The impact of moderate wine consumption on the risk of developing prostate cancer

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Objective: To investigate the impact of moderate wine consumption on the risk of prostate cancer (PCa). We focused on the differential effect of moderate consumption of red versus white wine.

Design: This study was a meta-analysis that includes data from case-control and cohort studies.

Materials and methods: A systematic search of Web of Science, Medline/PubMed, and Cochrane library was performed on December 1, 2017. Studies were deemed eligible if they assessed the risk of PCa due to red, white, or any wine using multivariable logistic regression analysis. We performed a formal meta-analysis for the risk of PCa according to moderate wine and wine type consumption (white or red). Heterogeneity between studies was assessed using Cochranes’s Q test and I2 statistics. Publication bias was assessed using Egger’s regression test.

Results: A total of 930 abstracts and titles were initially identified. After removal of duplicates, reviews, and conference abstracts, 83 full-text original articles were screened. Seventeen studies (611,169 subjects) were included for final evaluation and fulfilled the inclusion criteria. In the case of moderate wine consumption: the pooled risk ratio (RR) for the risk of PCa was 0.98 (95% CI 0.92–1.05, p=0.57) in the multivariable analysis. Moderate white wine consumption increased the risk of PCa with a pooled RR of 1.26 (95% CI 1.10–1.43, p=0.001) in the multivariable analysis. Meanwhile, moderate red wine consumption had a protective role reducing the risk by 12% (RR 0.88, 95% CI 0.78–0.999, p=0.047) in the multivariable analysis that comprised 222,447 subjects.

Conclusions: In this meta-analysis, moderate wine consumption did not impact the risk of PCa. Interestingly, regarding the type of wine, moderate consumption of white wine increased the risk of PCa, whereas moderate consumption of red wine had a protective effect. Further analyses are needed to assess the differential molecular effect of white and red wine conferring their impact on PCa risk.

Keywords: wine, prostate cancer, alcohol, risk of cancer, meta-analysis

Introduction

Prostate cancer (PCa) is the most commonly diagnosed cancer among men in the USA with an estimated 161,360 new cases in 2017.1 Worldwide, it is the second most common cancer and the sixth cause of cancer death among men,2 with an estimated 1.1 million cases and 307,000 deaths in 2012.3 There are well-established risk factors for PCa, such as family history,4,5 hereditary genes,6 racial/ethnic background (eg, African ethnicity),7 and age. Also, a wide variety of exogenous/environmental/lifestyle factors have been shown to impact the risk of PCa development and progression.8 For example, alcohol intake has been recently suggested as a risk factor for PCa.
development in a meta-analysis that included 27 studies showing a significant dose–response relationship between the level of alcohol intake and the risk of PCa. On the other hand, a large prospective European cohort study failed to observe an association between alcohol consumption and PCa risk. Both studies did not assess the type of alcohol consumption. Despite association between alcohol intake and PCa risk, the effect of wine consumption on PCa risk is not yet fully understood. Furthermore, association between wine consumption and risk of PCa demands further investigation as several studies have suggested that polyphenols from red wine have a chemoprotective role in PCa cell lines.

Therefore, we hypothesized that wine, specifically red wine, has a protective effect on PCa development. To test this hypothesis, we performed a meta-analysis assessing the effect of moderate wine consumption on PCa in a first step and then that of red and white wine differentially.

**Materials and methods**

A systematic search of Web of Science, Medline/PubMed, and Cochrane library was performed using the terms “wine” and “prostate cancer” on December 1, 2017. All original articles that fulfilled the inclusion criteria were included. We performed additional cross-checking of reference lists, including those of previous meta-analyses and “hand-searched” for additional references in the selected articles, reviews, and meta-analyses reporting on the topic.

Informed consent was not required for this type of study.

**Inclusion and exclusion criteria**

The PICOS (Population, Intervention, Comparator, Outcome and Study design approach was utilized to define study eligibility according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria ([www.prisma-statement.org](http://www.prisma-statement.org)). Studies were considered eligible if they assessed the risk of PCa due to red and white wine and wine in general using multivariable logistic regression analysis in the general population or compared with a control group of individuals without PCa. For each selected study, the following items were recorded: first author’s name, year of publication, country, number of patients, age, and variables used in the multivariable analysis, risk ratios (RRs) of PCa in multivariable analysis, dose of wine and follow-up in case of cohort studies. Two independent investigators (MDV and SK) assessed study quality using the Newcastle-Ottawa Scale (NOS) for cohort studies. A total score of 5 or less was considered low; 6–7 was considered intermediate, and 8–9 was considered high quality. Most included studies had intermediate and high quality score according to NOS (Figure S1).

**Statistical analysis**

We performed a formal meta-analysis for the risk of PCa according to moderate wine consumption and moderate consumption of type of wine (white or red). RRs with their 95% CIs from each study were used to calculate pooled RRs. Pooled estimates were calculated with the fixed effect model, if no significant heterogeneity was identified; alternatively, the random effect model was used when significant heterogeneity was detected. Statistical heterogeneity was defined based on Cochrane’s Q p-value or I² statistics. We performed “leave-one-out” sensitivity analysis. To evaluate publication bias, Egger linear regression and funnel plots were examined. In case of reporting only RRs for low- and high-risk PCa, we included in the meta-analysis the RRs for high-risk PCa. Statistical analyses were performed using Stata 11.0 statistical software (Stata Corp., College Station, TX, USA).

**Results**

A total of 930 abstracts and titles were initially identified. After removal of duplicates, reviews, and conference abstracts, 83 full-text original articles were screened. Finally, 17 studies (a total of 611,169 subjects) were included for final evaluation fulfilling the inclusion criteria. The PRISMA flow chart summarizing the process of study selection is shown in Figure 1. Potential publication bias was examined by both a funnel plot and an Egger’s test and we did not find any publication bias (Figure 2). Assessment of the main studies biases are shown in the risk bias table (Figure S2).

**Effect of moderate consumption of wine on PCa risk**

Overall, 14 studies (455,413 subjects) fulfilled the inclusion criteria regarding moderate wine consumption and risk of PCa (6 cohort and 8 case–control studies). The main characteristics of the studies, as well as dose of wine consumption, are shown in Table 1. In the first meta-analysis, we included all the studies regardless of design. The pooled RR for the risk of PCa was 0.98 (95% CI 0.92–1.05, p=0.57) in the multivariable analysis (Figure 3). The Cochrane’s Q test (χ²=17.6; p=0.19) and I² test (I²=23.8%) did not show a significant heterogeneity. The funnel plots identified one study over the pseudo 95% CI (Figure 2A). Furthermore, we performed a second meta-analysis in which we included only cohort studies (438,302 subjects from which...
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Figure 1 PRISMA flow chart of the study selection process.
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

Figure 2 Funnel plots with pseudo 95% confidence limits for the association between moderate wine intake and the risk of PCa in all the included studies (A), only in cohort-studies (B), association between moderate white wine intake and the risk of PCa (C), and association between moderate red wine intake and the risk of PCa (D).
Abbreviations: PCa, prostate cancer; SE, standard error; HR, hazard ratio.
| No. | Study | Year | Country | Study type | No. of pts | Age (years) | Variables | RRswine and risk of PCa | Dose | Follow-up (years) |
|-----|-------|------|---------|------------|------------|-------------|-----------|------------------------|------|------------------|
| 1   | Jain et al | 1998 | Canada  | Case–control | 637/617 PCa | 69.8 | Age, smoking status, total energy intakes, and consumption of other types of alcohol | 0.77 (0.60–0.99) | 0–9 g/day | – |
| 2   | Schuurman et al | 1999 | the Netherlands | Case–cohort | 58.279/680 | 55–69 | Age, socioeconomic status and family history of PCa | 1.1 (0.8–1.4) | 0.1–4 g/day | 6.3 |
| 3   | Sesso et al | 2001 | USA | Case–cohort | 7,612/366 PCa | 66.6 | Age, BMI, physical activity, smoking status, and family history of PCa | 1.05 (0.49–2.27) | 0.1–4 drinks/day | 6 |
| 4   | Albertsen and Grønbaek | 2002 | Denmark | Case–cohort | 12,989/233 | NA | Age, education, physical activity, BMI, smoking status, and study of origin | 1.15 (0.85–1.56) | 1–13 drinks/week | 12.3 |
| 5   | Crispo et al | 2004 | Italy | Case–control | 1,451/1,294 PCa | 45–75 | Age, center, education, BMI, physical activity, and family history of PCa | 0.95 (0.64–1.39) | 3–4 drinks/day | – |
| 6   | Platz et al | 2004 | USA | Case–cohort | 47,843/2,479 PCa | 40–75 | Age, BMI at age 21 years, height, pack-years of smoking in the previous decade, family history of PCa, major ancestry, diabetes, vasectomy, vigorous physical activity, and intakes of total energy, calcium, fructose, tomato sauce, red meat, fish, vitamin E (>15 mg/day), and α-linolenic acid | 1.10 (0.96–1.25) | 2–5.9 g/day | 12 |
| 7   | Chang et al | 2005 | Sweden | Case–control | 1,130/1,499 PCa | 45–79 | Age, smoking history, BMI, family history of PCa, intake of other alcohol types, dairy products, red meat, and fruits and vegetables | 1.0 (0.8–1.3) | 0–15 g/day | – |
| 8   | Schoonen et al | 2005 | King County, WA, USA | Case–control | 703/753 PCa | 40–64 | Age, PSA screening, total lifetime number of female sexual partners, smoking status, and consumption of other types of alcohol | 1.22 (0.71–2.11) | ≥8 drinks/week | – |
| 9   | Baggetto et al | 2006 | Melbourne, Australia | Case–cohort | 16,872/732 PCa | 27–75 | Age, education, BMI, smoking, total energy intake, and previous medical conditions | 0.97 (0.81–1.17) | 1–19 g/day | >10 |
| 10  | Benedetti et al | 2009 | Canada | Case–control | 507/374 PCa | Mean 59.7/62.9 | Age, smoking status, cigarette-year, respondent status, ethnicity, census tract income, years of schooling, and time since quitting | 0.93 (0.59, 1.45) | >7 drinks/week | – |
| Study    | Year | Location       | Study Design  | N/Number | Age Range | Follow-up | Risk Estimates | Description |
|----------|------|----------------|---------------|----------|-----------|------------|----------------|-------------|
| 11 Watters et al | 2010 | 11 States from USA | Case-cohort | 294,707/17,227 PCa | 50–71 | 1.05 (1–1.09) Low-grade PCa 0.99 (0.79–1.33) High-grade PCa | Age, race, education, marital status, height, BMI, physical activity, family history of PCa, diabetes, self-reported health status, cigarette smoking, prostate-specific antigen screening and digital rectal examination, total energy excluding alcohol, a-tocopherol, calcium, red meat, fish, tomato, a-linolenic acid, and selenium |
| 12 McGregor et al | 2013 | Alberta, Canada | Case-control | 1,039/947 PCa ≥Stage II | Mean 68.5/69.8 | 0.8 (0.6–1) | Age, residence region, education, family history of PCa, BPH, number of DRE tests, number of PSA tests |
| 13 Demoury et al | 2016 | Montreal, Canada | Case-control | 1,994/1,933 PCa | Mean 65/64 | 1.12 (0.88–1.43) Low-grade PCa 0.99 (0.72–1.37) High-grade PCa | Age, ancestry, family history of PCa, education, smoking, physical activity, BMI, fruit and vegetables consumption, history of diabetes, and other types of beverages |
| 14 Papa et al | 2017 | Victoria, Australia | Case-control | 951/1,282 agg. PCa | Median 62.9/66.8 | 0.64 (0.45–0.91) | Age, family history of PCa, smoking status, BMI, socioeconomic status, ethnicity and country of birth, and intakes of the other beverage types |

**Abbreviations:** PCa, prostate cancer; BMI, body mass index; PSA, prostate-specific antigen; BPH, benign prostatic hyperplasia; DRE, digital rectal examination; agg, aggressive (high-grade or advanced disease); pts, patients; RRs, risk ratios.
19,238 developed PCa during observation/follow-up. The results were confirmed with a pooled RR of 1.06 (95% CI 0.96–1.15, \(p=0.22\)) in the multivariable analysis (Figure 4). The Cochrane’s Q test (\(\chi^2=1.9; p=0.86\)) and \(I^2\) test (\(I^2=0\%\)) did not show a significant heterogeneity. The funnel plots identified all studies in the pseudo 95% CI (Figure 2B). The results did not differ when we performed a sensitivity analysis “leave-one-out.”

**Effect of the type of wine consumed on PCa risk**

Five studies investigated the risk of PCa according to consumption of white or red wine. We used RRs reported for moderate consumption (the same dose for white and red wine was considered). Four were cohort studies (222,447 subjects, from which 6,184 developed PCa during observation/follow-up)\(^{16,23,25,28}\) and one was a case–control study.\(^{22}\)

![Figure 3](https://example.com/figure3.png)

**Figure 3** Forest plot for risk of PCa in the case of moderate consumption of wine (all studies).

**Abbreviations:** PCa, prostate cancer; pts, patients.

| Study                  | Year | No. pts | HR (95% CI)          | % Weight |
|------------------------|------|---------|----------------------|---------|
| Jain et al\(^{15}\)   | 1998 | 617     | 0.77 (0.60–0.99)     | 7.47    |
| Schuurman et al\(^{16}\) | 1999 | 58,279  | 1.10 (0.80–1.40)     | 5.98    |
| Sesso et al\(^{17}\)  | 2001 | 7,612   | 1.05 (0.49–2.27)     | 3.80    |
| Albertsen and Grønbaek\(^{18}\) | 2002 | 12,989  | 1.15 (0.85–1.56)     | 5.08    |
| Crispo et al\(^{19}\) | 2004 | 1,294   | 0.95 (0.64–1.39)     | 3.11    |
| Platz et al\(^{20}\)  | 2004 | 47,843  | 1.10 (0.96–1.25)     | 26.87   |
| Chang et al\(^{21}\)  | 2005 | 1,499   | 1.00 (0.80–1.30)     | 7.94    |
| Schoonen et al\(^{12}\) | 2005 | 753     | 1.22 (0.71–2.11)     | 1.58    |
| Baglietto et al\(^{24}\) | 2006 | 16,872  | 0.97 (0.81–1.17)     | 13.84   |
| Benedetti et al\(^{26}\) | 2009 | 374     | 0.93 (0.59–1.45)     | 2.32    |
| Watters et al\(^{27}\) | 2010 | 294,707 | 0.99 (0.79–1.23)     | 9.55    |
| McGregor et al\(^{29}\) | 2013 | 947     | 0.80 (0.60–1.00)     | 7.17    |
| Demouy et al\(^{30}\) | 2016 | 1,933   | 0.99 (0.72–1.37)     | 4.52    |
| Papa et al\(^{21}\)   | 2017 | 1,282   | 0.64 (0.45–0.91)     | 3.78    |
| Overall (\(I^2=23.8\%, p=0.197\)) |  |         | 0.98 (0.92–1.05)     | 100.00  |

![Figure 4](https://example.com/figure4.png)

**Figure 4** Forest plot for risk of PCa in the case of moderate consumption of wine (cohort studies).

**Abbreviations:** PCa, prostate cancer; pts, patients.
The main characteristics of the included studies, as well as dose of wine consumption, are shown in Table 2 for white wine and in Table 3 for red wine. Moderate white wine consumption increased significantly the risk of PCa with a pooled RR of 1.26 (95% CI 1.10–1.43, \(p=0.001\)) in the multivariable analysis (Figure 5). The Cochrane’s Q test (\(\chi^2=4.6; p=0.2\)) and \(I^2\) test (\(I^2=34.4\%\)) did not show a significant heterogeneity. The funnel plots identified all studies in the pseudo 95% CI (Figure 2C). When we excluded from the analysis the results reported by Sutcliffe et al,25 moderate white wine consumption was not associated with an increased risk of PCa: pooled RR 1.05 (95% CI 0.87–1.28, \(p=0.56\)). In all the other cases of exclusion, one study from the analysis showed that white wine was associated with an increased risk of PCa.

Moderate red wine consumption was associated with a decreased risk of PCa with a pooled RR of 0.88 (95% CI 0.78–0.999, \(p=0.047\)) in the multivariable analysis (Figure 6). The Cochrane’s Q test (\(\chi^2=2.16; p=0.53\)) and \(I^2\) test (\(I^2=0\%\)) did not show a significant heterogeneity. The funnel plots identified all studies in the pseudo 95% CI (Figure 2D). The results remain significant also after the addition of the RRs from the case–control study of Schoonen et al22 with a pooled RR of 0.86 (95% CI 0.76–0.97, \(p=0.01\)). However, in this case the heterogeneity increased, but not to a significant level, Cochrane’s Q test (\(\chi^2=6.06; p=0.19\)) and \(I^2\) test (\(I^2=34\%\)). When we excluded from the analysis the results reported by Sutcliffe et al,25 moderate red wine consumption was not associated with a decreased risk of PCa: pooled RR

### Table 2: Studies investigating the impact of white wine consumption on the risk of PCa

| No. | Study          | Year | Country           | Study type     | No. of pts | Age (years) | Variables                                                                 | RRs white wine and risk of PCa | Dose Follow-up (years) |
|-----|----------------|------|-------------------|----------------|------------|-------------|---------------------------------------------------------------------------|-------------------------------|------------------------|
| 1   | Schuurman et al16 | 1999 | the Netherlands   | Case–cohort    | 58,279/680 | 55–69       | Age, socioeconomic status, family history of PCa                          | 1.0 (0.7–1.4)                 | 0.1–4 g/day            | 6.3                  |
| 2   | Schoonen et al22 | 2005 | King County, WA, USA | Case–control   | 703/753   | 40–64       | Age, PSA screening, total lifetime number of female sexual partners, smoking status, and consumption of other types of alcohol | 0.91 (0.44–1.86)              | ≥8 drinks/week         | –                    |
| 3   | Velicer et al23  | 2006 | Washington, USA   | Case–cohort    | 34,565/816 | 50–76       | Age, PSA, other types of alcohol consumed                                 | 1.12 (0.74–1.68)              | 5 drinks/week          | 4                    |
| 4   | Sutcliffe et al25 | 2007 | USA               | Case–cohort    | 45,433/3,348 | 40–75     | Age, race/ethnicity, BMI, cumulative family history of PCa, height, cigarette smoking in the past 10 years, baseline intakes of total energy, tomato sauce, red meat, fish, calcium and vitamin E, baseline energy-adjusted intake of fructose and a-linolenic acid, physical activity and updated diabetes mellitus type 2 and vasectomy status, and all other specific alcoholic beverage types | 1.42 (1.19–1.69)              | 2–4 drinks/week        | 16                   |
| 5   | Chao et al28     | 2010 | California, USA   | Case–cohort    | 84,170/1,340 | 45–69     | Age, race/ethnicity, income, BMI, intake of other alcoholic beverage, meat consumption, family history of PCa, person history of PSA testing, STI, BPH, BPH surgery, prostatitis, and diabetes mellitus | 1.10 (0.81–1.49)              | >1 drink/day           | 5                    |

**Abbreviations:** PCa, prostate cancer; pts, patients; RRs, risk ratios; BMI, body mass index; PSA, prostate-specific antigen; STIs, sexually transmitted infections; BPH, benign prostatic hyperplasia.
Table 3  Studies investigating the impact of red wine consumption on the risk of PCa

| No. | Study                | Year | Country               | Study type      | No. of pts | Age (years) | Variables                                                                 | RR (95% CI)                      | Dose          | Follow-up (years) |
|-----|----------------------|------|-----------------------|-----------------|------------|-------------|---------------------------------------------------------------------------|----------------------------------|---------------|------------------|
| 1   | Schuurman et al16     | 1999 | the Netherlands        | Case–cohort     | 58,279/ 680 PCa | 55–69       | Age, socioeconomic status, family history of PCa                          | 1.0 (0.7–1.3)                    | 0.1–4 g/day   | 6.3              |
| 2   | Schoonen et al22      | 2005 | King County, WA, USA  | Case–control    | 703/ 753 PCa  | 40–64       | Age, PSA screening, total lifetime number of female sexual partners, smoking status, and consumption of other types of alcohol | 0.45 (0.23–0.85)                  | ≥8 drinks/ week | –                |
| 3   | Velicer et al23       | 2006 | Washington, USA        | Case–cohort     | 34,565/ 816 PCa | 50–76       | Age, PSA, other types of alcohol consumed                                 | 0.98 (0.72–1.33)                 | 5 drinks/ week | 4                |
| 4   | Sutcliffe et al25     | 2007 | USA                   | Case–cohort     | 45,433/ 3,348 PCa | 40–75      | Age, race/ethnicity, BMI, cumulative family history of PCa, height, cigarette smoking in the past 10 years, baseline intakes of total energy, tomato sauce, red meat, fish, calcium and vitamin E, baseline energy-adjusted intakes of fructose and α-linolenic acid, physical activity and updated diabetes mellitus type 2 and vasectomy status, and all other specific alcoholic beverage types | 0.79 (0.64–0.97)                 | 2–4 drinks/ week | 16               |
| 5   | Chao et al28          | 2010 | California, USA        | Case–cohort     | 84,170/ 1,340 PCa | 45–69      | Age, race/ethnicity, income, BMI, intake of other alcoholic beverage, meat consumption, family history of PCa, person history of PSA testing, STI, BPH, BPH surgery, prostatitis, and diabetes mellitus | 0.88 (0.70–1.12)                 | >1 drink/day  | 5                |

Abbreviations: PCa, prostate cancer; pts, patients; RRs, risk ratios; BMI, body mass index; PSA, prostate specific antigen; BPH, benign prostatic hyperplasia; STIs, sexually transmitted infections.

Figure 5  Forest plot for the risk of PCa in the case of moderate consumption of white wine (cohort studies).

Abbreviations: PCa, prostate cancer; pts, patients.
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Table 1

| Study             | Year | No. of pts | HR (95% CI) | Weight |
|-------------------|------|------------|-------------|--------|
| Schuurman et al16 | 1999 | 58,279     | 1.00 (0.70–1.30) | 16.75  |
| Velicer et al23   | 2006 | 34,565     | 0.98 (0.72–1.33) | 17.05  |
| Sutcliffe et al25  | 2007 | 45,433     | 0.79 (0.64–0.97) | 37.13  |
| Chao et al28      | 2010 | 84,170     | 0.88 (0.70–1.12) | 29.07  |
| Overall (F²=0.0%, p=0.539) |      |            | 0.88 (0.78–1.00) | 100.00 |

Test for overall effect: Z=1.98, p=0.047

Figure 6 Forest plot for risk of PCa in the case of moderate consumption of red wine (cohort studies).

Abbreviations: PCa, prostate cancer; pts, patients.

Discussion

This study is to our knowledge the first meta-analysis to investigate the impact of moderate wine consumption and the risk of developing PCa, including 611,169 subjects from 17 studies. According to this meta-analysis moderate wine consumption is not a risk factor for PCa development. Interestingly, the analysis regarding type of wine consumed sustains the fact that moderate wine consumption does not impact PCa risk. We found an antagonist effect as moderate white wine consumption increases the risk of PCa, whereas moderate red wine consumption had a protective role against PCa. However, when we excluded the results reported by Sutcliffe et al25 (45,433 subjects with 16 years follow-up), there was not a significant association between type of wine consumed and risk of PCa.

Nevertheless, our meta-analysis has several limitations. First, there is a selection bias in the studies as all were nonrandomized observational or case–control studies. Second, the definition of moderate consumption is imprecise with differences between studies introducing heterogeneous results. Still, all studies had a maximum of one glass of wine per day as moderate consumption. Third, despite a large number of patients in our analyses, the number of studies in our meta-analysis was limited to 17. Fourth, most studies were done in western countries with a likely preponderance of Caucasians. Metabolization and polymorphisms are highly variable between races and habits. Fifth, we decided to restrict the present meta-analysis to “moderate consumption” of wine alone, thus precluding analyses of dose–response relationship. We analyzed only the effect of moderate consumption; as in many countries, there are dietary habits that include one glass of wine per day during meals and the scope of the meta-analysis was not to encourage alcohol/wine consumption, but instead to point out the effects of responsible wine drinking on the risk of PCa.

The relationship between alcohol consumption and the risk of PCa remains a controversial issue.32 Middleton Fillmore et al demonstrated in a meta-analysis that heavy alcohol consumption is associated with a higher risk of developing PCa.33 Similarly, Zhao et al’s meta-analysis showed a significant dose–response relationship between level of alcohol intake and risk of PCa.9 On the contrary, a large prospective European study that included 142,607 male participants found no association between alcohol consumption and PCa risk.10 Regarding types of alcohol consumption, in a large cohort of 3,927 subjects, Demoury et al showed that beer was associated with a 37% increase risk of high-grade PCa.30 In the present study, we found that wine is not associated with an increased risk of PCa as other alcohol or beer consumption is. This could be based on several factors that make wine less harmful than other types of alcohols. One of the factors might be the chemical composition of wine, which is a hydroalcoholic solution (~78% water) with a wide range of bioactive chemical components, including

0.88 (95% CI 0.71–1.09, p=0.24). In all the other cases of exclusion, only one study from the analysis showed that red wine was associated with a decreased risk of PCa.

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aldehydes, esters, ketones, lipids, minerals, organic acids, phenolics, soluble proteins, sugars, and vitamins. Second, the anticarcinogenic effect of polyphenols mainly contained by red wine may balance any other harmful effects of wine consumption. Third, in the case of beer, the bioavailability of the phenolic compounds is very low, thus decreasing their potential anticarcinogenic effects.

Furthermore, the mechanism between alcohol consumption and carcinogenesis is not fully understood. It seems to be based on acetaldehyde, the first metabolite of ethanol that has been suggested to be carcinogenic by promoting cancer development though various mechanisms, such as interference with DNA replication, induction of DNA damage, and formation of DNA adducts. However, wine consumption, especially red wine, has been associated with decreased inflammation and overall mortality as well as moderate alcohol consumption. Schoonen et al. found, in large cohort studies, that red wine consumption decreases the risk of PCa, whereas white wine does not. Red wine’s protective role against PCa development could be due to the bioactivity of polyphenols that are a complex mixture of flavonoids (such as anthocyanins and flavan-3-ols) and nonflavonoids (such as resveratrol, cinnamates, and gallic acid). Resveratrol is the most studied compound and its concentration is 10-fold higher than in white wine. Resveratrol is added from the skin of red grapes during the creation process. Its concentration in red wine ranges from 1.2 to 2.0 g/L. It has been studied regarding its anticarcinogenesis including PCa, and many studies showed that resveratrol causes cell growth, proliferation inhibition, and activation of apoptosis in human PCa cell lines including PC3, DU145, and LNCaP. Sgambato et al. found that resveratrol not only inhibits cell proliferation but also prevents the accumulation of reactive oxygen species production and oxidative DNA damage in cells exposed to oxidative agents. On the other hand, white wine contains also a small amount of resveratrol, but despite an experimental study that showed an association between white wine and antiproliferative effect, clinical studies do not support this finding. Nevertheless, the beneficial effects of moderate red wine consumption might be due to all its compounds and not only due to resveratrol.

Although we focused only on “moderate” consumption of red wine in this study, it is unclear whether effectiveness of red wine polyphenols depends on the amount of consumption or not. To better assess the relationship between wine consumption, especially the appropriate amount of red wine and PCa risk in the general population, further studies are needed.

**Conclusion**

In this meta-analysis, moderate wine consumption did not influence the risk of PCa. However, moderate consumption of white wine increased the risk of PCa, whereas moderate consumption of red wine had a protective role. This hypothesis-generating data should serve as a rationale for uncovering the molecular underpinnings of this differential effect in order to potentially devise prevention strategies in the at-risk population.

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**Author Contributions**

All authors contributed towards data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

**Disclosure**

The authors report no conflicts of interest in this work.

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**Supplementary materials**

| Study and year                  | Selection | Comparability | Exposure |
|--------------------------------|-----------|---------------|----------|
| Jain et al, 1998               | ★ ★ ★     | ★ ★           | ★ ★ ★    |
| Schuurman et al, 1999          | ★         | ★ ★           | ★ ★ ★    |
| Sesso et al, 2001              | ★ ★ ★     | ★ ★           | ★ ★ ★    |
| Albertsen and Grønbaek, 2002   | ★ ★       | ★ ★           | ★ ★ ★    |
| Crispo et al, 2004             | ★ ★       | ★ ★           | ★ ★ ★    |
| Platz et al, 2004              | ★ ★       | ★ ★           | ★ ★ ★    |
| Chang et al, 2005              | ★ ★ ★     | ★ ★           | ★ ★ ★    |
| Schoonen et al, 2005           | ★ ★ ★     | ★ ★           | ★ ★ ★    |
| Baglietto et al, 2006          | ★ ★       | ★             | ★ ★ ★    |
| Benedetti et al, 2009          | ★ ★ ★     | ★ ★           | ★ ★ ★    |
| Watters et al, 2010            | ★ ★ ★     | ★ ★           | ★ ★ ★    |
| McGregor et al, 2013           | ★ ★ ★     | ★ ★           | ★ ★ ★    |
| Demoury et al, 2016            | ★ ★       | ★ ★           | ★ ★ ★    |
| Papa et al, 2017               | ★ ★       | ★ ★           | ★ ★ ★    |
| Velicer et al, 2006            | ★ ★ ★     | ★ ★           | ★ ★ ★    |
| Sutcliffe et al, 2007          | ★ ★ ★     | ★ ★           | ★ ★ ★    |
| Chao et al, 2010               | ★ ★ ★     | ★             | ★ ★ ★    |

**Figure S1** Newcastle-Ottawa Scale.

**Notes:** Each study was judged on eight items, categorized into three groups: the selection of the study groups; the comparability of the groups; and the ascertainment of the exposure of interest for cohort studies. There was a maximum of 4 stars for the selection, 2 stars for the comparability, and 3 stars for exposure components. The highest quality studies are awarded up to 9 stars.
Table A: Risk of bias summary of the studies that analyses the association between moderate wine consumption and PCa risk (red: high risk; green: low risk). (B) Risk of bias summary of the studies that analyses the association between moderate white and red wine consumption and PCa risk (red: high risk; green: low risk).

| Study and year | Assessment of the main biases | Analysis of PCa risk |
|---------------|-------------------------------|----------------------|
| Jain et al, 1998 | 7 | | | |
| Schuurman et al, 1999 | 6 | | | |
| Sesso et al, 2001 | 7 | | | |
| Albertsen and Gronbaek, 2002 | 6 | | | |
| Crispo et al, 2004 | 7 | | | |
| Platz et al, 2004 | 6 | | | |
| Chang et al, 2005 | 7 | | | |
| Schoonen et al, 2005 | 8 | | | |
| Baglietto et al, 2006 | 6 | | | |
| Benedetti et al, 2009 | 7 | | | |
| Watters et al, 2010 | 8 | | | |
| McGregor et al, 2013 | 7 | | | |
| Demoury et al, 2016 | 6 | | | |
| Papa et al, 2017 | 6 | | | |

Table B: Risk of bias summary of the studies that analyses the association between moderate wine consumption and PCa risk (red: high risk; green: low risk). (B) Risk of bias summary of the studies that analyses the association between moderate white and red wine consumption and PCa risk (red: high risk; green: low risk).

| Study and year | Assessment of the main biases | Analysis of PCa risk |
|---------------|-------------------------------|----------------------|
| Schuurman et al, 1999 | 6 | | | |
| Schoonen et al, 2005 | 8 | | | |
| Velicer et al, 2006 | 7 | | | |
| Sutcliffe et al, 2007 | 6 | | | |
| Chao et al, 2010 | 7 | | | |

Figure S2 (A) Risk of bias summary of the studies that analyses the association between moderate wine consumption and PCa risk (red: high risk; green: low risk). (B) Risk of bias summary of the studies that analyses the association between moderate white and red wine consumption and PCa risk (red: high risk; green: low risk). 

Abbreviation: NOS, Newcastle-Ottawa Scale.
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