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Fruit and vegetable consumption and risk of lung cancer: A dose–response meta-analysis of prospective cohort studies

Yaopeng Wang[1], Fei Li[1], Zizong Wang, Tong Qiu, Yi Shen, Mingzhao Wang*

Department of Thoracic Surgery, The Affiliated Hospital of Medical College of Qingdao University, Jiangsu Road, No. 19, Qingdao 266001, Shandong, PR China

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ABSTRACT

Objectives: A meta-analysis was conducted to summarize evidence from prospective cohort studies about the association of fruit and vegetable consumption with the risk of lung cancer.
Materials and methods: Pertinent studies were identified by a search of Embase and PubMed databases to October 2014. A random-effects model was used to combine study-specific relative risks and 95% confidence interval [RR (95% CI)]. Dose–response relationship was assessed by restricted cubic spline.
Results: The RR (95% CI) of lung cancer for highest versus lowest category of fruit and vegetable (FV) consumption was 0.87 (0.79–0.95) (8 studies including 12,942 cases among 1,571,494 subjects), and the effect was 0.84 (0.79–0.90) for fruit (16 studies including 15,421 cases among 1,791,469 subjects) and 0.90 (0.84–0.96) for vegetable (19 studies including 16,422 cases among 1,877,375 subjects). The above-mentioned associations did not differed significantly in subgroup analysis by country, age, number of covariates adjusted, quality score, sex, smoking status and histological subtypes; however, studies with follow-up duration of $\geq$10 years and with FV assessed by interview showed a stronger association than those of <10 years and by self-administrated food frequency questionnaires, respectively. The risk of lung cancer decreased by 3% (P = 0.07), 5% (P < 0.01) and 3% (P = 0.09) for every 1 serving/day increment in FV, fruit and vegetable consumption, respectively. There was a threshold around 2 servings/day of fruit and 2 servings/day of vegetable, respectively, after which the risk of lung cancer did not reduce further.
Conclusions: Fruit and vegetable consumption are inversely associated with risk of lung cancer.

1. Introduction

Worldwide, lung cancer is the most frequently diagnosed cancer and the leading cause of cancer death in males, comprising 17% of the total new cancer cases and 23% of the total cancer deaths [1]. Among females, it is the fourth most commonly diagnosed cancer and the second leading cause of cancer death, accounting for 11% of the total female cancer deaths [1]. Lung cancer has an extremely poor prognosis, with an overall 5 year survival of 16% in the USA and less than 10% in the UK [2]. Smoking accounts for 80% of the worldwide lung cancer burden in males and at least 50% of the burden in females [3,4], and 10–14% of lung cancers are attributed to radon exposure [5]. Interventions aimed at increasing the intake of fruit and vegetable to the recommended level (500 g/d) were found effective for lung cancer prevention in Europe countries [6] and earlier observational studies also found an inverse association between fruit and vegetable consumption and risk of lung cancer [7–9]. The most recent report (2007) from the World Cancer Research Fund/American Institute for Cancer Research concluded that the association was probable for fruit and limited-suggestive for vegetable [10]. Results from recent prospective cohort studies [11–16] (including 12,121 lung cancer cases among 1,518,665 participants) are still not consistent, and these prospective cohort studies [11–16] have not been summarized quantitatively with a meta-analysis. In addition, levels of fruit and vegetable consumption that give the greatest protection on lung cancer remain unknown [17]. Therefore, we conducted a dose–response meta-analysis to quantitatively summarize the evidence from prospective cohort studies about the association of fruit and vegetable consumption with risk of lung cancer.

* Corresponding author at: Department of Thoracic Surgery, The Affiliated Hospital of Medical College of Qingdao University, No. 19, Jiangsu Road, Shinan District, Qingdao 266001, Shandong, PR China. Tel.: +86 0532 82911325; fax: +86 0532 82911325.
E-mail address: qdwangmz1966@163.com (M. Wang).
[1] Yaopeng Wang and Fei Li contributed equally to this paper.

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2. Materials and methods

2.1. Literature search and selection

Relevant studies were identified by searching PubMed and Embase databases up to October 2014, using the search terms ((fruit*) OR vegetable*) AND lung cancer, without limitations. We reviewed the reference lists from retrieved articles to search for further relevant studies. Inclusion criteria includes: a prospective cohort design; exposure of interest was fruit or vegetable; outcome of interest was lung cancer; and relative risk with 95% confidence interval [RR (95% CI)] was provided. For duplicated publications, the one with the largest number of cases was included; otherwise, the most recent one was included.

2.2. Data extraction

We recorded the following characteristics in the identified studies: first author, publication year, cohort name, country, duration of follow-up, method of assessment of fruit and vegetable consumption as well as lung cancer, participants' age, number of cases, sample size, RR (95% CI) for the highest versus lowest fruit and vegetable consumption, and adjusted covariates. In dose–response analysis, the number of cases and participants or person-years and RR (95% CI) for each category of fruit and vegetable consumption were also extracted. We assigned the median consumption in each category of fruit and vegetable consumption to the corresponding RR estimate. If upper boundary of the highest category was open ended, we assumed that the boundary had the same amplitude as the adjacent category. The study selection and the data extraction were conducted by two authors independently.

2.3. Statistical analysis

A random effects model was adopted to combine study-specific logarithms of RR (95% CI), using the inverse variance weighted method. The heterogeneity across studies was assessed by I2 statistic, and I2 values of 25%, 50%, and 75% represent low, moderate, and high heterogeneity [18], respectively. Subgroup analysis and meta-regression were conducted to explore potential sources of heterogeneity, and a permutation test of 1000 was used to control spurious findings in meta-regression. A sensitivity analysis was conducted in which 1 study at a time was removed and the rest analyzed to evaluate whether the results could have been affected markedly by a single study. Publication bias was evaluated with Egger regression test. Study quality was assessed using the 9-star Newcastle–Ottawa scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp, accessed 12/21/2014).

The dose–response relationship was estimated by using a 2-stage random-effect dose–response meta-analysis [19]. We first estimated a restricted cubic spline model using a generalized least squares regression, with 3 knots at percentiles 25%, 50%, and 75% of the distribution of fruit and vegetable consumption, and then the 2 regression coefficients (3 knots minus 1) and the variance/covariance matrix within each study were combined in a multivariate random-effects meta-analysis using the restricted maximum likelihood method [20]. The average serving was calculated as 80 g. A P value for non-linearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to 0. Stata 12.0 was used, and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Literature search and study characteristics

The flow chart for study inclusion is shown in supplementary Fig. 1. A total of 20 articles were included in this meta-analysis. For fruit and vegetable (FV), 10 results from 8 articles [11–13,15,21–24] were included involving 12,942 cases among 1,571,494 subjects, because 2 results (men and women) were available in 2 articles [12,21]. For fruit, 20 results from 16 articles [11–13,15,21,23–33] were included involving 15,421 cases among 1,791,469 subjects, because 4 results (men and women) were available in 4 articles [12,21,31,32]. For vegetable, 24 results from 19 articles [11–16,21,23–34] were included involving 16,422 cases among 1,877,375 subjects, because 5 results (men and women) were available in 5 articles [12,21,30–32]. Among the 20 studies, 7 were conducted in USA, 4 in Europe, 8 in Asia (Japan and China), and 1 study is a pooled analysis including 8 cohorts [11].

The follow-up duration ranged from 5.5 to 25 years. Dietary information were assessed by self-administrated food frequency questionnaire (FFQ) in 13 studies, and by interview in the other 7 studies. Results from 17 articles adjusted for smoking. All included studies met the quality score of 5–8 stars, and the main quality issues involved self-report of FV consumption, follow-up duration of less than 10 years and failure to report the rate of loss to follow-up or the effect of loss to follow-up to the result. Detailed information of included studies are shown in supplementary Table 1.

3.2. Quantitative synthesis

The main results are summarized in Table 1.

3.2.1. FV consumption and risk of lung cancer

Highest versus lowest levels of FV consumption were inversely associated with the risk of lung cancer: 0.87 (0.79–0.95), I2 = 61.9% (Fig. 1). No publication bias was detected ($P = 0.18$, supplementary Fig. 2). Sensitivity analysis showed that the overall pooled estimate did not vary substantially with the exclusion of any one study.

For dose–response analysis, because the pooled analysis including 8 cohorts [11] did not provide the information for a dose–response analysis, 2 separate cohort studies [35,36] were included. A total of 4 studies [12,24,35,36] were included in this dose–response analysis, including 8502 cases. Although the departure from a linear relationship was not significant (P for non-linearity = 0.42), the risk of lung cancer decreased slowly after 4 servings/day of FV. The risk of lung cancer was 0.97 (0.95–0.99), 0.94 (0.90–0.98), 0.91 (0.87–0.97), 0.89 (0.84–0.95), 0.88 (0.82–0.94) and 0.87 (0.80–0.95) for 1, 2, 3, 4, 5 and 6 servings/day of FV consumption, respectively, and the risk of lung cancer decreased by 3% [0.97 (0.93–1.00), $P = 0.07$] for every 1 serving/day increment in FV consumption (Fig. 2).

3.2.2. Fruit consumption and risk of lung cancer

Highest versus lowest levels of fruit consumption were inversely associated with the risk of lung cancer: 0.84 (0.79–0.90), I2 = 21.1% (Fig. 3). No publication bias was detected ($P = 0.15$, supplementary Fig 2). Sensitivity analysis showed that the overall pooled estimate did not vary substantially with the exclusion of any one study.

For dose–response analysis, because the pooled analysis including 8 cohorts [11] did not provide the information for a dose–response analysis, 2 separate cohort studies [35,36] were included. A total of 8 studies [12,24,25,27–29,35,36] were included in this dose–response analysis, including 10,155 cases. The departure from a linear relationship was significant (P for non-linearity = 0.03), and the risk of lung cancer did not decrease further after 2 servings/day of fruit. The risk of lung cancer was 0.96