Introduction

Prostate cancer ranks as the second most common cancer and the sixth major cause of cancer death among men in the world. An estimated 913,000 new cases and 261,000 deaths from prostate cancer occurred in 2008 worldwide (Ferlay et al., 2010). Although the etiology of this disease remains largely elusive, age, race/ethnicity, and family history of prostate cancer are generally considered possible risk factors for this cancer (Jemal et al., 2009). In addition, increasing evidence suggests a significant influence of environment factors, especially dietary factors, on prostate cancer incidence.

Allium vegetables, such as garlic and onions, are a group of vegetables commonly consumed across the world and are good sources of a variety of nutrients and phytochemicals, including organosulfur and flavonols that might have excellent cancer-fighting properties. In epidemiological studies, such as case-control and cohort studies, the possible relationship between allium vegetables intake and prostate cancer risk has been investigated (Key et al., 1997; Schuurman et al., 1998; Hsing et al., 2002; Hodge et al., 2004; Galeone et al., 2006; Kirsh et al., 2007; Brasky et al., 2011; Hardin et al., 2011; Salem et al., 2011), but the findings are not all clearly consistent, possibly as a result of a lack of statistical power in the individual studies. In addition, to our knowledge, up to now no meta-analysis regarding the relationship between them has been published.

The purpose of the present study was to estimate the quantitative association between allium vegetables intake and prostate cancer risk by using a meta-analysis of case-control and cohort studies. We also performed subgroup meta-analysis based on the type of Allium vegetables (garlic or onions), type of study design (case-control or cohort study), method of exposure assessment (questionnaire or interview), and geographical region of the study (USA, Europe or Asia).

Materials and Methods

Publication search

We carried out a search in PubMed, EMBASE, Scopus, Web of Science, Cochrane register, and Chinese National Knowledge Infrastructure (CNKI) databases, covering all the papers published from their inception to May 2013, using the following search algorithm: (prostatic neoplasms or prostatic cancer or prostate neoplasms or prostate cancer) and (Allium or onion or garlic or leek or Chinese chive or scallion or garlic stalk or Welsh onion or vegetable). We evaluated potentially relevant publications by examining their titles and abstracts and all the studies matching the eligible criteria were retrieved. We also checked the references from retrieved articles and
Table 1. Study Characteristics of Published Cohort and Case–control Studies on Allium Vegetables Intake and Prostate Cancer

<table>
<thead>
<tr>
<th>First author, year of publication</th>
<th>Region and design</th>
<th>Cases/controls or cohort</th>
<th>Follow-up assessment</th>
<th>Allium vegetables assessment</th>
<th>Specific Allium vegetables</th>
<th>Total OR (95% CI)</th>
<th>Matched or adjusted variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salem et al, 2011</td>
<td>Iran</td>
<td>194/317</td>
<td>Interview</td>
<td>Garlic</td>
<td></td>
<td>0.58 (0.32-1.01)</td>
<td>Age, BMI, occupation, smoking, alcohol, family history of prostate cancer, education level, total dietary calories</td>
</tr>
<tr>
<td>Hardin et al, 2011</td>
<td>USA</td>
<td>470/512</td>
<td>Questionnaire</td>
<td>Garlic</td>
<td></td>
<td>0.66 (0.46-0.96)</td>
<td>Age, race, institution, history of first-degree relative with prostate cancer, energy intake</td>
</tr>
<tr>
<td>Bresky et al, 2011</td>
<td>USA</td>
<td>1,602/33,637</td>
<td>Median: 6.3 y</td>
<td>Questionnaire</td>
<td>Garlic</td>
<td>1 (0.85-1.17)</td>
<td>Age, race, education, BMI, PSA, test, diabetes, vitamin use, benign prostate biopsy, enlarged prostate, family history of prostate cancer</td>
</tr>
<tr>
<td>Kirsh et al, 2007</td>
<td>USA</td>
<td>1,338/29,361</td>
<td>Average: 4.2 y</td>
<td>Questionnaire</td>
<td>Garlic and Onions</td>
<td>0.95 (0.85-1.05)</td>
<td>Age, total energy, race, study center, BMI, family history of prostate cancer, energy intake, physical activity, intake, diabalsupplemental vitamin E intake, total fat intake, red meat intake, aspirin use, previous number of prostate cancer screening examinations during the follow-up period</td>
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<td>Gallo et al, 2006</td>
<td>Italy and Switzerland, HCC</td>
<td>1,294/1,450</td>
<td>Questionnaire</td>
<td>Garlic and Onions</td>
<td></td>
<td>1.04 (0.63-1.69)</td>
<td>Age, BMI, education, BMI, energy intake, lifestyle factors, family history of prostate cancer</td>
</tr>
<tr>
<td>Hodge et al, 2004</td>
<td>Australia, PCC</td>
<td>858/905</td>
<td>Interview</td>
<td>Onions</td>
<td></td>
<td>0.7 (0.5-0.9)</td>
<td>State, age, group, country of birth, socioeconomic group, energy intake, and family history of prostate cancer</td>
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<td>Hoing et al, 2002</td>
<td>China, PCC</td>
<td>238/471</td>
<td>Interview</td>
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<td></td>
<td>0.51 (0.34-0.76)</td>
<td>Age and total calories</td>
</tr>
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<td>Schaumman et al, 1998</td>
<td>Netherlands, HCC, Cohort</td>
<td>610/58,279</td>
<td>Questionnaire</td>
<td>NA</td>
<td></td>
<td>0.95 (0.69-1.33)</td>
<td>Age, family history of prostate cancer, income, education level, total dietary calories, BMI, total fruit consumption, socioeconomic status, and total fruit consumption</td>
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<td>Key et al, 1997</td>
<td>UK</td>
<td>328/328</td>
<td>Interview</td>
<td>Garlic and Onions</td>
<td></td>
<td>0.75 (0.39-1.44)</td>
<td>Social class</td>
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**Statistical methods**

To compute a summary OR with its 95% CI, we used the study-specific most-adjusted OR or RR (highest compared with lowest amounts of Allium vegetables intake) and its 95% CI in all analyses. Some studies reported risk estimates according to the different types of Allium vegetables and did not report the effect of total Allium vegetables intake. In this situation, the study-specific effect size in overall analysis was recalculated by pooling the risk estimates of such various Allium vegetables types by using the inverse-variance method (Woof, 1955). Homogeneity of ORs across studies was tested by Q statistic and the I² score. The null hypothesis that the studies are homogeneous was rejected if the P value for heterogeneity was < 0.10 or I² was > 50%. When substantial heterogeneity was detected, the combined ORs and 95% CI were estimated by the DerSimonian and Laird random effects models (DerSimonian et al., 1986). Otherwise, the ORs were obtained by Mantel–Haenszel method in a fixed effect model (Mantel et al., 1959). Subgroup analyses were carried out by Allium vegetables type, study design, study region, method of exposure assessment. Sensitivity analysis was also performed, in which the meta-analysis estimates were computed after omission of every study in turn. Potential publication bias was assessed by Begg’s test (rank correlation method) (Begg et al., 1994) and Egger’s test (linear regression method) (Egger et al., 1997). All of the statistical analyses were performed with STATA 11.0 (StataCorp, College Station, TX), using two-sided P-values.

**Results**

**Study characteristics**

Nine studies were included in this meta-analysis on the association of Allium vegetables intake with prostate cancer risk. These studies were conducted in the following regions: Europe (n=3), USA (n=3), Asia (n=2), and Australia (n=1). All included studies were published between 1997 and 2011, of which three were cohort and six were case–control studies. Information on...

Allium Vegetables and Risk of Prostate Cancer: Evidence from 132,192 Subjects

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In the sensitivity analysis, the influence of each study

Sensitive analysis

on the pooled OR was examined by repeating the meta-

analysis while omitting each study, one at a time. The

9 study-specific ORs ranged from a low of 0.76 (95%

CI 0.65-0.90) to a high of 0.85 (95% CI 0.76-0.96) via

omission of the study by Brasky et al and the study by

Hsing et al, respectively.

Publication bias

Publication bias existed ($P_{\text{Begg}} = 0.175; P_{\text{Egger}} = 0.015$).

Discussion

To the best of our knowledge, this is the first meta-

analysis evaluating the relationship between Allium

vegetables and prostate cancer risk. The combined results

of present quantitative meta-analysis provided limited

evidence for a protective association of high Allium

vegetables, especially garlic intake, with prostate cancer

risk. Although the meta-analysis from the case–control

studies suggested a significant reduction in risk, the results

from the cohort studies were null. There was statistically

significant heterogeneity across all studies ($P = 0.012$).

However, no evidence of heterogeneity was noted among 3

cohort ($P = 0.868$) and 5 case–control studies ($P = 0.538$).

The biologic mechanism whereby Allium vegetables

reduce the risk of prostate cancer is likely to be

multifactorial. The protective effect of garlic at least

partly is attributed to the high content of organosulfur

and flavonoids compounds, which have anti-mutagenic

effects and tumor inhibitory properties (Hsing et al., 2006).

Flavonoids could inhibit cell cycle progression in prostate

cancer cells (Kobayashi et al., 2002). Diallyl disulfide

(DADS), an organosulfur compound of garlic has been

demonstrated to exert a potential chemopreventive activity

in rat prostate carcinogenesis (Arunkumar et al., 2006) and

induced apoptosis of prostate cancer cell line in a dose

dependent manner (Gunadharini et al., 2006; Arunkumar

et al., 2007). In addition, in vivo research has shown the

potential use of garlic constituent S-allylmercaptocysteine

as an E-cadherin up-regulating antimetastatic agent for

the treatment of androgen-independent prostate cancer

(Howard et al., 2007).

There are several important limitations to be

considered in interpreting the results of our meta-analysis.

First, Egger’s test indicated that publication bias existed.

This may be because we did not attempt to search for

unpublished observations and not include studies with

insufficient information to estimate an adjusted OR,

which could bring publication bias. Second, there are

no standardized assessments or measurements for the

amounts of the Allium vegetables, thus we failed to

evaluate a dose-response relation between the Allium

vegetables intake and prostate cancer risk. Third, the

number of selected studies was still relatively small, and

the significant between-study heterogeneity was detected

in some comparisons, which may distort the meta-analysis.

In conclusion, despite the limitations, our analysis

indicates that high consumptions of Allium vegetables,

especially garlic intake, are related with a low incidence

of prostate cancer. Because of the limited number of

studies, further well-designed cohort or intervention

Figure 2. Relative Risks for the Association Between Intake of Allium Vegetables and Risk for Prostate Cancer

Table 2. Summary of Pooled Relative Risks of Prostate Cancer in Subgroups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Study number</th>
<th>OR (95% CI)</th>
<th>Heterogeneity test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Q</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>0.80 (0.70-0.92)</td>
<td>19.59</td>
</tr>
<tr>
<td>Allium vegetables type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garlic</td>
<td>7</td>
<td>0.77 (0.64-0.91)</td>
<td>16.5</td>
</tr>
<tr>
<td>Onions</td>
<td>4</td>
<td>0.84 (0.62-1.13)</td>
<td>5.93</td>
</tr>
<tr>
<td>Study design</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort</td>
<td>3</td>
<td>0.96 (0.89-1.05)</td>
<td>0.28</td>
</tr>
<tr>
<td>Case-control</td>
<td>6</td>
<td>0.70 (0.60-0.80)</td>
<td>4.08</td>
</tr>
<tr>
<td>Geographical region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>3</td>
<td>0.95 (0.87-1.03)</td>
<td>4.15</td>
</tr>
<tr>
<td>Europe</td>
<td>3</td>
<td>0.83 (0.70-0.99)</td>
<td>0.94</td>
</tr>
<tr>
<td>Asia</td>
<td>2</td>
<td>0.53 (0.38-0.74)</td>
<td>0.13</td>
</tr>
<tr>
<td>Exposure assessment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Questionnaire</td>
<td>5</td>
<td>0.89 (0.78-1.02)</td>
<td>7.87</td>
</tr>
<tr>
<td>Interview</td>
<td>4</td>
<td>0.70 (0.59-0.84)</td>
<td>3.99</td>
</tr>
</tbody>
</table>

Allium vegetables intake was obtained by interview or self-administered questionnaire. Table 1 presents the basic characteristics of each study included in our meta-analysis.

Overall and subgroup analyses

Figure 2 plot the pooled risk estimates for Allium vegetables intake. We found a significantly decreased risk of prostate cancer for intake of Allium vegetables (OR = 0.80, 95% CI 0.70-0.92). There was statistically significant heterogeneity among studies ($p = 0.012$ for heterogeneity; $I^2 = 59.2\%$).

We also performed subgroup analysis by Allium vegetables type, study design, study region, and method of exposure assessment (Table 2). In the subgroup analysis by Allium vegetables type, we found a significantly decreased risk of prostate cancer for intake of garlic (OR = 0.77, 95% CI 0.64-0.91), but no association with onions (OR = 0.84, 95% CI 0.62-1.13). Furthermore, when separately analyzed by exposure assessment, more significant associations were observed in studies using an interview (OR = 0.70, 95% CI 0.59-0.84) than studies using a self-administered questionnaire (OR = 0.89, 95% CI 0.78-1.02). In addition, when stratifying by geographical area, a more pronounced protective effect was observed in Asia (OR = 0.53, 95% CI 0.38-0.74) than Europe (OR = 0.83, 95% CI 0.70-0.99) or USA (OR = 0.95, 95% CI 0.87-1.03).
studies are warranted to confirm the findings from our study. In addition, the underlying mechanisms and active compounds in Allium vegetables that may be responsible for the relationship remain to be further elucidated.

Acknowledgements

The author(s) declare that they have no competing interests.

References


