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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,