0.71-1.08)	0.2	materially.
			4. Fruit & Salad: high intake of salad greens and fruit	Quartile 1 Quartile 2 Quartile 3 Quartile 4	1.00 (Ref.) 1.14 (0.96-1.36) 1.10 (0.92-1.32) 1.00 (0.81-1.23)	0.6	

[1] Food Frequency Questionnaire; [2]Principal Component Analysis; [3]Eigenvalues; [4]Variance Explained; [5]Factor Analysis; [6]Body Mass Index;

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Case-control studies were published between 2005 and 2015, two were population-based [26,33] and 7 were hospital-based [25,27-32]. Two were conducted in Uruguay [27,29] and Jamaica [28,30], and one each in Canada [25], Australia [26], Italy [31], Iran [32] and Argentina [33]. Cohort studies were published between 2004 and 2009, two were conducted in the United States [34,35] and one was conducted in Australia [36]. All of 12 included articles used a food frequency questionnaire (FFQ) to collect dietary information (64 to 131 items). Two studies reported the association of PC risk with 2 different dietary patterns [32,35] two studies considered 3 dietary patterns [26,34], six studies considered 4 dietary patterns [25,27,28,30,33,36] and two studies considered 5 different dietary patterns [29,31]. All of the 12 articles identified both an "Healthy pattern" and a "Western pattern" while four studies identified a "Carbohydrate pattern". On the other hand, only two studies identified a "Drinker pattern" and they were small in number to conduct a meta-analysis on them [27,29]. Study-specific quality scores are summarized in supplementary Tables S1 and S2 for case-control and cohort studies, respectively (available online). For case-control studies, the range of quality score was from 5 to 8 (median:8, mean ± SD: 7.1±1.2) and high-quality was reached by 6 studies [26,27,29-31,33], while all three cohort studies reached a quality score of 8 [34-36].

3.3. *Meta-analysis*

The associations between the highest compared with the lowest intake categories of "Healthy pattern" and PC risk are shown in Figure 2. When data from all studies were pooled together there was no evidence of significant reduction of PC risk associated with Healthy pattern (OR=0.96; 95% CI: 0.88, 1.04; p=0.284). Similar results were obtained when the analysis was carried out separately for case-control and cohort studies (Table 3). The heterogeneity was not apparent in any case (Table 3). Figure 3 shows the associations between the highest compared with the lowest intake categories of "Western pattern" and PC risk for the all studies included in the meta-analysis. There was an evident significant increment of PC risk associated with Western pattern (OR=1.34; 95% CI: 1.08, 1.65; p=0.007) but the heterogeneity was rather high (I^2=74.63 %, p=0.0001) (Table 3). Subgroup analysis according to study design showed that heterogeneity remains evident in the case-control studies (I^2=54.61 %, p=0.024), where an increase in the risk of PC was shown (OR=1.58; 95% CI: 1.25; 2.01; p=0.0001), while in the cohort studies, there was no evidence of heterogeneity (I^2=4.14%, p=0.352) and there was no evidence of a difference in the risk of PC (OR=0.97; 95% CI: 0.87, 1.08; p=0.352) (Table 3). In Figure 4 are shown the associations between the highest and lowest intake categories of "Carbohydrate pattern" and PC risk for the four case-control studies included in the meta-analysis. It was observed a significant increment of PC risk associated with Carbohydrate pattern (OR=1.64; 95% CI: 1.35, 2.00; p=0.0001), in the absence of heterogeneity (I^2=0.00%, p=0.393) (Table 3).

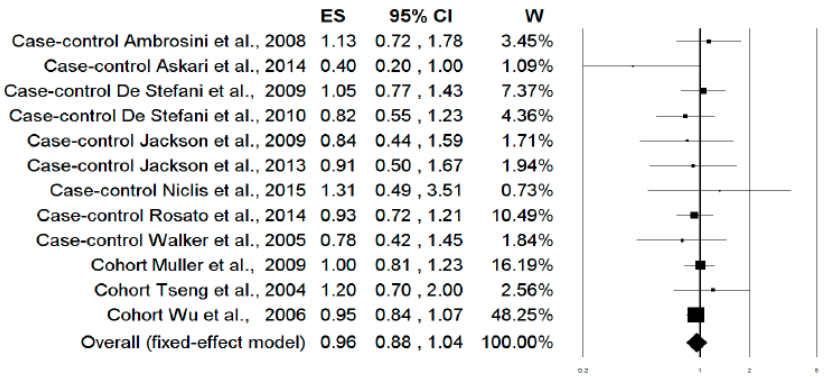

Figure 2. Forest plot of the highest compared with the lowest categories of intake of the "Healthy" dietary pattern and prostate cancer risk

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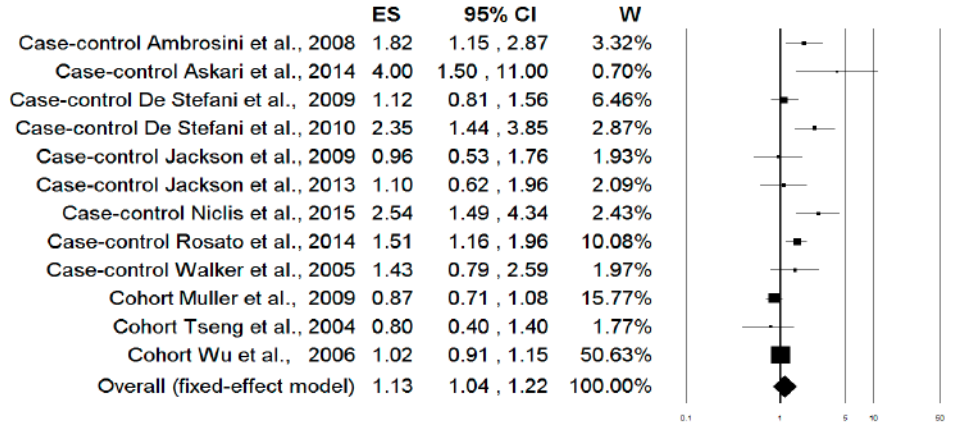

Figure 3. Forest plot of the highest compared with the lowest categories of intake of the "Western" dietary pattern and prostate cancer risk

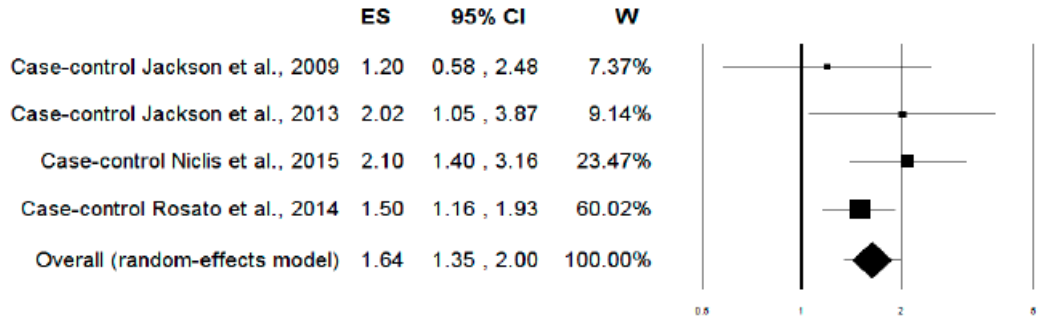

Figure 4. Forest plot of the highest compared with the lowest categories of intake of the "Carbohydrate" dietary pattern and prostate cancer risk

Table 3. Results of stratified analysis of the risk estimates for the highest compared with the lowest intake categories of different dietary patterns on the basis of study type[1,2].

	Combined risk estimate		Test of heterogeneity			Publication bias	
	Value (95% CI)	*p*	Q	I^2 %	*p*	*p* (Egger test)	*p* (Begg test)
Healthy pattern							
Case-control (n=9)[3]	0.92 (0.80-1.07)	0.294	6.77	0.00	0.562	0.343	0.404
Cohort (n=3)	0.97 (0.88-1.08)	0.567	0.83	0.00	0.661	0.003	0.117
Pooled[4] (n=12)	0.96 (0.88-1.04)	0.284	7.88	0.00	0.724	0.538	0.583
Western pattern							
Case-control (n=9)	1.58 (1.25-2.01)	0.0001	17.62	54.61	0.024	0.349	0.677
Cohort (n=3)	0.97 (0.87-1.08)	0.623	2.09	4.14	0.352	0.414	0.602
Pooled[4] (n=12)	1.34 (1.08-1.65)	0.007	43.36	74.63	0.0001	0.045	0.583
Carbohydrate pattern							
Case-control (n=4)	1.64 (1.35-2.00)	0.0001	2.99	0.00	0.393	0.799	1.000

[1]The analysis was performed when a number of data ≥3 were available; [2]The risk estimates ware calculated using the random-effect model; [3]In brackets are indicated the number of articles included in the analysis; [4]Analysis was performed on case-control and cohort studies combined together;

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3.4. Dose-response analysis

We started analyzing papers which reported complete observations. Eight studies were considered, six case control studies [25,26,29-31,33] and two cohort studies [34,35]. Figures S1 and S2 (on line) summarize data with estimated trends of ln OR according to the level of dietary consumption in each study for Healthy and Western pattern, respectively. For the "Healthy diet" a clear trend was not evident. In fact, the result didn't shown an increase in PC risk. The summary OR for each percentile increment was 0.999 (95% CI: 0.998, 1.001) with no evidence of heterogeneity (I^2=0%, p=0.82). Furthermore, the linear dose-response curves showed a slightly inverse, but not significant (p=0.345), association between Healthy diet consumption and PC risk. In contrast, for the western diet PC risk increased with the percentile of dietary adherence. The summary OR ranged from 1.004 (95% CI: 1.001, 1.008) for each percentile increment in the intake of Western diet, with high heterogeneity (I^2=74.9%, p=0.001). A linear trend was evident (p=0.011) as shown in Figure 5. The model predicted values for 20% percentiles which corresponded to 1.093 (95% CI: 1.021, 1.170). Using the missing imputation previously explained, we repeated the analysis with the inclusion of two studies [28-36]. Non significant changes occurred for the Healthy pattern. The summary OR for the Western diet was 1.003 (95% CI: 1.001, 1.006; p=0.021) with always high evidence of heterogeneity (I^2=73.7 %, p=0.001). Farther, considering studies without missing data, we conducted a subgroup analysis severaly for the case-control studies. We did not repeat the analysis for the cohort studies because there were only two cohort studies available for the dose-response analysis. A linear trend for the Western pattern was still evident in the case-control studies (p=0.002). The summary OR was 1.007 (95% CI: 1.003, 1.010). The heterogeneity was still quite high (I^2=51.1%, p=0.069) but less than in the dose-response analysis which considered the whole sample. In a sensitivity analysis excluding one study at a time, no particular differences in the results arose. Even if only three studies identified a "Carbohydrate pattern" and showed complete data [30,31,33] we conducted a dose-response meta-analysis also on this dietary set. Data detected a linear trend statistically significant (p=0.005). The estimated OR was 1.007 (95% CI: 1.002, 1.010). There was a quite low heterogeneity (I^2=28.7 %, p=0.246).

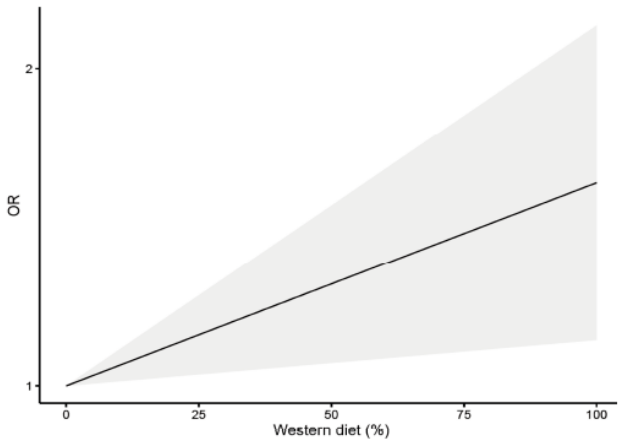

Figure 5. Dose-response plot of the linear relation between the intake of the "Western" dietary pattern and prostate cancer risk

3.5. Publication bias

Funnel plots showed a little evidence of asymmetry and therefore of publication bias (Figure S3, on line). The corresponding statistical evaluation by the Begg and Mazumdar's rank correlation test demonstrated no significant publication bias in any case (Table 3). On the other hand, the Egger's

linear regression test showed some publication bias for Healthy pattern in cohort studies (p=0.003) and for Western pattern in pooled analysis (p=0.045) (Table 3).

3.6. Sensitivity analysis

Sensitivity analyses investigating the influence of a single study on the PC risk estimate suggested that results were not substantially modified by removal any single study. In particular, not evident changes were found in the risk estimates after removal the outlier study of Askari et al. [32] on Healthy pattern (OR=0.96; 95% CI: 0.89, 1.05; p=0.399). In addition, the PC risk estimates associated to the Western pattern ranged from 1.26 (95% CI: 1.03-1.54, p=0.013) omitting the study of Niclis et al. [33] to 1.42 (95% CI: 1.13-1.79, p=0.003) omitting the study of Muller et al. [36]. Of note, omitting the study of Niclis et al. [33] in the Western pattern resulted in the absence of publication bias as evidenced by both Egger's regression (p=0.089) and Begg's rank correlation (p=0.586) tests.

4. Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis considering the effect of different dietary patterns identified by "a posteriori" methods on PC risk. From the selected articles we identified two very common dietary patterns "Western" and "Healthy" patterns. These two dietary patterns were present in all the selected studies, in addition four studies reported a further "Carbohydrate" pattern. The results indicate that both Western and Carbohydrate dietary patterns were significantly associated to an increase of PC risk while our analysis showed no association between Healthy dietary pattern and PC risk.

Several systematic reviews and meta-analysis have recently reported the association between dietary patterns and risk of cancer in different sites such as breast [42], colon and rectum [43,44], stomach [45], esophagus and lung [46,47]. Similar to our results, in some meta-analysis it was found that the consumption of a Western dietary pattern was positively associated to an increment of cancer risk in the colon [43], colorectal and stomach [44,45]. On the other hand, no significant correlation was evidenced for breast [42], rectal and esophagus cancers [43,46]. The Western pattern identified in the present investigation, likewise reported in the above reported meta-analysis, is characterized by high consumption of red meat, processed meat, eggs and sweets. These foods may be plausibly responsible, among the others, for the pro-carcinogenic properties of this diet. The consumption of processed meat and red meat has been recently classified by the International Agency for Research on Cancer (IARC) as "carcinogenic to humans" (Group 1) and "probably carcinogenic to humans" (Group 2A), respectively [48]. The carcinogenic activity of meat may be mediated by the presence of mutagenic compounds such as heterocyclic amines and polycyclic aromatic hydrocarbons which are formed during cooking at high temperatures or over the flame. However, a recent meta-analysis failed to show any positive correlation between red and processed meat, cooking methods and concentration of heterocyclic amines with the risk of PC [49]. This observation suggest that the Western dietary pattern may have a more complex interactions with PC risk than those expected for the red meat and processed meat considered as individual foods.

Regarding the Healthy pattern, previous meta-analysis showed an evident and significant inverse correlation with cancer risk in all anatomic sites considered with the exclusion of the rectum [42-47]. In contrast, our data suggest a small reduction of PC risk (4%, when comparing the highest with the lowest intake categories) which was not statistically significant. These results may be difficult to explain since the Healthy pattern is characterized by a high load for vegetables and fruits which are a rich source of anti-oxidants with potential chemopreventive activities. However, it should be considered that in this dietary pattern were also included other foods such as poultry, fish and whole grains. In any case, our results are in agreement with previous meta-analysis showing no effect of single vegetable foods and fish on PC risk [7-12,13].

In our study we also found a Carbohydrate dietary pattern which was associated with a statistically significant 64% increment of PC risk. This result is of particular interest, considering that the Carbohydrate pattern had high-factor loading for bread, pasta and rice. However, the data should be interpreted with caution since they were obtained from only four studies. Further epidemiological evidences are necessary to confirm this trend considering also that a recent meta-analysis showed no correlation between consumption of dietary fiber, whole grains and carbohydrate with PC risk [50].

One of the great limitations of meta-analysis is that the results are combined from studies conducted with different methods in different populations, resulting in heterogeneity. In our analysis heterogeneity was more evident in the results of the "Western pattern", this could be due to the difficult to characterize this pattern. Moreover, a possible misclassification within the considered dietary patterns may be present. Factor analysis and/or principal component analysis are subjective techniques with opportunities for variation at almost every step [16]. Other limitations of our meta-analysis could be linked to the fact that pooled findings were directly driven by the included studies, which have their weaknesses relative to study design. In addition, risk estimates in the various studies were adjusted for different potential confounders.

In conclusion, we pooled information from twelve studies that identified different a posteriori dietary pattern in terms of single food or nutrient items mainly correlated to them. We selected two main dietary pattern which were analyzed in all the studies and a dietary pattern which was reported just in four of them. From the dietary pattern named as "Healthy", mainly based of high consumption of vegetables and fruits, poultry, fish and whole grains, a statistical significance association with PC risk was not highlighted. Different results emerged from dietary pattern named as "Western" and "Carbohydrate", characterized by high loading of red meat, processed meat, eggs, sweets and bread, pasta and rice, respectively. An increase in PC risk was pointed out in the highest compared with the lowest categories of dietary pattern in all pooled studies and in the dose response meta-analysis, even if the heterogeneity was quite high. As consequence of this, and considering also the small number of cohort studies so far published, further investigations are necessary to support these findings.

Supplementary Materials: The following are available online at www.mdpi.com/link, Figure S1: title, Table S1: title, Video S1: title. Figure S1: Dose-response plots of the relation between the intake of the "Healthy" dietary pattern and prostate cancer risk in the different studies included in the meta-analysis, Figure S2: Dose-response plots of the relation between the intake of the "Western" dietary pattern and prostate cancer risk in the different studies included in the meta-analysis, Figure S3: Funnel plots of studies included in the meta-analysis evaluating the association between different dietary patterns (Healthy, Western and Carbohydrate) and prostate cancer risk. Table S1: Methodological quality of case-control studies included in the meta-analysis, Table S2. Methodological quality of cohort studies included in the meta-analysis

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Author Contributions: RF and LM conceived and drafted the manuscript. RF and GB collected all data. RF, LM and GB analyzed and interpreted data. LM and SB critically revised the manuscript. All authors approved the final version of the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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