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Association between dietary flavonoids intake and prostate cancer risk: A case-control study in Sicily

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ABSTRACT

Objectives: The aim of this study is to test the association between dietary flavonoids intake and prostate cancer (PCa) in a sample of southern Italian individuals.
Design: A population-based case–control study on the association between PCa and dietary factors was conducted from January 2015 to December 2016, in a single institution.
Setting: Patients with elevated PSA (Prostate Specific Antigen) and/or suspicion of PCa underwent transperineal prostate biopsy (≥12 cores). A total of 118 histopathological-verified PCa cases were collected and matched with controls, which were selected from a sample of 2044 individuals randomly recruited among the same reference population. Finally, a total of 222 controls were selected.
Main outcome measures: Prevalence of PCa.
Results: Consumption of certain groups of flavonoids significantly differed between controls and cases, in particular: flavonols (63.36 vs 37.14 mg/d, P < 0.001), flavanols (107.61 vs. 74.24 mg/d, P = .016), flavanones (40.92 vs. 81.32 mg/d, P < 0.001), catechins (63.36 vs. 36.18 mg/d, P = .006). In the multivariate model, flavanols and flavones were associated with reduced risk of PCa, despite not in the highest quartile of intake. Higher flavonol and catechin intake was consistently associated with reduced risk of PCa (Odds Ratio (OR) = 0.19, 95% CI: 0.06–0.56 and OR = 0.12, 95% CI: 0.04–0.36). In contrast, the highest intake of flavanones was positively associated with PCa.
Conclusion: Flavonols and catechins have proved to be the most promising molecules for a potential protective role against PCa. Nevertheless, further research on flavanones is needed to better establish whether they are associated with PCa.

1. Introduction

Prostate cancer (PCa) is the most common cancer in men with incidental diagnosis.[1] Current statistics predicted that in the USA new cases of PCa will be more than 150,000 per annum over the next few years [2]. Although major efforts have been paid to prevent this cancer, including identification of risk factors (racial/ethnic background and family history) [3], there are aspects of etiopathogenesis still not clarified. Identifying causal factors of PCa would lead to new prevention methods. Also for PCa, as for benign prostatic hyperplasia, it has been hypothesized the possibility that the etiopathogenesis of the disorder is linked to chronic inflammation: the main pathway proposed suggests that the presence of oxidative stress associated to chronic inflammation in the cellular environment causes an increase of pro-inflammatory cytokines and growth factors, which in turn may determine an increase of the speed of cell replication, and therefore the possibility of incurring mutations [4,5]. If there is a correlation between prostate diseases, oxidative stress and chronic inflammation, the role of compounds with antioxidant action could play an important role in the prevention of PCa.

Current evidence suggests that adherence to plant-based dietary patterns, such as the Mediterranean diet, may reduce risk of PCa [6–8]. Moreover, patients exhibiting greater adherence to the Mediterranean diet after diagnosis of non-metastatic PCa were associated with lower

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overall mortality [9]. Interestingly, pure vegetarian dietary patterns did not show the same inverse association with risk of PCa [10], suggesting that the retrieved associations are related to beneficial compounds rather than only reduction of unhealthy ones (i.e., trans-fatty acids). Among the others, important components of the Mediterranean diet that have been hypothesized to be responsible for its potential beneficial effects are polyphenols [11]. These compounds occur naturally in plant-derived foods, such as fruits and vegetables, nuts, whole-grains, olive oil, coffee and tea. Based on their biochemical structures, they are divided into different subclasses of which, the most representative, are flavonoids [12]. In turn, the six principal subclass of flavonoids are flavonols, flavones, flavanones, flavanols, and anthocyanidins [13]. The interest on studying flavonoids as anti-cancer substances depends on a variety of properties and potential mechanisms of action that may affect the risk of cancer [14–17]. In example, flavonoids were shown to modulate several molecular pathways implicated in PCa carcinogenesis process; in particular, by targeting important transcription factors, such as NF-kB (Nuclear Factor kappa-light-chain-enhancer of activated B cells) and AP-1 (activator protein-1), implicated in regulation of inflammatory response. Results on the association between dietary flavonoid intake and human health are promising, but research in relation to cancer is still ongoing and rather incomplete [18]. Some studies investigated the relation between dietary flavonoids and PCa [19,20]: however, the relation between PCa and flavonoid subclasses remains unclear. Thus, the aim of this article is to test the association between dietary flavonoids, including all major subclasses, and PCa in a sample of southern Italian individuals.

2. Material and methods

2.1. Study population

A population-based case–control study on the association between PCa and dietary factors was conducted from January 2015 to December 2016 in a single institution of the municipality of Catania, southern Italy. Patients with elevated PSA and/or suspicious PCa underwent transperineal prostate biopsy (≥12 cores). A total of 118 histopathological-verified PCa cases were collected.

Controls were selected from a sample of 2044 individuals included in a cohort study [21]: individuals were randomly selected among the same reference population of the cases, and matched by age, BMI, and smoking status with cases. A total of 222 controls were selected.

All the study procedures were carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association and participants provided written informed consent after accepting to participate. The study protocol was approved by the ethic committee of the referent health authority (Policlinico Hospital of Catania, Registration number: 41/2015).

2.2. Data collection

Demographics (including age, and educational level) and lifestyle characteristics (including physical activity, smoking and drinking habits) were collected. Educational level was categorized as (i) low (primary/secondary), (ii) medium (high school), and (iii) high (university). Physical activity level was evaluated through the International Physical Activity Questionnaires (IPAQ) [22] which comprised a set of questionnaires (5 domains) investigating the time spent being physically active in the last 7 days: based on the IPAQ guidelines, final scores allows to categorized physical activity level as (i) low, (ii) moderate, and (iii) high. Smoking status was categorized as (i) non-smoker, (ii) ex-smoker, and (iii) current smoker. Alcohol consumption was categorized as (i) none, (ii) moderate drinker (0.1–12 g/d) and (iii) regular drinker (> 12 g/d).

2.3. Dietary assessment

Dietary data was collected by using two food frequency questionnaires (FFQs) specifically developed and validated for the Sicilian population[23,24]. The long-version FFQ consisted of 110 food and drink items. Patients were specifically asked whether they changed their diet due to course of the disease and to answer to the questionnaire referring to their habitual diet before the disease. Participants were asked how often, on average, they had consumed foods and drinks included in the FFQ, with nine responses ranging from “never” to “4-5 times per day”. Intake of food items characterized by seasonality referred to consumption during the period in which the food was available and then adjusted by its proportional intake in one year.

2.4. Estimation of flavonoid intake

The methodology used to retrieve dietary flavonoids has been widely used in literature and largely described elsewhere [25]. Briefly, data on the polyphenol content in foods was obtained from the Phenol-Explorer database (www.phenol-explorer.eu). A new module of the Phenol-Explorer database containing information on the effects of cooking and food processing on polyphenol contents was used whenever possible in order to apply polyphenol-specific retention factors [26]. A total of 75 items were searched in the database after exclusion of foods that contained no polyphenols. Following the standard portion sizes used in the study, food items were converted in g or ml and then proportioned to 24-h intake. Next, a search was carried out in the Phenol-Explorer database to retrieve mean content values for flavonoid (total and major subclasses) contained in the foods obtained and their intake was then calculated by multiplying the flavonoid content by the daily consumption of each food. Finally, intake of flavonoids was adjusted for total energy intake (kcal/d) using the residual method.

2.5. Statistical analysis

Categorical variables are presented as frequency and percentage, continuous variables are presented as mean and standard deviation. Differences of frequency between groups were calculated by Chi-square test. Total flavonoid intake distribution was tested for normality distribution with the Kolmogorov-Smirnov test and it followed a slightly asymmetric normal distribution due to extreme values of the upper side. Mann-Whitney *U* test and Kruskall-Wallis test were used to compare differences in intakes between groups, as appropriate. Association between dietary intake of total and subclasses of flavonoid and PCa was calculated through logistic regression analysis adjusted for age (years, continuous), energy intake (kcal/d, continuous), weight status (normal, overweight, obese), smoking status (smokers, non-smokers), alcohol consumption (< 12 g/d, ≥12 g/d), physical activity level (low, medium, high), family history of PCa. All reported *P* values were based on two-sided tests and compared to a significance level of 5%. SPSS 17 (SPSS Inc., Chicago, IL, USA) software was used for all the statistical calculations.

3. Results

Table 1 lists the baseline characteristics of cases and controls. Besides the characteristics for which controls were matched with cases, most of other variables had different distribution between groups: specifically, among cases there was a higher prevalence of low education, low physical activity level, higher alcohol consumption and family history of PCa than controls, despite mean BMI levels were lower in the former than in the latter.

No significant differences between cases and controls have been found concerning total dietary flavonoids (Table 2). However, regarding flavonoid subclasses, differences between intake of some compounds were statistically significant: flavonols (63.36 vs. 37.14,

Table 1
Baseline characteristics of cases and controls.

	Cases (n = 118)	Controls (n = 222)	P-value
Age (y), mean (SD)	69.13 (6.60)	68.09 (8.18)	0.238
BMI, mean (SD)	26.49 (3.34)	27.49 (3.28)	< 0.001
Weight status, n (%)			0.220
Normal	42 (35.6	59 (26.6)	
Overweight	60 (50.8)	127 (57.2)	
Obese	16 (13.6)	36 (16.2)	
Smoking status, n (%)			0.220
Non-smoker	68 (57.6)	143 (64.4)	
Current smoker	50 (42.4)	79 (35.6)	
Alcohol intake, n (%)			< 0.001
< 12 g/d	55 (46.6)	153 (68.9)	
≥12 g/d	63 (53.4)	69 (31.1)	
Education, n (%)			< 0.001
Primary	96 (81.4)	49 (22.1)	
Secondary	22 (18.6)	173 (77.9)	
Physical activity level, n (%)			< 0.001
Low	38 (32.2)	49 (26.2)	
Medium	64 (54.2)	67 (35.8)	
High	16 (13.6)	71 (38.0)	
Family history of prostatic cancer, n (%)	43 (36.44)	9 (4.05)	< 0.001

Table 2
Mean differences of total and subclasses of flavonoid intake between cases and controls.

	Cases (n = 118)	Controls (n = 222)	P-value
Flavonoids, mean (SD)	268.68 (166.87)	286.04 (207.38)	0.434
Anthocyanins, mean (SD)	59.82 (51.55)	59.09 (55.57)	0.903
Flavonols, mean (SD)	37.14 (29.23)	63.36 (46.85)	< 0.001
Flavanols, mean (SD)	74.24 (71.42)	107.61 (139.97)	0.016
Flavanones, mean (SD)	81.32 (76.94)	40.92 (40.38)	< 0.001
Flavones, mean (SD)	9.86 (13.84)	8.50 (8.70)	0.266
Catechins, mean (SD)	36.18 (46.43)	63.36 (100.11)	0.006

P < 0.001), flavanols (107.61 vs. 74.24, P = 0.016), flavanones (40.92 vs. 81.32 P < 0.001), and catechins (63.36 vs. 36.18, P = 0.006). There was no statistical significant difference in the subclasses of flavones and anthocyanins between PCa group when compared to controls.

The univariate logistic regression analysis showed that intake of various compounds was associated with PCa (Table 3). When analysis was adjusted for potential confounding factors (including age, energy intake, weight status, smoking status, alcohol consumption, physical activity level, family history of prostatic cancer), only the highest intake of flavonol and catechin intake was consistently associated with less likelihood of having PCa (OR = 0.19, 95%CI: 0.07–0.50 and OR = 0.12, 95%CI: 0.04–0.36, respectively). Moreover, flavanol and flavone intake was also associated with PCa, despite the significant association was relative to third quartile of intake, while the highest showed no significant results (Table 3). In contrast, the highest quartile of flavanone intake was directly associated with higher likelihood of having PCa compared to the lowest (Table 3). No significant association between total flavonoid intake and PCa was found.

4. Discussion

In this study, we tested the association between dietary flavonoid intake and PCa in a sample of individuals living in the Mediterranean area. Although results were not consistently significant for all the various compounds tested, higher intake of nearly all flavonoids was inversely associated with PCa compared to lower intake.

Published data on flavonoid intake and risk of PCa is somehow contrasting. Some individual studies and recent meta-analyses showed

Table 3
Association between quartiles of total and subclasses of flavonoid intake and prostate cancer.

	Q1	Q2	Q3	Q4
Flavonoids				
No. of cases	30	35	19	36
OR (95% CI)[a]	Ref.	0.93 (0.49–1.76)	0.48 (0.24–0.97)	0.75 (0.39–1.45)
OR (95% CI)[b]	Ref.	1.44 (0.57–3.63)	0.51 (0.18–1.42)	1.10 (0.40–2.99)
Anthocyanins				
No. of cases	28	31	32	27
OR (95% CI)[a]	Ref.	1.09 (0.57–2.09)	0.98 (0.51–1.85)	0.62 (0.31–1.25)
OR (95% CI)[b]	Ref.	0.58 (0.23–1.45)	0.51 (0.20–1.31)	0.36 (0.12–1.06)
Flavonols				
No. of cases	64	28	15	11
OR (95% CI)[a]	Ref.	0.44 (0.24–0.79)	0.21 (0.10–0.42)	0.11 (0.53–0.26)
OR (95% CI)[b]	Ref.	0.44 (0.18–1.04)	0.19 (0.07–0.50)	0.19 (0.06–0.56)
Flavanols				
No. of cases	106	9	2	1
OR (95% CI)[a]	Ref.	0.71 (0.29–1.72)	0.03 (0.003–0.33)	0.35 (0.04–3.04)
OR (95% CI)[b]	Ref.	0.76 (0.22–2.58)	0.02 (0.002–0.31)	1.84 (0.17–19.4)
Flavanones				
No. of cases	18	10	19	71
OR (95% CI)[a]	Ref.	0.51 (0.21–1.21)	0.96 (0.45–2.06)	3.03 (1.56–5.87)
OR (95% CI)[b]	Ref.	0.26 (0.07–0.90)	1.59 (0.50–5.02)	5.76 (2.06–16.09)
Flavones				
No. of cases	37	32	10	39
OR (95% CI)[a]	Ref.	0.82 (0.44–1.51)	0.24 (0.11–0.55)	0.84 (0.46–1.54)
OR (95% CI)[b]	Ref.	0.61 (0.25–1.45)	0.33 (0.12–0.91)	0.87 (0.34–2.21)
Catechins				
No. of cases	50	22	31	15
OR (95% CI)[a]	Ref.	0.39 (0.21–0.75)	0.49 (0.27–0.89)	0.20 (0.097–0.41)
OR (95% CI)[b]	Ref.	0.21 (0.08–0.55)	0.35 (0.14–0.90)	0.12 (0.04–0.36)

[a] OR adjusted for energy intake (kcal/d, continuous).

[b] OR adjusted for age (years, continuous), energy intake (kcal/d, continuous), weight status (normal, overweight, obese), smoking status (smokers, non-smokers), alcohol consumption (< 12 g/d, ≥12 g/d), physical activity level (low, medium, high), family history of prostatic cancer.

that a direct association between specific classes of flavonoids (i.e., flavanones and anthocyanins) and likelihood of having PCa may exist, while results on other classes are largely inconsistent [19,20,27]. Thus, our findings are only partially in line with existing literature, as we found a potential protective association for certain classes, while we also reported direct association between flavanone intake and PCa.

Regarding the potential detrimental effects, it has been hypothesized that excessive antioxidants consumption may actually increase risk of cancer [28]. Despite not relative to flavanones, there is evidence that certain antioxidant vitamins, including ascorbic acid, may have detrimental effects on reactive oxygen species production processes related to PCa [29–31]; it is noteworthy that major source of ascorbic acid coincide with those of flavanones (i.e., citrus fruits), thus potentially leading to collinearity and confusing the interpretation of results on this flavonoid class.

Regarding the potential protective effects of flavonoids, there is evidence of general beneficial effects of dietary flavonoids on metabolic health [32,33] and metabolic status has been shown in a recent meta-analysis to be a mediating factor for PCa risk [34]. Flavonoids may act as activator of the transcription factor NF-kB that regulate a variety of cellular activities that include inflammation, immune response, cell growth and death, therefore resulting in a cascade of events that may lead to carcinogenesis [33]. Overexpression of NF-kB leads to the activation of several signalling pathways, among which also the activation of COX-2 (cyclooxygenase-2), which increases levels of pro-inflammatory cytokines, a perfect scenario for developing PCa cells. It has been shown, that synthetized analogs of flavanols are promising category of compounds that can inhibit cell growth and interfere with the components of the androgen receptor and PSA proteins in human-derived PCa cell line [35] or directly compromise the PCa cell vitality of several prostate cancer cell lines, including: 22Rv1, TRAMP C2, PC-3

and LNCaP [36] Moreover, flavonols may expression of several genes, such as MMP-1 (matrix metalloproteinase-1), MMP-9 (matrix metalloproteinase-9), MMP-14 (matrix metalloproteinase-14), c-Fos (proto-oncogene), c-Jun (a subunit of the transcription factor), and VEGF (vascular endothelial growth factor), that have been previously shown to be associated with PCa [36] and in particular in changing the ratio Bcl-2 (B-cell lymphoma 2)/Bax (apoptosis regulator) mRNA, which directly determines neoplastic cell sensitization for the apoptotic pathway [37,38].

Among individual compounds, higher intake of flavonols and, specifically, catechins was found to be significantly inversely associated with having PCa. Catechins are typically contained in tea, one of the most widely consumed beverage in the world [39]. The tea plant (*Camellia sinensis*) produced in Asia, China, Japan, and Thailand has been traditionally used in natural medicine[40]. The most represented individual compounds contained in tea, such as epigallocatechin (EGC), epicatechin-3-gallate (ECG), epicatechin (EC), and epigallocatechin-3-gallate (EGCG), have been studied in relation to PCa[41]. Among the main mechanisms of action, these molecules may play a role in the prevention of etiopathogeneiss of PCa by inducing cell growth arrest and apoptosis primarily via p53-dependent pathway or inhibiting COX-2 (inducible enzymatic isoform, rapidly induced by growth factors, tumor promoters, oncogenes, and carcinogens) without affecting COX-1 (cyclooxygenase-1), at both the mRNA and protein levels [15,40], Besides these biological properties, previous data found no association between PCa risk and green tea intake [42–44]. However, a recent meta-analysis showed that green tea intake might reduce the incidence of PCa with a linear dose–response effect and decrease PCa risk significantly with daily intake of over 7 cups/day [45]. There is still only limited evidence from randomized clinical trials investigating the association of green tea catechins with the risk of PCa, however showing that green tea catechins had a significant effect on the reduction of PCa risk compared to placebo [46,47].

Some limitations of the present analysis have to be addressed for a better interpretation of the results. First, the observational nature of study does not permit to assess causal relationships, rather only associations. Second, the variety of flavonoid composition is complex and use of FFQs may lead to measurement errors. Third, our sample was based on patients with no previous biopsy and PCa diagnosis could have been underestimated. In contrast, controls were selected from the general population, thus we are unaware whether undiagnosed PCa cases existed.

5. Conclusion

In conclusions, flavonoids may have different levels of protection against PCa. Among the compounds tested in our study, flavonols and catechins have proved to be the most interesting molecules for a protective value. Future randomized clinical trials are needed to strengthen the findings obtained in this study and provide adequate evidence of the potential protective effects of flavonoids toward PCa risk.

Compliance with ethical standards

All the study procedures were carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association and participants provided written informed consent after accepting to participate. The study protocol was approved by the ethic committee of the referent health authority (Policlinico Hospital of Catania, Registration number: 41/2015).

Conflict of interest

Each author declares no conflict of interest.

Author's contribution

G.R.: Manuscript writing
G.I.R.: Protocol/project development, data management, manuscript editing
F.R.: Data Collection
M.D.: Data Collection
D.C.: Data Collection
A.L.: Data Collection
M.M.: Supervision
R.R.: Supervision
V.F.: Supervision
S.C.: Supervision
G.M.: Supervision

References

1. Dy GW, Gore JL, Forouzanfar MH, Naghavi M, Fitzmaurice C. Global burden of urologic cancers, 1990–2013. *Eur Urol.* 2017;71(3):437–446.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics. *CA Cancer J Clin.* 2017;67(1):7–30.
3. Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol.* 2017;71(April (4)):618–629. http://dx.doi.org/10.1016/j.eururo.2016.08.003 [Epub 2016 Aug 25].
4. De Nunzio C, Kramer G, Marberger M, et al. The controversial relationship between benign prostatic hyperplasia and prostate cancer: the role of inflammation. *Eur Urol.* 2011;60(1):106–117.
5. Kruslin B, Tomas D, Dzombeta T, Milkovic-Perisa M, Ulamec M. Inflammation in prostatic hyperplasia and carcinoma-basic scientific approach. *Front Oncol.* 2017;7:77.
6. Schwingshackl L, Hoffmann G. Adherence to Mediterranean diet and risk of cancer: an updated systematic review and meta-analysis of observational studies. *Cancer Med.* 2015;4(12):1933–1947.
7. Grosso G, Bella F, Godos J, et al. Possible role of diet in cancer: systematic review and multiple meta-analyses of dietary patterns, lifestyle factors, and cancer risk. *Nut Rev.* 2017;75(June (6)):405–419.
8. Russo G.I., Campisi D., Di Mauro M., et al. Dietary consumption of phenolic acids and prostate cancer: a case-control study in sicily.
9. Kenfield SA, DuPre N, Richman EL, Stampfer MJ, Chan JM, Giovannucci EL. Mediterranean diet and prostate cancer risk and mortality in the Health Professionals Follow-up Study. *Eur Urol.* 2014;65(5):887–894.
10. Godos J, Bella F, Sciacca S, Galvano F, Grosso G. Vegetarianism and breast, colorectal and prostate cancer risk: an overview and meta-analysis of cohort studies. *J Hum Nutr Diet.* 2017;30(June (3)):349–359.
11. Godos J, Rapisarda G, Marventano S, Galvano F, Mistretta A, Grosso G. Association between polyphenol intake and adherence to the Mediterranean diet in Sicily, southern Italy. *NFS J.* 2017;8:1–7.
12. Del Rio D, Costa LG, Lean ME, Crozier A. Polyphenols and health: what compounds are involved? *Nutr Metab Cardiovasc Dis.* 2010;20(1):1–6.
13. Del Rio D, Rodriguez-Mateos A, Spencer JP, Tognolini M, Borges G, Crozier A. Dietary (poly)phenolics in human health: structures, bioavailability, and evidence of protective effects against chronic diseases. *Antioxid. Redox Signal.* 2013;18(14):1818–1892.
14. Ramos S. Effects of dietary flavonoids on apoptotic pathways related to cancer chemoprevention. *J Nutr Biochem.* 2007;18(7):427–442.
15. Khan N, Adhami VM, Mukhtar H. Review: green tea polyphenols in chemoprevention of prostate cancer: preclinical and clinical studies. *Nutr Cancer.* 2009;61(6):836–841.
16. Adhami VM, Malik A, Zaman N, et al. Combined inhibitory effects of green tea polyphenols and selective cyclooxygenase-2 inhibitors on the growth of human prostate cancer cells both in vitro and in vivo. *Clin Cancer Res.* 2007;13(5):1611–1619.
17. Abbas A, Patterson 3rd W, Georgel PT. The epigenetic potentials of dietary polyphenols in prostate cancer management. *Biochem Cell Biol.* 2013;91(6):361–368.
18. Grosso G, Micek A, Godos J, et al. Dietary flavonoid and lignan intake and mortality in prospective cohort studies: systematic review and dose-response meta-analysis. *Am J Epidemiol.* 2017;185(12):1304–1316.
19. Guo K, Liang Z, Liu L, Li F, Wang H. Flavonoids intake and risk of prostate cancer: a meta-analysis of observational studies. *Andrologia.* 2016;48(10):1175–1182.
20. Grosso G, Godos J, Lamuela-Raventos R, et al. A comprehensive meta-analysis on dietary flavonoid and lignan intake and cancer risk: level of evidence and limitations. *Mol Nutr Food Res.* 2017;61(Apr (4)).
21. Grosso G, Marventano S, D'Urso M, Mistretta A, Galvano F. The Mediterranean healthy eating, ageing, and lifestyle (MEAL) study: rationale and study design. *Int J food Sci Nutr.* 2016:1–10.
22. Craig CL, Marshall AL, Sjostrom M, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc.* 2003;35(8):1381–1395.
23. Marventano S, Mistretta A, Platania A, Galvano F, Grosso G. Reliability and relative validity of a food frequency questionnaire for Italian adults living in Sicily: southern Italy. *Int J Food Sci Nutr.* 2016:1–8.

24. Buscemi S, Rosafio G, Vasto S, et al. Validation of a food frequency questionnaire for use in Italian adults living in Sicily. *Int J Food Sci Nutr.* 2015;66(4):426–438.
25. Godos J, Rapisarda G, Marventano S, Galvano F, Mistretta A, Grosso G. Association between polyphenol intake and adherence to the Mediterranean diet in Sicily, southern Italy. *NFS J.* 2017;8(Aug):1–7.
26. Rothwell JA, Perez-Jimenez J, Neveu V, et al. Phenol-Explorer 3.0: a major update of the Phenol-Explorer database to incorporate data on the effects of food processing on polyphenol content. *Database (Oxford).* 2013;2013:bat070.
27. Bosetti C, Bravi F, Talamini R, et al. Flavonoids and prostate cancer risk: a study in Italy. *Nutr Cancer.* 2006;56(2):123–127.
28. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. *Cochrane Database Syst Rev.* 2012(3):D007176.
29. Fukumura H, Sato M, Kezuka K, et al. Effect of ascorbic acid on reactive oxygen species production in chemotherapy and hyperthermia in prostate cancer cells. *J Physiol Sci.* 2012;62(3):251–257.
30. Grosso G, Bei R, Mistretta A, et al. Effects of vitamin C on health: a review of evidence. *Front Biosci (Landmark Ed.).* 2013;18:1017–1029.
31. Heaney ML, Gardner JR, Karasavvas N, et al. Vitamin C antagonizes the cytotoxic effects of antineoplastic drugs. *Cancer Res.* 2008;68(19):8031–8038.
32. Grosso G, Stepaniak U, Micek A, Stefler D, Bobak M, Pajak A. Dietary polyphenols are inversely associated with metabolic syndrome in Polish adults of the HAPIEE study. *Eur J Nutr.* 2017;56(June (4)):1409–1420.
33. Mansuri ML, Parihar P, Solanki I, Parihar MS. Flavonoids in modulation of cell survival signalling pathways. *Genes Nutr.* 2014;9(3):400.
34. Gacci M, Russo GI, De Nunzio C, et al. Meta-analysis of metabolic syndrome and prostate cancer. *Prostate Cancer Prostatic Dis.* 2017;20(2):146–155.
35. Britton RG, Horner-Glister E, Pomenya OA, et al. Synthesis and biological evaluation of novel flavonols as potential anti-prostate cancer agents. *Eur J Med Chem.* 2012;54:952–958.
36. Hill CU, Saad SE, Britton RG, et al. Inhibition of prostate cancer cell growth by 3',4',5'-trimethoxyflavonol (TMFol). *Cancer Chemother Pharmacol.* 2015;76(1):179–185.
37. Lewandowska U, Szewczyk K, Owczarek K, et al. Flavanols from evening primrose (Oenothera paradoxa) defatted seeds inhibit prostate cells invasiveness and cause changes in Bcl-2/Bax mRNA ratio. *J Agric Food Chem.* 2013;61(12):2987–2998.
38. Lewandowska U, Szewczyk K, Owczarek K, et al. Flavanols from Japanese quince (Chaenomeles japonica) fruit inhibit human prostate and breast cancer cell line invasiveness and cause favorable changes in Bax/Bcl-2 mRNA ratio. *Nutr Cancer.* 2013;65(2):273–285.
39. Cimino S, Sortino G, Favilla V, et al. Polyphenols: key issues involved in chemoprevention of prostate cancer. *Oxid Med Cell Longev.* 2012;2012:632959.
40. Pandey M, Gupta S. Green tea and prostate cancer: from bench to clinic. *Front Biosci (Elite Ed.).* 2009;1:13–25.
41. Khan N, Mukhtar H. Modulation of signaling pathways in prostate cancer by green tea polyphenols. *Biochem Pharmacol.* 2013;85(5):667–672.
42. Zheng J, Yang B, Huang T, Yu Y, Yang J, Li D. Green tea and black tea consumption and prostate cancer risk: an exploratory meta-analysis of observational studies. *Nutr Cancer.* 2011;63(5):663–672.
43. Lin YW, Hu ZH, Wang X, et al. Tea consumption and prostate cancer: an updated meta-analysis. *World J Surg Oncol.* 2014;12:38.
44. Fei X, Shen Y, Li X, Guo H. The association of tea consumption and the risk and progression of prostate cancer: a meta-analysis. *Int J Clin Exp Med.* 2014;7(11):3881–3891.
45. Guo Y, Zhi F, Chen P, et al. Green tea and the risk of prostate cancer: a systematic review and meta-analysis. *Medicine (Baltimore).* 2017;96(13):e6426.
46. Brausi M, Rizzi F, Bettuzzi S. Chemoprevention of human prostate cancer by green tea catechins: two years later. *Follow-Up Update Eur Urol.* 2008;54(2):472–473.
47. Kumar NB, Pow-Sang J, Egan KM, et al. Randomized, placebo-controlled trial of green tea catechins for prostate cancer prevention. *Cancer Prev Res (Phila).* 2015;8(10):879–887.