Association about dietary vitamin C intake on the risk of ovarian cancer: A meta-analysis

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Abstract

Background: Changes in dietary vitamin C intake have been related to the risks of various cancers. However, the association between dietary vitamin C intake and the risk of ovarian cancer has not been fully determined. A meta-analysis was performed to evaluate the relationship between vitamin C intake and ovarian cancer risk. Methods: Observational studies that evaluated the association between vitamin C intake and ovarian cancer risk were identified via systematic search of PubMed and Embase databases. A random effect model was used to combine relative risk (RR) with corresponding 95% confidence intervals (CI). Results: Sixteen studies (5 cohort studies and 11 case-control studies) with 4,553 cases and 439,741 participants were included. Pooled results showed that dietary vitamin C intake had non-significant association on the risk of ovarian cancer (RR=0.95, 95%CI=0.81-1.11, I² = 52.1%, P for heterogeneity= 0.008). Subgroup analyses according to characteristics including geographic location and study design showed consistent results with the overall result. Conclusions: In summary, findings from this study indicated that dietary vitamin C intake is not associated with the risk of ovarian cancer.

Introduction

According to Globocan’s estimate in 2018, cancer is the second leading cause of death worldwide, with an estimated 9.6 million deaths [1]. Ovarian cancer is still the most deadly gynecologic malignancy [2]. Meanwhile, it is also the leading cause of cancer-related death in women [2,2]. Previous paper estimated that there were 22440 new cases and 14080 deaths of ovarian cancer in 2017 [2]. Therefore, primary prevention of ovarian cancer is necessary. Although ovarian
Cancer is confirmed to be associated with many genetic factors [1, 4]. Some dietary factors may also affect the development and risk of ovarian cancer. Dietary vitamin C intake has been linked to many cancers, such as pancreatic cancer [5, 6], cervical neoplasia [7], renal cell carcinoma [8], esophageal cancer [9], prostate cancer [10], and so on. However, no comprehensive meta-analysis was performed to explore the relationship about vitamin C intake on the risk of ovarian cancer recently. Up to now, several studies have investigated the effectiveness of dietary vitamin C intake on the risk of ovarian cancer, and these results should be re-evaluated to provide robust pooled results. Therefore, the current meta-analysis of available observational studies was conducted to determine the role of vitamin C intake on the risk of ovarian cancer.

Materials And Methods

Data Sources, Search Strategy, and Selection Criteria

This study was performed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement issued in 2009 [12]. Electronic searches for relevant studies about vitamin C intake and the risk of ovarian cancer were conducted of PubMed and Embase from their inception to May 31th, 2019. The search terms included ‘vitamin C’ OR ‘vatmin*’ combined with ‘ovarian cancer’
OR ‘ovarian tumor’. We manually searched the reference lists of the retrieved studies to identify any other eligible papers.

Two authors independently conducted the literature search and selected the studies by reading the titles, abstracts, and full-text articles, and any disagreement was resolved by an additional author until consensus was reached.

Studies were included if they met the following criteria: (1) Patients: patients diagnosed with ovarian cancer and ≥18 years of age; (2) Study design: all the observational studies were acceptable; (3) Interested and outcomes: the studies should assess the association about dietary vitamin C intake on the risk of ovarian cancer; (4) Data: the study should provide the available data of relative risk (RR) and 95% confidence intervals (CI).

Furthermore, we only included studies which explore the relationship about dietary vitamin C intake only, but not vitamin C supplement, on the risk of ovarian cancer.

Data Collection

One author conducted the data collection according to a standard flowchart, while another author checked it. If any disagreement was detected, they discussed the issue until consensus was reached. The data collected included the family name of the first author, publication year, country, cases and participants, age, category of vitamin C intake, the value of RR and 95%CI, adjustment for factors.

Statistical Analysis

The combined RR and 95%CI was pooled using STATA software (version 10.0, College Station, TX, USA) with a random-effects model [13]. Heterogeneity among the included studies was calculated using I-square and P values for Q statistic, and significant heterogeneity was defined as an I-square >50.0% or P <0.10 [13].
The robustness of the pooled results was measured using a sensitivity analysis by sequential exclusion of individual trials. Funnel plot [16] and Egger test [17] were used to evaluate potential publication bias. The inspection levels for all pooled results were 0.05.

Results

Literature Search

The initial electronic searches produced 243 articles and one article was identified from the reference of reviews; of them, 205 were excluded due to irrelevant topics and duplication. The remaining 39 full articles were reviewed; of them, 16 articles [18-32] involving 4,553 cases and 437,689 participants were included in the final analysis. Fourteen of the included studies come from North America, one from Europe and one from Asia. Five of the 16 articles were cohort design and the remaining 11 articles were case-control design. Table 1 summarizes the general characteristics of the patients and studies.

Dietary vitamin C intake and ovarian cancer risk

Pooled RR suggested that highest category of dietary vitamin C intake was not associated with the risk of ovarian cancer (RR= 0.95, 95%CI= 0.81-1.11, $I^2= 52.1\%$, $P_{\text{for heterogeneity}}= 0.008$) (Figure 2), when compared with the lowest category. As seen in Figure 2, the association was not significant between dietary vitamin C intake and ovarian cancer risk in North America populations (RR= 1.02, 95%CI= 0.90-1.15, $I^2= 2.0\%$, $P_{\text{for}}$)
Subgroup analysis by study design got a consistent result both in case-control studies (RR = 0.86, 95% CI = 0.71-1.04, $I^2 = 51.8\%$, $P_{\text{for heterogeneity}} = 0.023$) and in cohort studies (RR = 1.15, 95% CI = 0.93-1.42, $I^2 = 20.2\%$, $P_{\text{for heterogeneity}} = 0.286$).

**Publication bias and sensitivity analysis**

The funnel plots were symmetry on visual inspection (Figure 3). Results of Egger’s regression tests also did not indicate significant publication biases ($P = 0.790$). Sensitivity analysis showed that no single study had a potential influence on the pooled result (Figure 4).

**Discussion**

In the current meta-analysis of 16 studies with 4,553 cases and 437,689 participants, we found that the highest category compared to the lowest category of dietary vitamin C intake had no significant association on the risk of ovarian cancer. Moreover, by pooling the subgroup results of geographic locations and study design, we got consistent results with the overall result.

Significant heterogeneity ($I^2 = 52.1\%$, $P_{\text{for heterogeneity}} = 0.008$) was found in the overall result about vitamin C intake on the risk of ovarian cancer. As far as we know, between-study heterogeneity is common in a meta-analysis, and it is an essential part to explore the sources of heterogeneity. We used meta-regression to explore the causes of heterogeneity for covariates of publication year, study design, geographic locations and number of cases. We found that geographic locations ($P = 0.017$) may be a covariate that could influence this high heterogeneity. As seen in figure 2, when we did the hierarchical analysis by geographic locations, the heterogeneity in North America was very low ($I^2 = $...
2.0%, $P_{\text{for heterogeneity}} = 0.427$). The $I^2$ in Europe and Asia was not detected due to only one study in each group. Even though, the result in North American populations was consistent with the overall result.

Although dietary vitamin C intake which is one of antioxidants had some potential role on preventing of cancers [6, 7, 8].

Due to inactivating free radicals and reducing oxidative DNA damage, we did not obtain an inverse association between dietary vitamin C intake and ovarian cancer. In our included studies, almost all researches got a non-significant relationship about vitamin C intake on the risk of ovarian cancer. The study by Chang et al. [30] indicated that dietary vitamin C intake ($>665$ mg/day vs. $\leq 75$ mg/day) could significantly increase the risk of ovarian cancer. The value of highest category ($>665$ mg/day) was more than that in any other included studies. Otherwise, Zhang et al. [27] suggested that dietary vitamin C intake ($\geq 140.25$ mg/day vs. $\leq 66.50$ mg/day) had a lower development on ovarian cancer risk. To our attention, the value of highest category ($\geq 140.25$ mg/day) was almost the lowest among all studies. Therefore, the current evidence showed that large amount of dietary vitamin C could not reduce the risk of ovarian cancer, and there may be harm.

Our study has limitations which should be considered in interpreting the results. Firstly, significant heterogeneity was detected among all the included studies, but it can be successfully explain by a covariate of geographic location. The association was not changed in North America populations. Secondly, only the subgroup analyses by geographic locations and study design were performed due to the limitation information
provided in each individual study. Thirdly, as a meta-analysis of observational studies, although all the included studies were adjusted for age, some related factors such as body mass index (BMI), total energy intake, duration of oral contraception use, and so on was not fully adjusted in every study. Fourth, almost all the included studies come from North America; therefore, more studies conducted in other populations are warranted to further explore the association between geographic locations and ovarian cancer risk. Finally, since we did not get a positive association between dietary vitamin C intake and the risk of ovarian cancer, the dose-response analysis between them was not performed.

Conclusions

In summary, findings from this study indicated that dietary vitamin C intake is not associated with the risk of ovarian cancer. Further large-scale cohort should be conducted to explore the effect of dietary vitamin C intake on the risk of ovarian cancer due to some limitations existed in our research.

Abbreviations

RR: relative risk; CI: confidence interval; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Declarations

Authors' contributions: YHL, HF and SMX participated in the design of the study, acquisition of data; JZW performed the statistical analysis; YHL and LHY draft the manuscript; ZJS reviewed and revised the manuscript. All authors read and approved the final manuscript.

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the current study are available in the manuscript.

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References

1. Globocan, Estimated cancer incidence, mortality and prevalence worldwide in 2018, International Agency for research on cancer WHO, 2018.

2. Siegel RL, Miller KD, Jemal A: Cancer Statistics, 2017. CA: a cancer journal for clinicians 2017, 67(1):7-30.

3. Rooth C: Ovarian cancer: risk factors, treatment and management. British journal of nursing 2013, 22(17):S23-30.

4. Chen H, Zhu J: Vitamin D receptor rs2228570 polymorphism and susceptibility to ovarian cancer: An updated meta-analysis. The journal of obstetrics and gynaecology research 2018, 44(3):556-565.

5. Zhao L, Li J, Liu M, Zhou H, Zou H, Wei Y, Sun K, Li G, Li S, Pang L: The clinicopathological parameters significance of CD133 and Nestin in epithelial ovarian cancer: a meta-analysis. Future oncology 2017, 13(28):2555-2570.

6. Hua YF, Wang GQ, Jiang W, Huang J, Chen GC, Lu CD: Vitamin C Intake and Pancreatic Cancer Risk: A Meta-Analysis of Published Case-Control and Cohort Studies. PloS one 2016, 11(2):e0148816.

7. Chen J, Jiang W, Shao L, Zhong D, Wu Y, Cai J: Association between intake of antioxidants and pancreatic cancer risk: a meta-analysis. International journal of food sciences and nutrition 2016, 67(7):744-753.

8. Cao D, Shen K, Li Z, Xu Y, Wu D: Association between vitamin C Intake and the risk of
cervical neoplasia: A meta-analysis. *Nutrition and cancer* 2016, 68(1):48-57.

9. Jia L, Jia Q, Shang Y, Dong X, Li L: Vitamin C intake and risk of renal cell carcinoma: a meta-analysis. *Scientific reports* 2015, 5:17921.

10. Bo Y, Lu Y, Zhao Y, Zhao E, Yuan L, Lu W, Cui L, Lu Q: Association between dietary vitamin C intake and risk of esophageal cancer: A dose-response meta-analysis. *International journal of cancer* 2016, 138(8):1843-1850.

11. Bai XY, Qu X, Jiang X, Xu Z, Yang Y, Su Q, Wang M, Wu H: Association between Dietary Vitamin C Intake and Risk of Prostate Cancer: A Meta-analysis Involving 103,658 Subjects. *Journal of Cancer* 2015, 6(9):913-921.

12. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine* 2009, 6(7):e1000097.

13. DerSimonian R, Laird N: Meta-analysis in clinical trials. *Controlled clinical trials* 1986, 7(3):177-188.

14. Higgins JP, Thompson SG, Deeks JJ, Altman DG: Measuring inconsistency in meta-analyses. *Bmj* 2003, 327(7414):557-560.

15. Higgins JP, Thompson SG: Controlling the risk of spurious findings from meta-regression. *Statistics in medicine* 2004, 23(11):1663-1682.

16. Begg CB, Mazumdar M: Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994, 50(4):1088-1101.

17. Egger M, Davey Smith G, Schneider M, Minder C: Bias in meta-analysis detected by a simple, graphical test. *Bmj* 1997, 315(7109):629-634.

18. Slattery ML, Schuman KL, West DW, French TK, Robison LM: Nutrient intake and ovarian cancer. *American journal of epidemiology* 1989, 130(3):497-502.

19. Tzonou A, Hsieh CC, Polychronopoulou A, Kaprinis G, Toupadaki N, Trichopoulou A,
Karakatsani A, Trichopoulos D: Diet and ovarian cancer: a case-control study in Greece. *International journal of cancer* 1993, 55(3):411-414.

20. Kushi LH, Mink PJ, Folsom AR, Anderson KE, Zheng W, Lazovich D, Sellers TA: Prospective study of diet and ovarian cancer. *American journal of epidemiology* 1999, 149(1):21-31.

21. Cramer DW, Kuper H, Harlow BL, Titus-Ernstoff L: Carotenoids, antioxidants and ovarian cancer risk in pre- and postmenopausal women. *International journal of cancer* 2001, 94(1):128-134.

22. Fairfield KM, Hankinson SE, Rosner BA, Hunter DJ, Colditz GA, Willett WC: Risk of ovarian carcinoma and consumption of vitamins A, C, and E and specific carotenoids: a prospective analysis. *Cancer* 2001, 92(9):2318-2326.

23. Fleischauer AT, Olson SH, Mignone L, Simonsen N, Caputo TA, Harlap S: Dietary antioxidants, supplements, and risk of epithelial ovarian cancer. *Nutrition and cancer* 2001, 40(2):92-98.

24. McCann SE, Moysich KB, Mettlin C: Intakes of selected nutrients and food groups and risk of ovarian cancer. *Nutrition and cancer* 2001, 39(1):19-28.

25. Salazar-Martinez E, Lazcano-Ponce EC, Gonzalez Lira-Lira G, Escudero-De los Rios P, Hernandez-Avila M: Nutritional determinants of epithelial ovarian cancer risk: a case-control study in Mexico. *Oncology* 2002, 63(2):151-157.

26. McCann SE, Freudenheim JL, Marshall JR, Graham S: Risk of human ovarian cancer is related to dietary intake of selected nutrients, phytochemicals and food groups. *The Journal of nutrition* 2003, 133(6):1937-1942.

27. Zhang M, Lee AH, Binns CW: Reproductive and dietary risk factors for epithelial ovarian cancer in China. *Gynecologic oncology* 2004, 92(1):320-326.

28. Tung KH, Wilkens LR, Wu AH, McDuffie K, Hankin JH, Nomura AM, Kolonel LN, Goodman
MT: Association of dietary vitamin A, carotenoids, and other antioxidants with the risk of ovarian cancer. *Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2005, 14(3):669-676.

29. Silvera SA, Jain M, Howe GR, Miller AB, Rohan TE: Carotenoid, vitamin A, vitamin C, and vitamin E intake and risk of ovarian cancer: a prospective cohort study. *Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2006, 15(2):395-397.

30. Chang ET, Lee VS, Canchola AJ, Clarke CA, Purdie DM, Reynolds P, Anton-Culver H, Bernstein L, Deapen D, Peel D et al: Diet and risk of ovarian cancer in the California Teachers Study cohort. *American journal of epidemiology* 2007, 165(7):802-813.

31. Gifkins D, Olson SH, Paddock L, King M, Demissie K, Lu SE, Kong AN, Rodriguez-Rodriguez L, Bandera EV: Total and individual antioxidant intake and risk of epithelial ovarian cancer. *BMC cancer* 2012, 12:211.

32. Terry PD, Qin B, Camacho F, Moorman PG, Alberg AJ, Barnholtz-Sloan JS, Bondy M, Cote ML, Funkhouser E, Guertin KA et al: Supplemental Selenium May Decrease Ovarian Cancer Risk in African-American Women. *The Journal of nutrition* 2017, 147(4):621-627.

Tables

Table 1 Characteristics of the included studies about vitamin C intake on ovarian cancer risk.
| Study, year | Design | Age | Participants, Cases | Country | Category | RR (95%CI) |
|-------------|--------|-----|---------------------|---------|----------|------------|
| Slattery et al., 1989 | PBCC | 20-79 | 577, 85 | United States | >159.1 vs. <97.8 mg/d | 0.70(0.3-1.4) |
| Tzonou et al., 1993 | HBCC | 18-75 | 389, 189 | Greece | Highest vs. lowest | 0.90(0.76-1) |
| Kushi et al., 1999 | Cohort | 55-69 | 29,083, 139 | United States | >321.9 vs. <129.2 mg/d | 1.05(0.63-1) |
| Cramer et al., 2001 | PBCC | >50 | 1,065, 549 | United States | >337 vs. ≤97 mg/d | 1.00(0.66-1) |
| Fairfield et al., 2001 | Cohort | 30-55 | 80,326, 301 | United States | Q5 vs. Q1 | 1.22(0.83-1) |
| Fleischauer et al., 2001 | HBCC | ≥18 | 419, 168 | United States | >180 vs. <100 mg/d | 1.04(0.57-1) |
| McCann et al., 2001 | HBCC | 20-87 | 1,921, 496 | United States | >250 vs. ≤112 mg/d | 0.69(0.47-1) |
| Salazar-Martinez et al., 2002 | HBCC | 20-79 | 713, 84 | Mexico | ≥184 vs. ≤78 mg/d | 1.28(0.72-2) |
| McCann et al., 2003 | PBCC | 40-85 | 820, 124 | United States | >244 vs. ≤123 mg/d | 0.82(0.42-1) |
| Zhang et al., 2004 | HBCC | 18-75 | 906, 254 | China | ≥140.25 vs. ≤66.50 mg/d | 0.31(0.18-0) |
| Tung et al., 2005 | PBCC | 45-75 | 1,165, 558 | United States | Q4 vs. Q1 | 0.89(0.62-1) |
| Silvera et al., 2006 | Cohort | 40-59 | 89,835, 264 | Canada | >206 vs. ≤115 mg/d | 0.90(0.58-1) |
| Chang et al., 2007 | Cohort | <84 | 97,275, 280 | United States | >665 vs. ≤75 mg/d | 1.96(1.11-3) |
| Thomson et al., 2008 | Cohort | 50-79 | 133,614, 451 | United States | >130 vs. ≤58 mg/d | 1.07(0.77-1) |
| Gifkins et al., 2012 | PBCC | >21 | 595, 205 | United States | >141.8 vs. ≤82.3 mg/d | 1.29(0.72-2) |
| Terry et al., 2017 | PBCC | 20-79 | 1,038, 406 | United States | >142.1 vs. ≤57.0 mg/d | 1.05(0.66-1) |

Abbreviations: RR: relative risk; CI: Confidence Intervals; PBCC: Population-based case-control study; HBCC: Hospital-based case-control study.

Figures
Figure 1

The flow diagram of screened, excluded, and analyzed publications.
Figure 2

The forest plot between dietary vitamin C intake and ovarian cancer risk hierarchical analysis by geographic locations.
Begg's funnel plot for publication bias of vitamin C intake and ovarian cancer risk.

Figure 3
Figure 4

Sensitivity analysis about vitamin C intake on the risk of ovarian cancer