Lycopene/Tomato Consumption and the Risk of Prostate Cancer: A Systematic Review and Meta-Analysis of Prospective Studies

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(Received October 18, 2012)

Summary Lycopene/tomato has been discussed as a potential effector in the prevention and therapy of prostate cancer; however, no systematic review has been reported to illustrate its effect recently. In the present study, a meta-analysis was carried out to determine whether intake of lycopene and tomato/tomato products could reduce the risk of prostate cancer. Eleven cohort studies and six nested case-control studies were identified through searching of international journal databases and reference lists of relevant publications. Two reviewers independently assessed the study quality and extracted data from each identified study; only studies with sufficient quality were included in the review. The main outcome of interest was incidence of prostate cancer. Compared with consumers of lower raw tomato intake, the odds ratio (OR) of incidence of prostate cancer among consumers of higher raw tomato intake was 0.81 [95% confidential interval (CI) 0.59–1.10]; for consumers of higher level of cooked tomato intake versus lower cooked tomato intake, this OR was 0.85 (95% CI 0.69–1.06); the OR of higher lycopene intake versus lower lycopene intake for prostate cancer was 0.93 (95% CI 0.86–1.01) and the OR for higher level of serum lycopene versus lower serum lycopene level was 0.97 (95% CI 0.88–1.08). It's suggested that tomato may play a modest role in the prevention of prostate cancer. Further research would be needed to determine the type and quantity of tomato products regarding their potential in preventing prostate cancer.

Key Words lycopene, tomato, prostate cancer, meta-analysis, systematic review

Prostate cancer is a common form of cancer with high incidence worldwide, which is also a common cause of death in developed countries with age-standardized mortality rates ranging from 16 per 100,000 males in the U.S. to 28 per 100,000 males in Norway and Sweden (1). As evidenced in the dietary supplements industry, consumers are increasingly turning to diet-based interventions and complementary medicines to maintain health and prevent diseases (2). An investigation in 2005 identified that up to 33% participants diagnosed with prostate cancer used some form of complementary and alternative products or practice, with an overall rate of 25% reporting of dietary supplements, such as lycopene (3).

Lycopene, a carotenoid found in high quantities in tomatoes and tomato-rich products, has been explored in association with prevention and treatment of various kinds of diseases, including prevention of prostate cancer. Besides, lycopene has been identified as an antioxidant compound with potential anti-cancer properties and no obvious side effects (4). The American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention suggested that eating five or more servings of vegetables and fruits (which may include lycopene) each day may protect against prostate cancer;

however, the effectiveness is still under investigation (5). In 2004, the FDA received two petitions for qualified health claims regarding tomatoes and/or lycopene and cancer risk reduction, then the scientific data for tomato and/or lycopene intake with respect to risk reduction for certain forms of cancer were reviewed accordingly; however, the FDA found no credible evidence to support an association of lycopene intake with a reduced risk of prostate, lung, colorectal, gastric, breast, ovarian, endometrial, or pancreatic cancer, and very limited evidence to support an association of tomato consumption with reduced risks of prostate, ovarian, gastric, and pancreatic cancers (6). In 2007, the World Cancer Research Fund reported that a high intake of fruit and vegetable may be beneficial in reducing the risk of cancer, including lycopene for prostate cancer (7).

Up to now, it's still controversial to ascertain a role of the nutritional supplementation in the prevention of prostate cancer considering current scientific evidence. In addition, there still remain some unanswered questions, e.g. whether this benefit varies with different preparations of tomatoes (e.g. cooked versus raw), and how closely circulating or tissue lycopene level reflected dietary intake.

To answer some of these questions and provide a more convincing statement, we therefore conducted a systematic review of all available prospective evidence relating to lycopene supplementation/tomato intake

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Fig. 1. Search strategy flow chart.

and/or serum lycopene and prostate cancer incidence to provide evidence-based recommendations for populations with a high risk of prostate cancer as well as the general public.

METHODS AND MATERIALS

Search strategy. OVID MEDLINE, EMBASE, Web of Science, Springer, CNKI and CENTRAL (The Cochrane Library) databases were systematically searched for relevant studies published before January 2012, and the literature reviewed was limited to studies in humans. Bibliographies of published reviews on lycopene and tomato were also screened for potentially relevant studies. A further search was done by scanning the reference lists of original and review publications. No language or other limitations were imposed. Figure 1 illustrates the study selection process.

Terms used for MEDLINE (and adopted for other databases) in both subject heading and text words were: (1) carotenoids or lycopene or antioxidants or tomato or dietary; (2) prostate cancer or prostatic neoplasm; (3) (1) and (2); (4) limit (3) to humans.

Studies were included if they met the following criteria: (1) the primary outcome was clearly defined as prostate cancer; (2) the exposure of interest was tomato consumption or lycopene intake, or measurement of serum lycopene; (3) odds ratio (OR) or relative risk (RR) estimates and their confidence intervals (CIs), or enough data to calculate them was provided; (4) the most confounding factors were adjusted. If data or population were duplicated in more than one study, the most recent study was included in the meta-analysis.

Data extraction and quality assessment. The papers identified through the initial search were reviewed and classified as potentially relevant by two independent reviewers (CJY and SY), data was evaluated and extracted independently from included studies by the

two reviewers. Any discrepancy was discussed and resolved in consensus and by consulting with the superior (ZLS).

Data extracted included first author, publication year, study setting, study design, study population, sample size, outcome assessment, duration of observation and follow-up, statistical methods, and risk estimators for the association of different exposure levels of lycopene/tomato with incidence. The references in relevant publications were checked for additional studies of interest. Missing data was dealt with by contacting the original study investigators to request the missing data, or provide further clarification on data. Analysis was performed on the available data in cases where the missing data was irretrievable.

Quality evaluation was carried out according to the guideline in strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement to assess the quality of the studies included in this review (8). The quality was independently evaluated for each study by the two reviewers; disagreements were resolved by consensus, and details are described in Tables 1–3.

Statistical analysis. Separate analysis for intakes of raw or cooked tomato, and lycopene with respect to risk of prostate cancer was carried out. Tomato and lycopene intake was reported as categorical data with a range in the studies included in this meta-analysis. An additional analysis focused on serum lycopene in association with prostate cancer.

An overall relative risk for lowest and highest range of lycopene/tomato intake level and serum lycopene was derived by meta-analysis combining estimates from fully adjusted models, and in all instances the ratios used compared the incidence of the highest range of lycopene/tomato intake and serum lycopene versus the lowest.

A summarized OR with a 95% CI was estimated by using both fixed-effect and random-effect models. If the data were homogeneous, the fixed-effect model would be applied and if the data were heterogeneous, the random-effect model would be adopted. Given the assumption that lycopene might play a more important role in the prevention of advanced prostate cancer, subgroup analysis was carried out for advanced prostate cancer among studies with available data.

Assessment of heterogeneity was performed using both χ^2 and I^2 . The χ^2 test assesses whether the differences in results are due to chance only (9). The I^2 assess the percentage of variability in the effect estimates that is due to heterogeneity rather than chance. I^2 values over 50% indicate that substantial heterogeneity may be present (9). Publication bias was assessed via visual inspection of the funnel plots. Sensitivity analysis was performed to strengthen the results of the meta-analysis. The analysis was performed using Review Manager 5.0 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen) (10).

RESULTS

Literature searching and characteristics of included studies

The literature search yielded 18 potential prospective

Table 1. Characteristics of studies for lycopene intake and serum lycopene included in this meta-analysis.

Study ID	Study country/ study name	Study population		Dietary assessment	Follow-up duration (y)	Definition of outcome	Measurement for association OR/ RR (95% CI) of the highest range with the lowest		Adjustments
		Case/control size or cohort size (cases)	Age (range/mean age (y))				Lycopene intake	Serum lycopene	
Cohort studies									
Kirsh, 2006 (11)	U.S./the Prostate, Lung, Colorectal, and Ovarian Trial	23,631 (1,338)	55–74/63.3	Self-administered semi- quantitative validated 137-item FFQ assess- ing diet and nutrient supplement (including 25 lycopene-containing items)	4.2 (2001– 2005)	Clinically screened PC	17,593 vs 5,052 $\mu\text{g}/\text{d}$ 0.95 (0.79–1.13) $p=0.33$	Adjusted for age, total energy, race, study cen- ter, family history of prostate cancer, body mass index, smoking status, physical activity, supplemental vitamin E intake, total fat intake, red meat intake, history of diabetes, aspirin use, and previous number of screening exams within the follow-up period	
Kristal, 2010 (12)	U.S. and Canada/ the Prostate Cancer Preven- tion Trial	9,559 (1,703)	$\geq 55/62.8$	Self-administered semi- quantitative 108-item validated FFQ, assess- ing diet and nutri- ent supplement (with questions about food preparation)	10 (1994– 2003)	Biopsy con- firmed PC	$>10,918$ vs $<3,999 \mu\text{g}/\text{d}$ 1.04 (0.90–1.20) (Calculated OR from the original data)	Adjusted for age, race/ethnicity, family his- tory of prostate cancer in first-degree relatives, treatment arm, and body mass index	
Giovannucci, 2002 (13)	U.S./Professionals Follow-up Study	47,365 (2,481)	40–75/—	Semi-quantitative, 131- item validated FFQ, assessing diet and nutrient supplement (estimates of the cor- relation of plasma lycopene and lycopene intake to be 0.46)	12 (1986– 1998)	Diagnosed PC	18,780 vs 3,415 $\mu\text{g}/\text{d}$ 0.84 (0.73–0.96) $p=0.003$	Adjusted for age, time period, ancestry, body mass index at age 21, and intakes of total energy, calcium, phosphorus, fructose, vitamin D, vitamin E, total fat, and linolenic acid	
Schuurman, 2002 (14)	Netherland/ Netherlands Cohort Study	58,279 (642/1525)	55–69/—	Semi-quantitative, 131- item validated FFQ, assessing diet and nutrient supplement	6.3 (1986– 1992)	Microscopically or histologi- cally confirmed, primary PC	2 vs 0.1 mg/d 0.98 (0.71–1.34) $p=0.58$	Adjusted for age, family history of prostate cancer, socioeconomic status, and alcohol from white or fortified wine	
Nest-control studies									
Gann, 1999 (17)	U.S./Physicians' Health Study	578/1,294	40–84/ 60.7/61.5	—	13 (1982– 1995)	Clinically confirmed PC	0.75 (0.54–1.06) $p=0.12$	Adjusted for exercise frequency, body mass index, plasma total cholesterol, alcohol, and multivitamin supplement; matched on age, follow-up time at risk, and smoking status	
Wu, 2004 (18)	U.S./Health Professionals Follow-up Study	450/450	40–75/—	Referring to reference (13), Giovannucci, 2002	5 (1993– 1998)	Non-stage A1 incident PC	0.66 (0.38–1.13) $p=0.33$	Matched by age, time, month, and year of blood donation; matching variables plus cholesterol levels, selenium supplementation, vitamin E supplementation, family history of prostate cancer, body mass index, height, vigorous exer- cise, history of vasectomy and current smoking	
Key, 2007 (19)	8 European countries/Euro- pean Prospective Investigation into Cancer and Nutrition study	966/1,064	—/60.4 $\pm$ 5.8/ 60.1 $\pm$ 5.7	Self-administered or face- to-face, semi-quantita- tive or quantitative vali- dated FFQ (containing 98–736 items)	8 (1992– 2000)	Diagnosed with incident PC	≥ 49.37 vs $<15.04 \mu\text{g}/\text{dL}$ 0.97 (0.70–1.34) $p=0.41$	Matched by study center, age, and date of recruitment; adjusted for BMI, smoking status, alcohol intake, physical activity level, marital status, and educational level	

Table 1. (Continued)

Study ID	Study country/ study name	Study population		Dietary assessment	Follow-up duration (y)	Definition of outcome	Measurement for association OR/ RR (95% CI) of the highest range with the lowest		Adjustments
		Case/control size or cohort size (cases)	Age (range/mean age (y))				Lycopene intake	Serum lycopene	
Huang, 2003 (20)	U.S., Maryland/ CLUE I; CLUE II cohort	324/648 182/364 142/284	45–64/—	—	22 (1974– 1996); (1989– 1996)	Histologically confirmed PC in Cancer Registry	By quintiles of the control 0.83 (0.46–1.48) <i>p</i> =0.72	Matched with two controls by age, gender, race, and date of blood donation; adjusted for total lipid levels in the blood, hours since last meal, and education, body mass index at age 21 y	
Peters, 2007 (21)	U.S./the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	28,243 (692/844)	—/64.7	—	8 (1993– 2001)	Histologically confirmed PC	30.5 vs 108.4 μg/dL (Median in quintiles) 1.14 (0.82–1.58) <i>p</i> =0.28	Matched for age, time since initial screening, and year of blood draw; adjusted for study center	
Nomura, 1997 (22)	Hawaii (Japanese Americans)	6,832 (142/142)	52–74/62	—	21 (1971– 1993)	Biopsy confirmed PC	By quintiles of the control 1.1 (0.5–2.2) <i>p</i> =0.86	Matched for age, time since initial screening	
Agalliu, 2011 (23)	Canada/Cana- dian Study of Diet, Lifestyle, and Health cohort	661/1,864	—/66.2±8.4/ 69.3±10.5	Self-administered, 166 -item validated FFQ, diet and nutrient supplement	7 (2003– 2010)	Clinically confirmed PC	15,871.0 vs 2,450.6 μg/d 0.82 (0.61–1.10) <i>p</i> = 0.54	Matched for age at baseline, race, BMI, exercise activity, and education	
Karppi, 2009 (24)	Finland/Kuopio Ischaemic Heart Disease Risk Fac- tor cohort	997 (55/856)	—/56.2	—	12.6 (1993– 2006)	Histologically confirmed PC	>0.19 vs <0.08 μmol/L 0.78 (0.37–1.66) <i>p</i> =0.524	Adjusted for age, examination year, intake of alcohol, family history of cancer, physical activ- ity, waist-to-hip ratio, education, years of smok- ing, and serum folate	
Beilby, 2010 (25)	Australia	96/225	—/69.8±7.2/ 69.3±6.7	—	14 (1990– 2004)	Histologically confirmed PC	0.31–1.30 vs 0–0.19 μmol/L 0.77 (0.40–1.47) <i>p</i> =0.36	Matched for age Adjusted for age, administered vitamin A supplement	
Kristal, 2011 (26)	U.S. and Canada/ the Prostate Cancer Preven- tion Trial	1,809/1,809 1,751/1,683	≥55/63.6±5.6/ 63.7±5.6	Self-administered, semi- quantitative, 108-item validated FFQ, 108- items assessing diet and nutrient supplement (with questions about food preparation)	10 (1994– 2003)	Histologically or biopsy confirmed PC	>46.6 vs <26.3 μg/dL 1.03 (0.91–1.17) Calculated OR from original data	Matched on distributions of age, treatment group, and a first-degree relative with PC, and were over sampled for nonwhites adjusted for age, race, diabetes, serum cholesterol, and BMI; models for total sample controlled in addition for treatment arm	

PC, prostate cancer; BMI, body mass index; FFQ, Food Frequency Questionnaire; OR, odds ratio; RR—relative risk.

Table 2. Characteristics of studies for raw tomato and cooked tomato intake included in this meta-analysis.

Study ID	Study country/ study name	Study population		Dietary assessment	Follow-up duration (y)	Definition of outcome	Measurement for association OR/RR (95% CI) of the highest range with the lowest		Adjustments
		Case/control size or cohort size (cases)	Age (range/mean age) (y)				Raw tomato	Cooked tomato	
Cohort studies									
Kirsh, 2006 (11)	U.S./the Prostate, Lung, Colorectal, and Ovarian Trial	23,631 (1,338)	55–74/63.3	Self-administered, semi- quantitative, 137-item validated FFQ, assessing diet and nutrient supple- ment (including 25 lycopene-containing items)	4.2 (2001– 2005)	Clinically diagnosed PC	>3 servings/wk vs <2.5 servings/mo 1.04 (0.86–1.27) <i>p</i> =0.84	Tomato sauce >2 servings/wk vs <1 servings/mo 0.96 (0.76–1.19)	Adjusted for age, total energy, race, study center, family history of pros- tate cancer, BMI, smoking status, physical activity, supplemental vitamin E intake, total fat intake, red meat intake, history of diabetes, aspirin use, and previous number of screening exams within the fol- low-up period
Giovannucci, 2002 (13)	U.S./Health Professionals Follow-up Study	47,365 (2,481)	40–75/—	Semi-quantitative, 131- item validated FFQ, assessing diet and nutri- ent supplement (estimates of the correlation of plasma lycopene and lycopene intake to be 0.46)	12 (1986– 1998)	Diagnosed PC		Tomato sauce: ≥2 servings/wk vs <1 servings/mo 0.77 (0.66–0.90) <i>p</i> <0.001	Adjusted for age, time period, ances- try, BMI at age 21, and intakes of total energy, calcium, phosphorus, fructose, vitamin D, vitamin E, total fat, and linolenic acid
Giovannucci, 1995 (15)	U.S./Health Professionals Follow-up Study	47,894 (773)	40–75/—	Referring to reference (13), Giovannucci, 2002	6 (1986– 1992)	Diagnosed non-stage A PC	≥5 vs 0 servings/wk 0.74 (0.58–0.93) <i>p</i> =0.03	Tomato sauce: ≥2–4 vs 0 servings/wk 0.66 (0.49–0.90) <i>p</i> =0.001 Tomato based food (raw and cooked); >10 vs <1.5 servings/wk 0.65 (0.44–0.95) <i>p</i> =0.01	Adjusted for total energy intake and age, BMI (weight divided by height squared), aspirin use, marital sta- tus, ancestry, geographic region of residence, level of physical activity, vasectomy status, smoking hab- its, and intake of other nutrients (including alcohol)
Mills, 1989 (16)	U.S./Seventh-day Adventist men	78,000 person years (181)	>25/—	FFQ with 24-h dietary recalls	6 (1976– 1982)	Histologically confirmed PC	>5 vs 0 servings/wk 0.60 (0.37–0.97) <i>p</i> =0.02		Adjusted for age, education, cur- rent use of meat, poultry, or fish, current use of fish only, beans, legumes or peas, citrus fruit, dry fruit, index of fruit, nuts, tomatoes, and exposure to Adventism
Nested case-control studies									
Salem, 2011 (27)	Iran	194/317	—/71.1±7.84/ 66.5±10.2	Semi-quantitative, 20-item interview validated FFQ, (with information on red tomato—fresh, extract and dressing)	3 (2005– 2008)	Newly diag- nosed, clinico- pathologically confirmed PC	Tomato and tomato product >100 vs <10 g/wk 0.33 (0.16–0.65), <i>p</i> =0.001		Unmatched: adjusted for total diet- ary calories, age, body mass index, occupation, educational level, smok- ing, alcohol, and family history of PC

PC, prostate cancer; mo, month; wk, week; BMI, body mass index; FFQ, Food Frequency Questionnaire; OR, odds ratio; RR, relative risk.

Table 3. Assessment of the quality of the prospective studies included in this meta-analysis.

Study ID	Clear definition of study population?	Clear description of method of observation?	Clear definition of outcomes and outcome assessment?	Are the main findings of the study clearly described?	Have the duration of follow-up be described?	Have the characteristics of subjects lost to follow-up been described?	Does the study provide estimates of the random variability in the data for the main outcomes?	Important confounders and prognostic factors identified?
Cohort study								
Kirsh, 2006 (11)	yes	yes	yes	yes	yes	yes	yes	yes
Kristal, 2010 (12)	yes	yes	yes	partially	yes	yes	yes	yes
Giovannucci, 2002 (13)	yes	yes	partially	yes	yes	yes	yes	yes
Schuurman, 2002 (14)	Yes	yes	yes	yes	yes	no	yes	yes
Giovannucci, 1995 (15)	yes	yes	yes	partially	yes	no	yes	yes
Mills, 1989 (16)	partially	yes	yes	partially	yes	yes	yes	yes
Nested case-control study								
Gann, 1999 (17)	yes	yes	yes	yes	yes	yes	yes	yes
Wu, 2004 (18)	yes	yes	no	yes	yes	yes	yes	yes
Key, 2007 (19)	yes	yes	yes	yes	yes	yes	yes	Yes
Huang, 2003 (20)	yes	yes	yes	no	yes	yes	yes	yes
Peters, 2007 (21)	yes	yes	yes	yes	yes	yes	yes	yes
Nomura, 1997 (22)	yes	yes	yes	no	yes	yes	partially	yes
Agalliu, 2011 (23)	yes	yes	yes	yes	yes	yes	yes	partially
Karppi, 2009 (24)	yes	yes	yes	partially	yes	yes	yes	yes
Beilby, 2010 (25)	yes	yes	yes	yes	yes	no	yes	Partially
Kristal, 2011 (26)	yes	yes	yes	partially	yes	yes	yes	yes
Salem, 2011 (27)	yes	yes	yes	no	yes	no	yes	yes

Fig. 2. Effect of raw tomato intake on risk of prostate cancer.

Fig. 3. Effect of cooked tomato intake on risk of prostate cancer.

Fig. 4. Effect of lycopene intake on risk of prostate cancer.

studies to be used in the systematic review and finally 17 studies, including six cohort studies (11–16) and 11 nested case-control studies (17–27), were entered in the meta-analysis (Fig. 1). One nested case-control study was excluded as it did not provide CIs of the OR or any other information that allowed for its calculation (28). The authors were contacted by e-mail trying to retrieve those missing data, but up to the time of completion of this article, we had not received this information. Data of one cohort study (29) were included in another follow-up cohort study (20), while the most recent reports were chosen for this review, and results of one cohort (Health Professionals Follow-up Study, HPFC) had been reported in both 1995 and 2002 (13, 15). However, raw tomato intake was only analyzed in 1995 (15); thus updated data about lycopene and cooked tomatoes was adopted from the 2002 analysis (13). The characteristics of the included studies are listed in Tables 1 and 2.

A food frequency questionnaire (FFQ) was the usual method used to collect dietary intake information. In the cohort studies, dietary intake was captured at the time of enrollment in the study, with the follow-up period ranging from 4.2 to 22 y. In HPFC (15), dietary intake was adopted as the cumulative average updated using the average of all the diet questionnaires available to that point in the follow-up period (1986, 1990, 1994).

Three cohort studies (11, 15, 16) presented data on raw tomato intake and one nested case-control study

(27) reported unspecified tomato intake. Three cohort studies (11, 13, 15) presented data for cooked tomatoes. As for lycopene, four cohort studies (11–14) and one nested case-control study (23) presented data on lycopene intake, while nine nested case-control studies (17–22, 24–26) presented results referring to serum lycopene level which was measured at the time of enrollment.

Raw tomatoes and cooked tomatoes with prostate cancer

As shown in Fig. 2, compared with people having the lowest range of consumption of raw tomatoes, the risk estimate of prostate cancer of those having highest range of intake was 0.81 (95% CI 0.59–1.10), $\chi^2 = 7.63$, $df = 2$, $p = 0.03$, $I^2 = 74\%$.

The pooled risk estimate for all four prospective studies on cooked tomato intake was 0.85 (95% CI 0.69–1.06), $\chi^2 = 2.79$, $df = 1$, $p = 0.09$, $I^2 = 64\%$ (Fig. 3). Since no universally accepted converted serving for cooked tomato products was available, and the four studies investigated multiple categories of cooked tomato, e.g. pizza, tomato sauce, etc. (11, 15) and tomato sauce (13), the risk associated with specific categories of cooked tomatoes could not be calculated. Therefore, the pooled OR of cooked tomatoes was conducted based on the data on tomato sauce, which contributes a considerable amount of cooked tomato consumption.

Lycopene intake and serum lycopene

Compared with people having the lowest range of

Fig. 5. Effect of serum lycopene on risk of prostate cancer.

Fig. 6. Effect of lycopene intake on risk of advanced prostate cancer.

Fig. 7. Effect of serum lycopene on risk of advanced prostate cancer.

consumption of lycopene, the OR of prostate cancer of those having highest intake was 0.93 (95% CI 0.86–1.01), $\chi^2 = 4.88$, $df = 3$, $p = 0.30$, $I^2 = 18\%$ (Fig. 4). The effect-estimate shown by increasing lycopene intake was slightly higher than that of concentrations of serum lycopene; as for the highest range of serum lycopene level compared with the lowest, the pooled risk estimate was 0.97 (95% CI 0.88–1.08), $\chi^2 = 7.15$, $df = 8$, $p = 0.52$, $I^2 = 0\%$ (Fig. 5).

Subgroup analysis for advanced prostate cancer

One cohort study—HPFC (13, 15)—reported the correlation of intake of raw tomatoes and cooked tomatoes with risk of advanced prostate cancer. RR for advanced prostate cancer (stage C and D or Gleason score ≥ 7) of combined intake of tomatoes, and cooked tomato products (which accounted for 82% of lycopene intake) was 0.65 (95% CI 0.44–0.95) for consumption frequency greater than 10 versus less than 1.5 servings per week.

Three cohort studies (11, 12, 14) and one nested case-control study (23) reported the risk estimate of lycopene intake with advanced prostate cancer. As shown in Fig. 6, the pooled estimate for the four studies on lycopene intake with risk of advanced prostate cancer was 1.03

(95% CI 0.83–1.26), $\chi^2 = 3.12$, $df = 3$, $p = 0.37$, $I^2 = 4\%$. Excluding the nested case-control study (23), the pooled risk estimate of the three cohort studies was 1.10 (95% CI 0.88–1.37), $\chi^2 = 1.00$, $df = 2$, $p = 0.61$, $I^2 = 0\%$.

Four nested case-control studies have reported correlation of serum lycopene with advanced prostate cancer (17, 19, 21, 26). The OR of the highest serum lycopene with the lowest in association with risk of advanced prostate cancer was 0.77 (95% CI 0.49–1.20), $\chi^2 = 10.46$, $df = 3$, $p = 0.02$, $I^2 = 71\%$ (Fig. 7).

Publication biases

Funnel plots (Fig. 8) for lycopene intake of five studies and for serum lycopene of nine studies for risk of prostate cancer were consistent with a symmetrical funnel with a large base and a sharp upper part, showing that there is no evidence for publication bias. However, funnel plots were not graphed due to the small number of included studies referring to raw tomatoes and cooked tomatoes and subgroup studies.

Sensitivity analysis

In an attempt to identify the studies contributing to the heterogeneity, a stepwise exclusion of each of the study results for lycopene intake on overall pros-

Fig. 8. Funnel plot for serum lycopene for risk of prostate cancer (left) and lycopene intake for risk of prostate cancer (right).

tate cancer was conducted. The risk estimate for lycopene intake was 0.88 (95% CI 0.80–0.98), $\chi^2=1.70$, $df=3$, $p=0.64$, $I^2=0\%$ and 0.98 (95% CI 0.88–1.08), $\chi^2=2.06$, $df=3$, $p=0.56$, $I^2=0\%$ for excluded study (12) and (13) respectively.

No sensitivity analysis was conducted on tomato intake or subgroup analysis due to limited number of included studies.

DISCUSSION

Summary of main results

Six cohort studies and 11 nested case-control studies reported from 1989 to 2011 were included in this meta-analysis. To sum up, the inverse associations of intake of raw tomatoes/cooked tomatoes, lycopene intake/serum lycopene with prostate cancer, as well as advanced prostate cancers, were all suggestive but statistically non-significant. Though it has been suggested that the higher concentration and bioavailability of lycopene in cooked tomato products might lead to a more beneficial health outcome, our finding didn't quite support the assumption.

This is the first systematic review and meta-analysis of prospective studies that focused on the effect of lycopene/tomato intake and serum lycopene in association with prostate cancer. The most relevant databases were searched, and a hand search of relevant reviews was also included, with two reviewers independently appraising the evidence quality and extracting data from included studies. Moreover, no publication year or other limitations were restricted. This study incorporated information from studies examining lycopene and tomato intake as well as serum lycopene to illustrate their effect on prostate cancer more clearly.

The quality of the evidence was assessed using the approach outlined in Tables 1–3. It's noteworthy that all the included prospective studies have adjusted data for possible confounding factors, and provided estimates

of random variability in the data for the main outcomes and useful information to evaluate the reliability of the studies, such as follow-up approaches, missing data, and dietary questionnaire descriptions. What also should be noted is that FFQ is the most widely adopted method to evaluation lycopene intake. Dietary assessment of lycopene intake may not reflect bioavailability as its absorption may be influenced by several factors including processing or cooking, the lipid content of the diet, and possibly genetic factors (30, 31). To date, there is no existing consensus for measuring lycopene intake or for developing a qualified FFQ, which complicated the interpretation of findings across studies. There was large variability in the number of items that were included in the FFQs: some studies captured as few as 20 items (27), while others incorporated up to 736 (19). It's quite possible that questionnaires do not always capture true variation in the lycopene status in a given population, which could result in misclassification and contribute to the notable heterogeneity. Moreover, as the duration of cohort studies generally stretches over years or even decades, the FFQ more ultimately become somewhat 'out-of-date' as new foods become available over the duration of the study and dietary patterns change (32). Therefore, consideration must be given to the possibility of attenuated risk estimates due to random error in quantifying and/or capturing the most relevant measure of intake.

This meta-analysis may further be subject to several limitations. Although there was little evidence of publication bias from the funnel plot, results from the studies that were not accepted for publication apparently may have changed the results of this meta-analysis. Heterogeneity was found among the studies of high intake of raw tomatoes ($p=0.03$, $I^2=74\%$), cooked tomatoes ($p=0.09$, $I^2=64\%$) on prostate cancer, and serum lycopene on risk of advanced prostate cancer ($p=0.02$, $I^2=71\%$). The heterogeneity could be attributed to sev-

eral factors. Recall bias may be present in dietary studies of tomato/lycopene intake included in our meta-analysis. In an attempt to be comprehensive and include as many qualified studies as possible, we included studies published in countries with various diet pattern and socio-cultural habits [European countries (14, 19, 24, 25), U.S. and Canada (11–13, 15–18, 20–23, 26), and Iran (27) and one specifically targeted in Japanese-Americans in Hawaii (22)]. Different countries consume different sources of lycopene and different food choice combinations, which may broaden the generalizability of the results, as well as contribute to the heterogeneity of some of the results. Few of the studies made adjustments for a large percentage of the factors (alcohol for instance) found to be important to the pathogenesis of prostate cancer. This may contribute to the heterogeneity in some of the analyses. Duration of follow-up years may also contribute to the heterogeneity, especially what was noted in serum lycopene analysis, given that the included blood-based studies relied on one plasma measurement, which may lead to misclassification of long-term exposure.

Residual confounding (confounding from unknown variables that is not eliminated by adjustment), as in any meta-analysis of observational studies, may introduce considerable bias, and the direction of this bias was probably unpredictable. Moreover, defining what represented a higher intake of lycopene/tomatoes is difficult as there is variability in the upper grade of lycopene/tomato intake used in the studies, as well as serum lycopene level.

Implication for practice and research

This systematic review has been undertaken to evaluate available prospective evidence for a protective effect of lycopene/tomatoes intake on occurrence of prostate cancer in order to provide evidence-based recommendations. In a meta-analysis of 5 cohorts studies, 5 nested case control studies and 11 case control studies published from the 1950s to 2003 (33), Etminan et al. concluded that there was a 1% relative risk reduction in the risk of prostate cancer diagnosis in men consuming a higher level of lycopene. To date, more updated and significant results of cohort studies have been reported; therefore, this systematic review would communicate more valuable information.

Though not strongly supporting the positive association of lycopene/tomato intake with reducing risk of prostate cancer, the above meta-analysis does, however, provide reasonable evidence that research on lycopene/tomato intake in association of prostate health should be carried out among more geographical and age groups and correlation of lycopene intake and plasma lycopene should be examined. Given that existing evidence is not overwhelming enough to recommend the use of lycopene supplements in the prevention of prostate cancer, and referring to the joint statement by World Cancer Research Fund/American Institute for Cancer Research (7), consumption of vegetables and fruits should still be recommended both for cancer prevention and for cancer survivors.

Acknowledgments

The authors declare that there was no conflict of interest. This work was supported by the National Natural Science Foundation of China (Grant Number 81030053) and the National High-technology Research and Development Program ("863" program) of China (Grant Number 2010AA023001).

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