

## RESEARCH ARTICLE

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

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### Abstract

**Objective:** To evaluate the relationship between allium vegetable intake and risk of prostate cancer. **Methods:** A systematic literature search up to May 2013 was carried out in PubMed, EMBASE, Scopus, Web of Science, Cochrane register, and Chinese National Knowledge Infrastructure (CNKI) databases, and the references of retrieved articles were also screened. The summary relative risks with 95% confidence interval for the highest versus the lowest intake of allium vegetables were calculated. Heterogeneity and publication bias were also evaluated. **Results:** A total of nine epidemiological studies consisting of six case-control and three prospective cohort studies were included. We found a significantly decreased risk of prostate cancer for intake of allium vegetables (OR = 0.82, 95% CI 0.70, 0.97). Moreover, in the subgroup analysis stratified by allium vegetable types, significant associations were observed for garlic (OR = 0.77, 95% CI 0.64–0.91) but not onions (OR = 0.84, 95% CI 0.62–1.13). **Conclusions:** Allium vegetables, especially garlic intake, are related to decreased risk of prostate cancer. Because of the limited number of studies, further well-designed prospective studies are warranted to confirm the findings of our study.

**Keywords:** Allium vegetables - garlic - onions - meta-analysis - prostatic neoplasms

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### 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

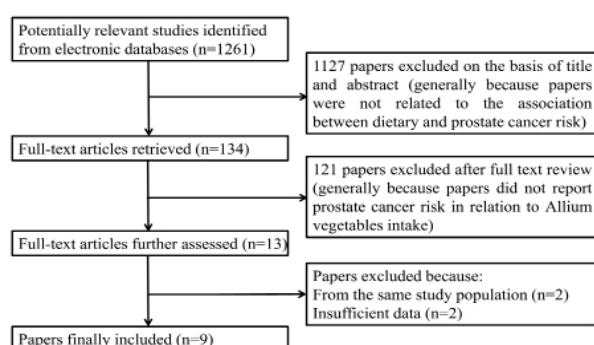
#### Publication search

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**

First author, year of publication	Region and design	Cases/controls or cohort	Follow-up	Allium vegetables assessment	Specific Allium vegetables	Total OR (95% CI)	Matched or adjusted variables
Salem et al, 2011	Iran; HCC	194/317	-	Interview	Garlic	0.58 (0.32-1.01)	Age, BMI, occupation, smoking, alcohol, family history of prostate cancer, education level, total dietary calories
Hardin et al, 2011	USA; HCC	470/512	-	Questionnaire	Garlic	0.66 (0.46-0.96)	Age, race, institution, history of first-degree relative with prostate cancer, energy intake
Brasky et al, 2011	USA; Cohort	1,602/33,637	Median: 6.1y	Questionnaire	Garlic	1 (0.85-1.17)	Age, race, education, BMI, PSA test, diabetes, multivitamin use, benign prostate biopsy, enlarged prostate, family history of prostate cancer
Kirsh et al, 2007	USA; Cohort	1,338/29,361	Average: 4.2y	Questionnaire	Garlic and Onions	0.95 (0.85-1.05)	Age, total energy, race, study center, BMI, family history of prostate cancer, smoking status, physical activity, intake, diabsupplemental vitamin E intake, total fat intake, red meat etc, aspirin use, previous number of prostate cancer screening examinations during the follow-up period
Galeone et al, 2006	Italy and Swiss; HCC	1,294/1,450	-	Interview	Garlic and Onions	0.79 (0.63-0.98)	Age, study center, education, BMI, energy intake, and family history of prostate cancer.
Hodge et al, 2004	Australia; PCC	858/905	-	Questionnaire	NA	0.7 (0.5-0.9)	State, age group, year, country of birth, socioeconomic group, total energy intake and family history of prostate cancer.
Hsing et al, 2002	China; PCC	238/471	-	Interview	Garlic, Onions, Scallions, Chinese chives, Leeks	0.51 (0.34-0.76)	Age and total calories
Schuurman et al, 1998	Netherlands; Cohort	610/58,279	6.3 y	Questionnaire	NA	0.95 (0.69-1.33)	Age, family history of prostate cancer, socioeconomic status, and total fruit consumption.
Key et al, 1997	UK; PCC	328/328	-	Interview	Garlic and Onions	0.75 (0.39-1.44)	Social class

OR, odd ratio; RR, relative risk; CI, confidence interval; PCC, population based case-control; HCC, hospital based case-control; y, year; BMI, body mass index; PSA, prostate-specific antigen

**Figure 1. Process of Study Selection**

reviews to identify any additional relevant study. Figure 1 summarizes the process of identifying and selecting studies. A total of 9 articles were finally included in this meta-analysis.

### Study Selection

Studies included in this meta-analysis had to meet all the following criteria: (a) evaluation of the Allium vegetables intake and prostate cancer risk, (b) had a case-control or cohort design, (c) reported the OR or RR and its 95% CI. If multiple publications from the same study population were available, the most recent or the largest study was eligible for inclusion in this meta-analysis.

### Data extraction

Data were extracted independently and cross-checked by two authors using a predefined data collection form. Disagreement was resolved by discussion. For each study, the following characteristics were collected: study name (together with the first author's name and year of publication), the country in which the study was carried out, study design, range for follow-up, sample size, exposure assessment, type of Allium vegetables, most-adjusted effect estimates for highest versus lowest level of consumption, and matched or adjusted variables in the design or data analysis. Considering that prostate cancer is a rare disease, the RR was assumed approximately the same as OR, and the OR was used as the study outcome. Adjusted ORs were extracted directly from the original reports.

### Statistical methods

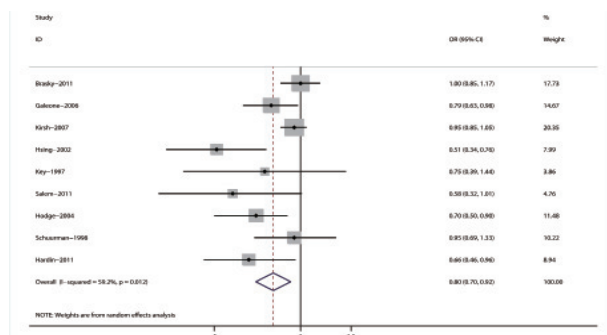
To compute a summary OR with its 95% CI, we used the study-specific most-adjusted OR or RR (highest compared with lowest amounts of Allium vegetables intake) and its 95% CI in all analyses. Some studies separated risk estimates according to the different types of Allium vegetables and did not report 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 (Woolf, 1955). Homogeneity of ORs across studies was tested by Q statistic and the  $I^2$  score. The null hypothesis that the studies are homogeneous was rejected if the P value for heterogeneity was  $<0.10$  or  $I^2$  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



**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**

Variables	Study number	OR (95% CI)	Heterogeneity test		
			Q	P	I <sup>2</sup> (%)
Total	9	0.80 (0.70-0.92)	19.59	0.012	59.2
Allium vegetables type					
Garlic	7	0.77 (0.64-0.91)	16.5	0.011	63.6
Onions	4	0.84 (0.62-1.13)	5.93	0.115	49.4
Study design					
Cohort	3	0.96 (0.89-1.05)	0.28	0.868	0
Case-control	6	0.70 (0.60-0.80)	4.08	0.538	0
Geographical region					
USA	3	0.95 (0.87-1.03)	4.15	0.126	51.8
Europe	3	0.83 (0.70-0.99)	0.94	0.719	0
Asia	2	0.53 (0.38-0.74)	0.13	0.627	0
Exposure assessment					
Questionnaire	5	0.89 (0.78-1.02)	7.87	0.096	49.2
Interview	4	0.70 (0.59-0.84)	3.99	0.263	24.7

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).

#### Sensitive analysis

In the sensitivity analysis, the influence of each study

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 flavonols 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

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.

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

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