

Review

Citrus Fruits Intake and Prostate Cancer Risk: A Quantitative Systematic Review

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Objectives : The purpose of this systematic review was to investigate the association between dietary intake of citrus fruits and prostate cancer risk.

Methods : Authors searched electronic databases and the reference lists of publications of diet and prostate cancer studies until August 2007. All of the epidemiological studies that obtained individual data on dietary intake of citrus fruits and presented risk estimates of the association between intake of citrus fruits and risk of prostate cancer were identified and included. Using general variance-based methods, study-specific odds ratios (OR)/ relative risk (RR) and associated confidence interval (CI)/ standard error (SE) for highest versus lowest intake of citrus fruits level were extracted from each paper.

Results : Eleven articles including six case-control studies, one nested case-control study and four cohort

studies, proved eligible. Overall summary OR using random effect model did not show an association in risk of prostate cancer with intake of citrus fruits (summary OR=1.03, 95% CI=0.89-1.19) with large heterogeneity across studies that we were unable to explain ($I^2=67.88\%$). The summary ORs in case-control studies and cohort studies were 1.10 (95% CI=0.97-1.22) and 1.05 (95% CI=0.96-1.14), respectively.

Conclusions : Pooled results from observational studies did not show an association between intake of citrus fruits and the risk of prostate cancer, although results vary substantially across studies.

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Key words : Citrus fruits, Prostate neoplasm, Meta-analysis, Cancer risk, Prevention

INTRODUCTION

Prostate cancer is the most frequently diagnosed malignancy among men in United States [1] and 1.33-fold increasing trend of incidence rate between 1999 and 2002 in Korean men [2]. The results of descriptive epidemiologic studies suggested an environmental etiology including diet and nutrition [3,4], but the evidence for any specific factors has generally not been consistent [5]. While overall consumption of fruits and vegetables has not shown a consistent reduction in risk of prostate cancer [6-8], some potentially modifiable factors such as lycopene from tomatoes have been identified [9]. Their etiologic relevance is still debated [10].

As lycopene is the most efficient quencher of oxygen radicals among the common carotenoids [11], investigators have undertaken

several large randomized chemoprevention trials of supplementation of β carotene [12,13], α tocopherol [14,15] and vitamin E [16,17] for prostate cancer. These studies have found no relationship between supplementation and prostate cancer among generally nonsmoking study populations [18]. In addition, the Physician's Health Study reported a 32 percent reduction in prostate cancer incidence for those men receiving β carotene supplementation who were in the lowest quartile of plasma beta-carotene when the study began [12]. This fact lends support to the hypothesis that β carotene may be protective at the doses available from dietary intake alone rather than from mega-doses in supplement form [19].

Moreover, investigators found the association between β carotene and prostate cancer in Hawaii to be entirely due to dietary intake of papaya, which is rich in β cryptoxanthin [6, 20-

22]. β -cryptoxanthin is another major carotenoid in human plasma and mainly derived from citrus fruits [23]. A pooled analysis of seven cohort studies showed a protective effect of β cryptoxanthin for lung cancer [24]. These considerations suggest a hypothesis that dietary intake of citrus fruits as dietary source of β cryptoxanthin as well as vitamin C might be associated with a reduced risk of prostate cancer. We conducted a systematic review to explore this hypothesis.

MATERIAL AND METHODS

I. Search Strategy

A computerized search of the PubMed English language literature on citrus fruit and prostate cancer yielded no relevant publication to August 2007. We therefore decided to use the key word 'fruits' as well as 'citrus'. Thus, the search terms were [prostate] AND [(neoplasm) OR (cancer)] AND [(fruit) OR

(citrus)]. We limited the search to human adults without language restrictions. We searched the 3 major electronic databases: PubMed, Ovid Medline and EMBASE. In addition, authors reviewed the references cited in the full-text articles and in the relevant review articles or meta-analyses identified in the search.

II. Study Selection

We chose the following inclusion criteria: (1) comparative epidemiological studies; (2) human adults participants; (3) addressed the association between fruits intake and prostate cancer. The full-text articles of all references selected after applying inclusion criteria were collected. To full-text articles including potential references listed by hand-search, reviewers applied the exclusion criteria: (1) no original data, i.e., reviews, meta-analysis; (2) studies of mortality instead of incidence of prostate cancer; (3) studies not measuring citrus fruit intake at the individual level. The eligibility of each abstract or full-text article was assessed independently with the same inclusion/exclusion criteria by 2 reviewers. Disagreements between reviewers were resolved by consensus.

III. Data Abstraction

The following information was extracted for all eligible studies: study design, country of origin, years of enrollment, sampling frame, number of subjects, range of age, comparison of exposure level, and potential confounding variables considered. From the eligible studies that met the inclusion criteria, estimates of odds ratio (OR)/ relative risk (RR), and their associated 95% confidence intervals (CIs), were extracted relating to intake of citrus fruits.

IV. Statistical Analyses

For using general variance-based methods [25], study-specific OR/RR and 95% CIs for highest versus lowest intake of citrus fruits level were extracted from each paper. For all

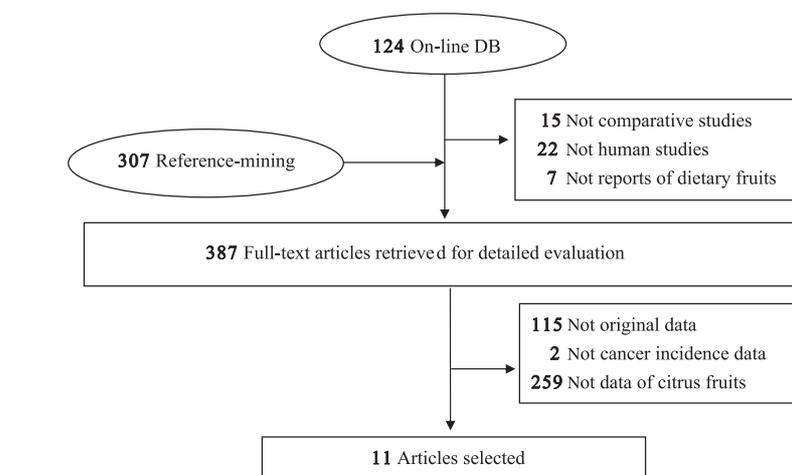


Figure 1. Flow of the searching and review of Literatures.

Table 2. Summary odds ratios (OR) and its 95% confidence interval (CI) by study design

| Study design | [Reference number] included in meta-analysis | F (%) | Summary OR (random) [95% CI] |
|-------------------------------------|--|-------|------------------------------|
| All articles in Table 1. | [18, 22, 31-39] | 67.8 | 1.03 [0.89, 1.19] |
| All articles in Table 1 except [38] | [18, 22, 31-37, 39] | 27.1 | 1.08 [0.98, 1.18] |
| Prospective cohort studies | [18, 31-33] | 0.0 | 1.05 [0.96, 1.14] |
| Case-control studies | [22, 34-39] | 79.4 | 1.10 [0.97, 1.24] |
| Case-control studies except [38] | [22, 34-37, 39] | 47.1 | 1.15 [0.96, 1.37] |

studies, the reported OR/RR estimate was adjusted for age. The standard error (SE) of the log OR/RR were calculated from the extracted OR/RR estimates and 95% CIs by using the following equation: $SE = [\ln(OR/RR_{upper}) - \ln(OR/RR_{lower})] / 3.92$.

We assessed heterogeneity with I^2 , which describes the percentage of total variation across studies because of heterogeneity rather than chance [26]. I^2 lies between 0% (no observed heterogeneity) and 100%. We used the random effect model to calculate the summary OR and its 95% CI [25,27]. In an attempt to detect publication bias, we visually explored asymmetry in funnel plot [28]. If visual inspection suggested a skewed distribution, we tested the degree of asymmetry of the funnel plot using Egger's regression asymmetry test [27]. We considered the funnel plot to be asymmetrical if the intercept of the regression line deviated from zero with a p-value of <0.10 . Sensitivity analyses were conducted by entering studies based on degree of adjustment and then evaluating the impact of the changes on the pooled odds ratios and

heterogeneity.

We used The Cochrane Collaboration software RevMan 4.2 to analyze the extracted data with random-effects model analysis [29]. STATA was used to conduct the Egger's regression asymmetry test by using the metabias command [30].

RESULTS

I. Search Results

The computerized search yielded 124 references of which, 80 were included after abstract review. Citation search identified another 307 articles. Of the 387 papers that were obtained for full-text review, we excluded 376 articles based on the exclusion criteria (Figure 1). Eleven articles were included in the meta-analysis consisting of four cohort studies [18,31-33], six case-control studies [22,34-38], and one nested case-control study [39].

II. Study Characteristics

Table 1 presents some details of the eligible studies. All articles were published in English.

Table 1. Summary of cohort (CO) and case-control (CC) studies selected in meta-analysis

| Study [Ref] Country; yr of enrollment (yr of publication) | Study design, No. of subjects (yr of FU: CO) | CO Population or Sources of controls | Age range | Exposure | Factors controlled for in analysis on citrus | Comparison of exposure level (Unit) | RR/OR (95% CI) | p-value of X ² trend |
|---|--|---|---------------------|----------------------------------|--|---|-------------------|------------------------------------|
| Mills [31], USA, 1974-6 (1989) | CO; 78,000 PY (7) | Seventh-day Adventist | 74 (mean) | Fresh citrus fruits | Age, education, meat, poultry, fish, beans, legumes or peas, dry fruit, nuts, tomatoes | <1 vs 5+ /week | 0.88 (0.52,1.47) | - |
| Giovannucci [32] USA, 1986 (1995) | CO; 47,894 (7) | Health professionals | 40-75 | Oranges | Age, energy intake | 0 vs 5+ /week | 0.94 (0.72,1.22) | 0.80 |
| Schuurman [39] Netherlands, 1986 (1998) | Nested CC; 610 & 624/1,688 (6.3) | Sub-cohort from 58,279 men | 55-69 | Citrus fruit | Age, family history, socioeconomic status, total vegetable consumption | Q1 vs Q5 (gram/day) | 1.27 (0.93,1.73) | 0.01 |
| Kolonel [22] USA/Canada/Japan/ China, 1987-91 (2000) | CC; 1,619/1,618 | Hawaii, San Francisco, Los Angeles, Vancouver, Toronto | -84 | Citrus fruits | Age, education, ethnicity, geographic area, calories | Q1 vs Q5 | 1.15 (0.91,1.45) | 0.40 |
| Jain [34] Canada, 1989-93 (1999) | CC; 617/636 | community | 69.8 (mean) | Citrus fruit | Total energy, vasectomy, age, smoking, marital status, study area, BMI, education, multivitamins, grains, fruit, vegetables, plants, carotenoids, folic acid, dietary fiber, vitamin E, vitamin C, retinol, total fat, linoleic acid | Q1 vs Q4 (gram/day) | 1.48 (1.12,1.96) | ND |
| Bosetti [35] Italy, 1991-2002 (2004) | CC; 1,294/1,451 | hospital | 46-74 | Citrus fruit | Age, study center, year of education, social class, BMI, family history, total caloric intake | Q1 vs Q5 | 0.90 (0.70,1.16) | 0.12 |
| Key [36] England, 1989-92 (1997) | CC; 328/328 | hospital | 68.1 (mean) | Citrus fruit | Age, social class | Never vs 5+/ week | 1.45 (0.93,2.52) | 0.091 |
| Cohen [37] USA, 1993-6 (2000) | CC; 628/602 | community | 40-64 | Citrus fruit | Fat, energy, race, age, cancer history, BMI, PSA test, education, total fruits or vegetables | <1 vs 3+ /week | 0.89 (0.60,1.31) | 0.70 |
| Stram [18] USA, 1993-96 (2006) | CO; 82,486 (5) | Hawaii, California | 45-75 | Citrus fruits | Age, BMI, education, family history | Q1 vs Q5 (g/1000kcal) | 1.08 (0.97,1.19) | 0.225 |
| Kirsh [33], USA, 1993-2001 (2007) | CO; 29,361 (8) | 10 cities of USA | 63.3 (mean) | Citrus, melon, berry fruit | Age, total energy, race, study center, family history, BMI, smoking, physical activity, supplemental vitamin E, total fat intake, red meat intake, diabetes, aspirin, number of prostate screening examination during follow-up | Q1 vs Q5 (average daily intake) | 1.01 (0.83,1.22) | 0.81 |
| Jian [38] China, 2001-2 (2005) | CC; 130/274 | hospital | 72.7 (case mean) | Citrus | Age, locality, education, family income, marital status, number of children, family history, BMI, tea drinking, caloric intake, fat intake | <4.10 vs 44.52< gram/day | 0.17 (0.07,0.37) | <0.001 |

FU: follow-up; PY: person-year; RR/OR: relative risk or odds ratio; BMI: body mass index; PSA: prostate specific antigen; yr:year

Seven studies were conducted among residents of North America [18,22,31-34,37], 3 in Europe [35,36,39], and the remaining study in Asia [38]. Three studies [18,22,33] conducted in North America involved multi-ethnic subjects such as White, African American, Hawaiian, Japanese, American natives, and Hispanics.

All of the studies matched or adjusted for age, 9 adjusted for education or socioeconomic status [18,22,31,34-39], 6 adjusted for total energy intake [22,32-35,38], and 5 adjusted for intakes of meat or total fat [31,33,34,37,38]. Other adjustment factors included race, area of residence, body mass index (BMI), prostate specific antigen (PSA) test, family history of prostate cancer, multi-vitamin supply, and total

vegetable consumption.

In all of the studies, intake of citrus fruits was part of a broader dietary assessment, and the relation between citrus fruits intake and prostate cancer had not been a primary hypothesis. The adjusted OR/RR for the highest category for citrus fruits intake varied enormously, with the ORs/RRs ranging from 0.17 to 1.48. Two studies reached the usual threshold p-value of 0.05 [34,38].

III. Heterogeneity and Pooled Results

There was a significant heterogeneity among the study results ($I^2=67.8%$; $p<0.001$). Overall summary OR using random effect model showed no association in risk of prostate

cancer with high intake of citrus fruits (summary OR=1.03, 95% CI=0.89-1.19). The forest plot (Figure 2) demonstrates that in only one study, Jian et al. [38], showed a confidence interval with no overlap with the CIs of summary OR. Another meta-analysis of new model excluding Jian et al. [38] from all 11 selected articles in Table 1 was conducted. The level of heterogeneity was changed from high ($I^2=67.8%$) into low ($I^2=27.1%$, $p=0.12$)[40], but the significance of summary OR did not change (summary OR=1.08, 95% CI=0.98-1.18)(Table 2).

In addition, we also calculated a pooled estimate of risk separately for cohort and case-control studies. An association between citrus fruits intake and prostate cancer risk was not

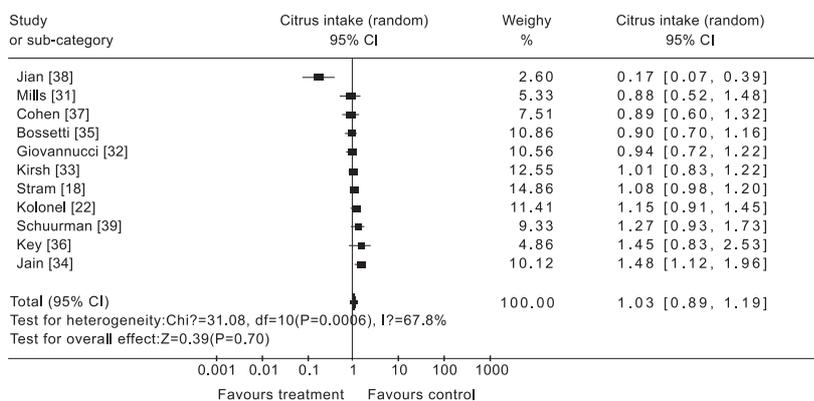


Figure 2. Summary estimates of the association between citrus fruits intake and prostate cancer risk sorted by effect estimate. (CI, confidence interval; d.f., degrees of freedom; Chi², chi-squared statistic; I², the percentage of total variation across studies that is due to heterogeneity rather than chance; OR, Odds ratios; random, using random-effect model.)

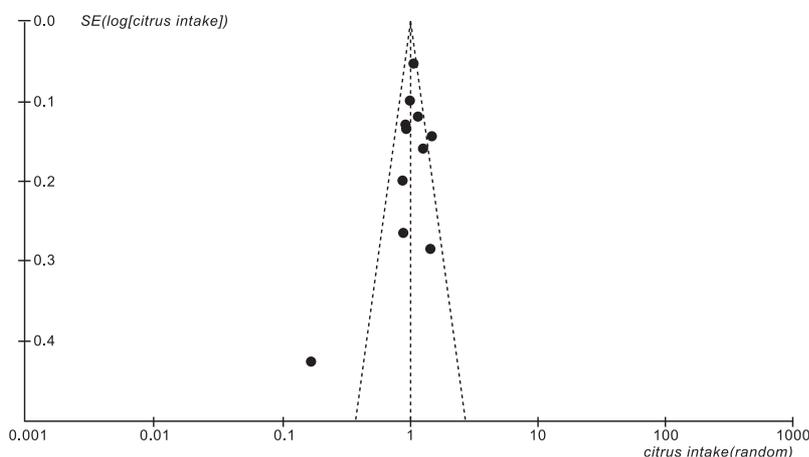


Figure 3. Funnel plot of all 11 studies evaluating the association between citrus fruits intake and prostate cancer risk (dot line: 95% pseudo-confidence interval)

observed both in 4 cohort studies (summary OR=1.05, 95% CI=0.96-1.14, I²=0.0%) and in 6 case-control studies (summary OR=1.15, 95% CI=0.96-1.37, I²=47.1%, p=0.12)(Table 2).

IV. Publication Bias

The visualization of the Begg's funnel plot excluding Jian et al. [38] does not suggest publication bias (Figure 3). Formal testing using the Egger's method does not support the notion of a publication bias (intercept= -1.07, p=0.33).

DISCUSSION

The primary finding of this study is that the best available evidence suggests no association

between citrus fruits and prostate cancer. Supporting this conclusion are strengths in the methods; explicit eligibility criteria, a comprehensive search, and a rigorous approach to data analysis, and the observation that the lack of effect was consistent across cohort and case-control studies. Furthermore, the review addressed incidence rather than cancer mortality. Incidence rate is preferable in the exploration of risk factors because cancer deaths reflect the failure of treatment as well as the occurrence of the cancer [41].

The limitations are those of the primary studies. Firstly, all data comes observational studies with a diversity of study designs, racial population, control groups, and definition of exposure [42]. Using the GRADE system of rating quality of evidence, these trials would

start as low quality. The large heterogeneity would rate the quality down further, resulting in an overall assessment of very low quality [43]. Thus, inferences from this systematic review are limited. In addition, methodological issues related specifically to meta-analysis, such as publication bias, could have particular impact when combining results of observational studies [44]. In this case, with the inclusion of positive and negative studies, publication bias seems less likely.

While making publication bias less likely, the diverse study results create problems in interpretation. Particularly challenging is explaining a positive association with risk of several fruits normally considered to be healthy [4]. One possibility is detection bias; in one study, 'healthy' dietary intake was related to greater use of the PSA screening test [45]. Such self-selection screening bias could mask a protective effect of citrus fruits in prostate cancer risk [18]. In addition, it has been suggested before that latent and non-latent or aggressive prostate tumors might have a different etiology [46]. By these reasons, consumption of fruits has not been consistently associated with a reduction in risk of prostate cancer overall [6], even if few studies have found this effect [20,47].

Citrus fruits include several implicated bioactive components such as vitamin C, β carotene, flavonoids, limonoids, folic acid, and dietary fiber [48]. The inhibition of developing carcinogen-induced cancers by citrus fruits has been investigated in a variety of different animal models, including models for stomach, lung, and skin cancer [49]. In addition, the peel is a rich source of flavonoids, associated with potential anti-oxidant, anti-inflammatory, and anti-tumor activities [50]. The result of this study provides a possible explanation for the finding that the incidence of stomach cancer is inversely related to that of prostate cancer even though diet could be a major risk of both cancers [51].

In summary, the results provide additional

evidence of the no risk of prostate cancer associated with citrus intake. However, this meta-analysis evaluated the association between citrus fruits intake and prostate cancer risk based on published results from epidemiological studies, so that we should conclude that there is insufficient information from the relatively few number of epidemiologic studies to provide a definitive assessment on the relationship between citrus fruits intake and prostate cancer risk in humans. Because prostate cancer is a disease of multifactorial etiologies, the key to understanding the progression and defining prevention programs will be found through multidisciplinary interactive research efforts involving epidemiologists, nutritional scientists, and cell or molecular biologists [6]. As the main concern in the meta-analysis for observational studies is to pose new hypothesis as an exploratory meta-analysis [52], authors hope that this meta-analysis will be used to shape future research questions by helping us understand the results from past studies, especially in the situation of increasing burden of prostate cancer in Korean men [53-54].

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