Arch Iran Med. June 2019;22(6):328-335

http www.aimjournal.ir

ARCHIVES OF IRANIAN MEDICINE

Open Access

Systematic Review

Dietary Total Antioxidant Capacity and Risk of Gastrointestinal Cancers: A Systematic Review and Meta-analysis of Observational Studies

Behzad Zamani, MSc[1,2]; Elnaz Daneshzad, PhD[1]; Leila Azadbakht, PhD[1,3,4*]

[1]Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran
[2]Students' Scientific Research Center (SSRC), Tehran University of Medical Sciences (TUMS), Tehran, Iran
[3]Diabetes Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran
[4]Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Background: Gastrointestinal (GI) cancers are common types of cancers. Among different factors that affect the etiology of GI cancers, diet has an important contribution. Dietary antioxidants decrease oxidative stress which plays a pivotal role in carcinogenesis. Several studies assessed the relation between dietary total antioxidant capacity (TAC) and risk of GI cancers. Dietary TAC was measured by three indices including FRAP (ferric ion reducing antioxidant power), TRAP (total radical-trapping antioxidant parameter), and TEAC (trolox equivalent antioxidant capacity). We performed a systematic review and meta-analysis of published studies to determine the association between dietary TAC and GI cancers risk.

Methods: Eligible studies were selected from PubMed, ISI Web of Science and Scopus databases from inception until May 2018. Case-control and cohort studies that reported GI cancer risk estimates for dietary TAC were included. We ignored the distinction between case-control and cohort studies. We applied random-effects to estimate pooled relative risks. Subgroup analysis was done based on study design.

Results: Among the seven observational studies that were included, four were cohort studies and three were case-control studies. Dietary FRAP, TRAP, and TEAC reduced GI cancer risk: FRAP; 0.71; 95% CI: 0.58–0.85, TRAP; 0.65; 95% CI: 0.57–0.75, TEAC; 0.70; 95% CI: 0.59–0.83, respectively.

Conclusion: This study indicated that dietary TAC significantly decreased the risk of GI cancers. Nevertheless, further prospective studies are required to clarify the association between dietary TAC and risk of GI cancers.

Keywords: Cancer risk, Dietary total antioxidant capacity, FRAP, Gastrointestinal cancers, TEAC, TRAP

Cite this article as: Zamani B, Daneshzad E, Azadbakht L. Dietary total antioxidant capacity and risk of gastrointestinal cancers: a systematic review and meta-analysis of observational studies. Arch Iran Med. 2019;22(6):328–335.

Received: August 2, 2018, Accepted: April 7, 2019, ePublished: June 1, 2019

Introduction

Cancer has been a serious problem in public health.[1] It is counted as the second cause of mortality in the world and the third one in Iran. Almost 17.5 million individuals were diagnosed with cancer and 8.7 million died of these lethal diseases in 2015.[2,3] The cancer incidence rate is increasing in developing countries and its outbreak is predicted to double by 2030.[1] Among different types of cancers, GI cancers have been considered to be one of the common types.[4] Inherited and environmental factors have a significant contribution to the pathogenesis of cancers.[5] Among environmental factors, diet has an important role in the etiology of GI cancers.[6]

Some studies showed that high consumption of red meat and fat is associated with the increased risk of GI cancers.[7,8] While fruit and vegetable intake could reduce the risk of GI cancers.[9] A western diet which is identified by high consumption of fat, meat, and low fiber intake enhances colorectal cancer risk.[10] Mediterranean diet has an inverse association with GI cancer risk, which may be due to the antioxidant-rich plant foods of this diet.[11,12] A meta-analysis indicated that soy intake, as a rich antioxidant food, decreases the risk of digestive tract cancers.[13] Some components existing in fruits, vegetables, and other plant foods have antioxidant properties. These bioactive compounds inhibit reactive oxygen species (ROS) and reduce oxidative stress.[14,15] Oxidative stress elevates carcinogenesis and can induce GI cancer. The digestive tract is the main site in which antioxidants are most active because carotenoids and flavonoids have lower absorption compare with some antioxidants such as vitamin C and E, consequently concentration of these antioxidants increase in GI tract.[16-18]

Plant foods comprise different antioxidants. It is best to consider all antioxidants existing in a diet together, because of their synergistic and cooperative effects. Dietary

***Corresponding Author:** Leila Azadbakht, PhD; Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, P. O. Box: 1416643931, Tehran Iran. Tel: +98/218/895 556, Fax: +98/218/8984 861, Email: azadbakhtleila@gmail.com

total antioxidant capacity (TAC) considers the entire antioxidants of the diet.[19,20] Studies showed significant relations between Dietary TAC and plasma TAC.[21] To calculate dietary TAC, several assays were used, which include Trolox equivalent antioxidant capacity (TEAC) ,which measures the ability of antioxidant molecules to quench the long-lived $ABTS^{+}$ compared to that of 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, Trolox, the total radical-trapping antioxidant parameter (TRAP) which measures the protection provided by antioxidants on the fluorescence decay of R-phycoerythrin (lag-phase) during a controlled peroxidation reaction and ferric ion reducing antioxidant power (FRAP) which measures in vitro the reduction of the Fe^{3+} (ferric ion) to Fe2+ (ferrous ion) in the presence of antioxidants.[22] Many studies have concluded that dietary TAC has a positive effect on the reduction of GI cancer risk. On the other hand, some studies have not found a significant association between dietary TAC and them.

Several observational studies evaluated relations between dietary TAC and different GI cancers. Because of inconsistent results, we performed a meta-analysis to determine the role of dietary TAC in GI cancer risk. The PICOS eligibility criteria were applied. Adults, with or without GI cancers, were compared based on highest vs. lowest ntiles of DTAC among cohort and case-control studies.

Materials and Methods

We conducted a systematic review and meta-analysis of observational (cohort and case-control) studies that evaluated the association between dietary TAC and gastrointestinal (GI) cancers. The methodology of preferred reporting items for systematic reviews and meta-analyses (PRISMA) were used for this study (Table 1).[23]

Search Strategy

We identified studies by searching in PubMed, ISI Web of Science and Scopus databases. The following terms were applied: ("Dietary total antioxidant capacity" OR "Dietary TAC" OR "Non enzymatic antioxidant capacity") AND ("gastrointestinal cancers" OR "esophageal cancer" OR "gastric cancer" OR "colorectal cancer" OR "pancreatic cancer" OR "liver cancer") from inception to May 2018. Language limitation was not exerted. We also checked the cited references of the retrieved articles to find potentially eligible studies.

Study Selection

Only studies were included that had prospective cohort and case-control study design, determined dietary TAC score, related to GI cancers and report risk estimates (relative risk, odds ratios, or hazard ratio) with 95% CIs or must report sufficient information to estimate data. We excluded studies that had a clinical trial design, animal or *in vitro* studies and review papers. Studies that examined the effect of single antioxidants or antioxidants of a specific food on GI cancers risk were excluded. Also, the studies in which supplementary sources of antioxidants are considered as part of total antioxidant capacity (TAC) were not included.

Quality Assessment

For quality assessment of included studies, Newcastle–Ottawa Scale (NOS) was used. This assessment tool uses for observational studies such as case-control and cohort studies. NOS score is between zero to nine.[24] A study with 6 scores or more is considered a high-quality study.[25]

Data Extraction

Two investigators (BZ and ED) extracted data, which was checked by one other (LA). We extracted the following information from each study: first authors name, years of publication, follow up period (if study was prospective cohort), design of the study, mean or range of age, gender, food intake evaluation tool and assay used, cancer site and risk estimates(relative risk, odds ratios, or hazard ratio).

Statistical Analysis

We ignored the distinction between case-control and cohort studies.[26] For this meta-analysis, we used hazard ratios (HR), relative risks (RR) and odds ratio (OR) of GI risks according to highest ntiles of dietary TAC assays compared to lowest ntiles in cohort and case-control studies. We used a random effects model because of variation between included studies. Heterogeneity between studies was assessed using I-squared tests (significant by $P < 0.1$). Formal statistical assessment of publication bias was done with Egger's test. All statistical analyses were performed using STATA, version 12. $P < 0.05$ was considered statistically significant.

Results

Study Characteristics

A total of 1852 studies were identified after a primary search. After deleting 346 duplicates, 1507 studies remained. We assessed title and if needed the abstract of the studies. In this step, 1209 irrelevant, 30 clinical trials, 126 animal, and 135 review studies were excluded. Eventually, seven studies were included in the systematic review and meta-analysis (Figure 1).[27-33] Of the seven studies, four were prospective cohort[27,30,32,33] and three were case-control.[28,29,31] All the studies were published between 2010 and 2016. All included studies were conducted in both male and female[28-33] except one that was conducted in male.[27] Six studies were from Europe[28-33] (4 from Italy and 2 from 10 European countries including Denmark, France, Germany, Greece, Italy, the Netherlands, Norway,

Table 1. Characteristics of Observational Studies Eligible in the Systematic Review and Meta-analysis

Code	Author (y)/Country	Study Design	Sample Size and Gender	Age Range (y)	Follow-up Period	Assay Used	Quality Assessment	Effect Size	Cancer Site	Adjusted Variables
1	Praud et al (2015) / Italy	Case-control	Case=230 Control=547 (male and female)	22–80	—	TEAC TRAP FRAP	8	OR	Gastric	Sex, age, year of interview, education, BMI, family history, smoking, total energy intake
2	Serafini et al (2011)/ Europe	Cohort	521457 (male and female)	35–70	14	TRAP FRAP	9	HR	Gastric	Sex, educational level, BMI, red meat intake and total energy intake
3	Mekary et al (2010)/USA	Cohort	47339 (men)	40–75	18	FRAP	7	RR	Colorectal	Age, aspirin use, family history of colorectal cancer, history of the previous endoscopy, supplement use containing antioxidants, BMI, energy intake, alcohol intake, physical activity, red meat consumption, total calcium intake, dietary folate intake, dietary vitamin D intake, smoking, and race
4	Vece MM et al (2015)/ Italy	Cohort	45194 (male and female)	35–70	15	TEAC	9	HR	Colorectal	Age, sex, study center, BMI, height, smoking status, education and total physical activity, intakes of alcohol, non-alcohol energy intake, red meat, processed meat, calcium, and dietary fiber
5	La Vecchia et al (2013)/ Italy	Case-control	Case=1953 Control=4154 (male and female)	19–74	—	TEAC TRAP FRAP	8	OR	Colorectal	Sex, age, study center, education, alcohol consumption, BMI, family history, physical activity, TAC from coffee, and energy intake
6	Lucas AL et al (2016)/Italy	Case-control	Case=326 Control=652 (male and female)	34–80	—	TEAC TRAP FRAP	8	OR	Pancreatic	Study center, sex, age, year of interview, education, BMI, tobacco smoking, alcohol intake, diabetes, and energy intake
7	Zamora-Ros et al (2013)/ Europe	Cohort	477206 (male and female)	35–70	19	FRAP TRAP	9	HR	Liver	Study center, sex, age, total energy, educational level, smoke intensity, alcohol lifetime and alcohol baseline, BMI, self-reported diabetes at baseline, physical activity, fiber intake

TEAC, Trolox equivalent antioxidant capacity; TRAP, Trolox, the total radical-trapping antioxidant parameter; FRAP, ferric ion reducing antioxidant power; OR, odds ratio; HR, hazard ratio; RR, relative risk

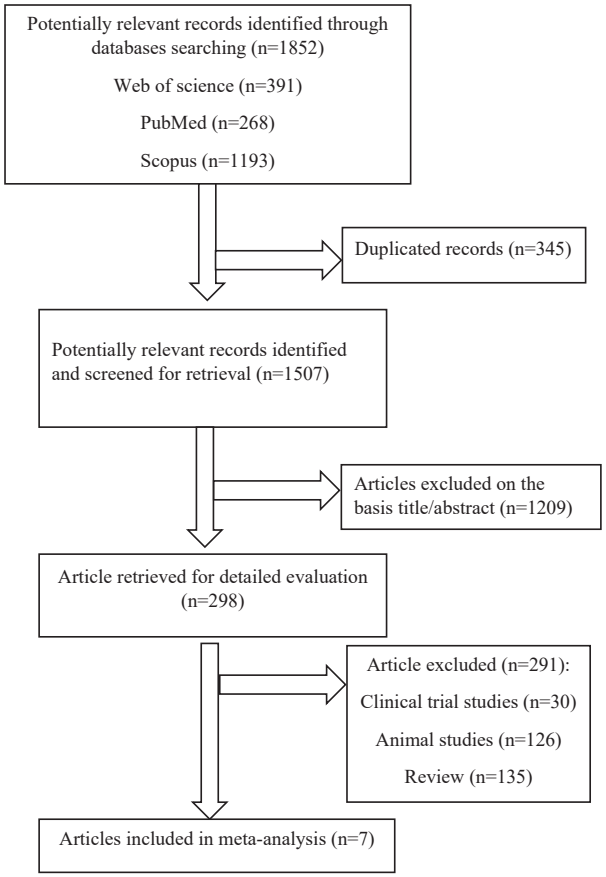

Figure 1. Flow Diagram of Study Selection.

Spain, Sweden, and the United Kingdom) and one other was from the United States.[27] To evaluate dietary TAC of three case-control studies, three assays of FRAP, TRAP, and TEAC were applied.[28,29,31] Also, in cohort studies, two studies applied two assays (FRAP and TRAP),[30,33] one just applied FRAP[27] and one applied TEAC[32] to evaluate dietary TAC. The follow-up period of cohort studies varied from 14 to 19 years, sample size ranged from 45194 to 521457 and the participants ranged from 35to 70 years. In case-control studies, participants' age was between 19 to 80 years, a sample size of cases ranged from 230 to 1953 and control ranged from 547 to 4154. Included studies had a quality score of 7–9, which was high quality. Characteristics of the seven included studies in the meta-analysis are summarized in Table 1. A meta-analysis was performed in all seven included articles.

Meta-analysis

FRAP and Gastrointestinal Cancers Risk

Among seven studies that were included in this meta-analysis, six studies used dietary FRAP to measure dietary TAC that three of them were case-control and three others were a cohort. We conducted a subgroup analysis by the design of the study. Subgroup analysis for case-control studies indicated that FRAP associated significantly with low GI cancers risk (0.67; 95% CI: 0.57–0.79, P <0.001) and there was no significant heterogeneity between studies (I^2 = 0%, P = 0.952). Also, a meta-analysis of cohort studies indicated that there was no association between FRAP and GI cancers risk (0.72; 95% CI: 0.48–1.06; P = 0.098) and significant heterogeneity was observed in this subgroup (I^2 = 74.3%, P = 0.020). A forest plot of six datasets showed significant inverse association between FRAP and GI cancers risk (0.71; 95% CI: 0.58–0.85; P <0.001) and heterogeneity was significant (I^2 = 51.2%, P = 0.068) (Figure 2). There is no publication bias for FRAP (P = 0.375)

TRAP and Gastrointestinal Cancers Risk

Subgroup analysis was conducted based on the study design. Subgroup analysis for case-control studies indicated that TRAP have significant inverse relation with risk of GI cancers (0.68; 95% CI: 0.58–0.80; P < 0.001) and Significant heterogeneity was not evident (I^2 = 0.0%, P = 0.630). As well as, subgroup analysis for cohort studies depicted that there is an inverse association between TRAP and GI cancers risk (0.56; 95% CI: 0.43-0.75; P = <0.001) without heterogeneity (I^2 = 0.0%, P = 0.463). A forest plot of five datasets depicted significant inverse association between TRAP and GI cancers risk (0.65; 95% CI: 0.57–0.75; P = <0.001) and we did not observe significant heterogeneity in overall (I^2 = 0.0%, P = 0.588) (Figure 3). Publication bias did not exist for TRAP (P = 0.359).

TEAC and Gastrointestinal Cancers Risk

The effect of the TEAC on GI cancers risk was evaluated in four studies of which three were case-control and only one was a cohort. We conducted a subgroup analysis based on the study design. Subgroup analysis for three case-control studies indicated inverse association between TEAC and GI cancers risk (0.66; 95% CI: 0.56–0.78; $P \leq 0.001$) with no statistically significant heterogeneity (I^2 = 0.0%, P = 0.612). We cannot identify meta-analysis and heterogeneity for a cohort study in the TEAC assay because it was only a single study. A forest plot of four datasets depicted significant inverse association between TEAC and GI cancers risk (0.70; 95% CI: 0.59–0.83; P <0.001) with a minimum heterogeneity (I^2 = 18.2%, P = 0.300) (Figure 4). For TEAC, no publication bias existed (P = 0.665)

Discussion

The present meta-analysis showed that high dietary TAC was associated with decreased GI cancer risk. To the best of our knowledge, this article is the first systematic review and meta-analysis that examined the relationship between dietary TAC and GI cancer risk.

This meta-analysis of prospective cohort and case-control studies showed a more credible outcome than an

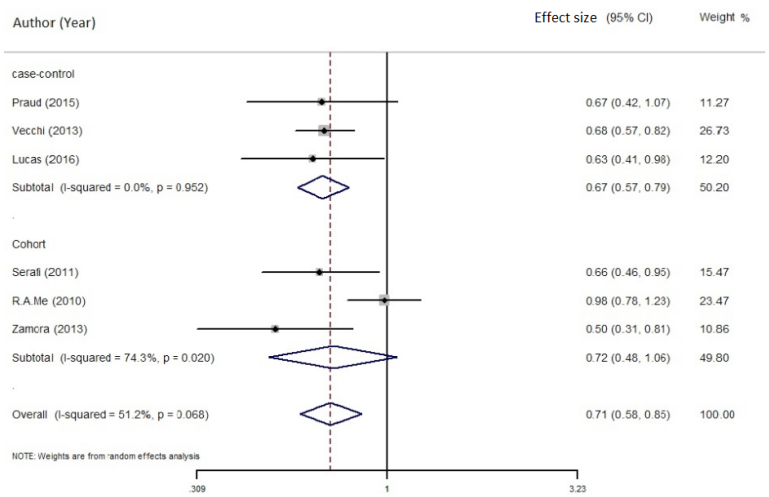

Figure 2. Forest Plot Showing Overall Association of FRAP with Gastrointestinal Cancers Risk and Subgroup Analysis Based on Study Design (Cohort and Case-Control Studies) Using Random Effects Model.

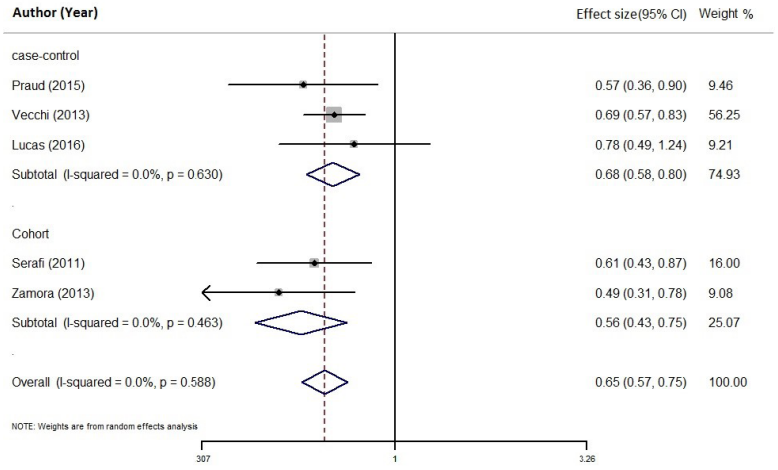

Figure 3. Forest Plot Showing Overall Association of TRAP with Gastrointestinal Cancers Risk and Subgroup Analysis Based on Study Design (Cohort and Case-Control Studies) Using Random Effects Model.

assessment of separate individual studies. As it has been shown in a meta-epidemiological study, no significant difference was reported regarding treatment effect estimates between case-control and cohort studies.[34] Besides, previous studies did not consider the differences between case-control and cohort studies as well.[35] Similar to the results of this meta-analysis, several studies have depicted inverse association between intake of dietary antioxidants and different cancers such as breast, endometrial, and prostate.[36-38] A review study by want et al indicated that the Mediterranean diet is related to decreasing of GI cancers risk.[11] A Mediterranean diet that is characterized by high consumption of fruits, vegetables, whole grains, nuts, legumes, and olive oil is high in antioxidants[39] and have a positive relationship with plasma TAC.[40] Other studies showed that intake of fruits, vegetables, coffee and tea which are important components of dietary antioxidants play a protective role against cancers of the digestive system.[9,41,42] Furthermore, multiple studies investigated the relation between dietary TAC and health outcomes, indicated an inverse association between dietary TAC and chronic diseases such as cancers, cardiovascular diseases, and metabolic syndrome.[43-45]

On the contrary, there are several studies that revealed inconsistent results. A meta-analysis of 14 randomized trials showed that not only antioxidant supplements did not decrease GI cancers risk but also apparently increased total mortality.[46] A randomized trial study depicted that high consumption of fruits and vegetables have not had relation with risk of colorectal cancer[47]; however, these findings may be due to people in intervention group over-reported the consumption of fruit and vegetables or other

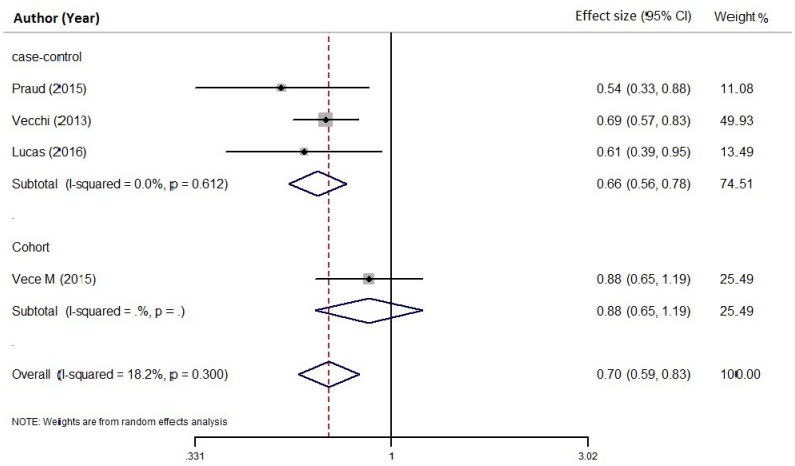

Figure 4. Forest Plot Showing Overall Association of TEAC with Gastrointestinal Cancers Risk and Subgroup Analysis Based on Study Design (Cohort and Case-Control Studies) Using a Random Effects Model.

dietary interventions were too low to result in a reduction of risk of recurrent adenomas.

There are several investigations that evaluated the association of single antioxidant and risk of cancers[48-50] but obviously, it is better to examine total antioxidants intake because of the synergistic interactions between different antioxidants which prevent carcinogenesis.[51] There are several methods to evaluate dietary TAC and each method may give a different score of dietary TAC.[52,53] The most common assays that are used to measure dietary TAC, include FRAP, TRAP, and TEAC.[43] Hence, studies included in this meta-analysis were analyzed based on dietary TAC assays.

In this meta-analysis, six of the studies have used FRAP assay, five studies used TRAP assay and four studies used TEAC assay to evaluate dietary TAC. Most studies used two or three of these methods. GI cancers risk was reduced in the highest vs. lowest ntiles of all three indices of FRAP, TRAP, and TEAC in these studies. Heterogeneity of TRAP and TEAC assays were not significant but the heterogeneity of FRAP assay was significant. When we conducted subgroup analysis based on the study design, heterogeneity of case-control studies was not significant but in the cohort studies, heterogeneity was significant that may relate to sample size, cancer site, and the difference in population. Because of the few numbers of studies in each subgroup, we could not characterize the source of heterogeneity. In most studies, the main contributors to dietary TAC were coffee, fruits, vegetables, and wine.

Oxidative stress that results from increased ROS production, induce DNA damage, gene mutation, and consequently carcinogenesis.[54-57] Dietary antioxidants are able to neutralize ROS, decrease DNA damage and consequently have a protective role against cancers.[58] Antioxidants have a more important role in GI cancers because the digestive tract is more accessible to ROS product.[18] Furthermore, Antioxidants play an important role in cell differentiation and DNA replication, prevent the function of phase I metabolic enzymes which may increase ROS product or activate phase II enzymes which eliminate residual toxic metabolites produced by the phase I enzymes.[59,60]

This meta-analysis has some strong points. All of the studies used a valid and reproducible food frequency questionnaire (FFQ) to evaluate food intake. In most studies, participants were from both gender except one that was from males. Four cohort studies included in this meta-analysis had a large sample size and long follow-up periods. Also, some limitations existed, such as all three indices applied for measurement of dietary TAC that does not measure *in vivo* antioxidant capacity and merely measures *in vitro* antioxidant capacity. TRAP and FRAP assays do not calculate lipophilic antioxidants that may underestimate dietary TAC. Despite controlling for various population demographic confounders, some of the included studies did not adjust for other components of diet such as fiber, calcium, folate, red and processed meat, and alcohol. Also, serum TAC was not considered as a confounder in included studies.

In conclusion, the results of this meta-analysis suggested that high dietary TAC is inversely associated with GI cancer risk. Further well-designed studies or randomized clinical trials can determine the relationship between DTAC and GI cancer risks.

Authors' Contribution

BZ designed and LA supervised the study. BZ, ED, and LA conducted the literature search, data extraction, and independent search and review. ED performed the statistical analyses and BZ prepared a first draft of the manuscript, and ED and LA finalized it.

Conflict of Interest Disclosures

The authors declare that they have no conflict of interest.

Ethical Statement

Not applicable.

Funding Source
This study was funded by the Tehran University of Medical Science, Tehran, Iran (Code: 9802-161-42370) and the National Elites Foundation in Iran (BN092) and Iran National Science Foundation.

References

1. Wiseman M. The second World Cancer Research Fund/ American Institute for Cancer Research expert report. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Proc Nutr Soc. 2008;67(3):253-6. doi: 10.1017/S002966510800712X.
2. Mousavi SM, Gouya MM, Ramazani R, Davanlou M, Hajsadeghi N, Seddighi Z. Cancer incidence and mortality in Iran. Ann Oncol. 2009;20(3):556-63. doi: 10.1093/annonc/mdn642.
3. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, et al. Global, Regional, Global Burden of Disease Cancer Collaboration and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol. 2017;3(4):524-548. doi: 10.1001/jamaoncol.2016.5688.
4. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin. 2009;59(4):225-49. doi: 10.3322/caac.20006.
5. Verberne L, Bach-Faig A, Buckland G, Serra-Majem L. Association between the Mediterranean diet and cancer risk: a review of observational studies. Nutr Cancer. 2010;62(7):860-70. doi: 10.1080/01635581.2010.509834.
6. Watson AJ, Collins PD. Colon cancer: a civilization disorder. Dig Dis. 2011;29(2):222-8. doi: 10.1159/000323926.
7. Chao A, Thun MJ, Connell CJ, McCullough ML, Jacobs EJ, Flanders WD, et al. Meat consumption and risk of colorectal cancer. JAMA. 2005;293(2):172-82. doi: 10.1001/jama.293.2.172
8. Carroll KK. Dietary fats and cancer. Am J Clin Nutr. 1991;53(4 Suppl):1064S-1067S. doi: 10.1093/ajcn/53.4.1064S.
9. La Vecchia C, Altieri A, Tavani A. Vegetables, fruit, antioxidants and cancer: a review of Italian studies. Eur J Nutr. 2001;40(6):261-7
10. Bernstein C, Holubec H, Bhattacharyya AK, Nguyen H, Payne CM, Zaitlin B, et al. Carcinogenicity of deoxycholate, a secondary bile acid. Arch Toxicol. 2011;85(8):863-71. doi: 10.1007/s00204-011-0648-7.
11. Wang Q, Hao J, Guan Q, Yuan W. The Mediterranean diet and gastrointestinal cancers risk. Recent Pat Food Nutr Agric. 2014;6(1):23-6.
12. Visioli F, Galli C. The role of antioxidants in the Mediterranean diet. Lipids. 2001;36 Suppl:S49-52.
13. Tse G, Eslick GD. Soy and isoflavone consumption and risk of gastrointestinal cancer: a systematic review and meta-analysis. Eur J Nutr. 2016;55(1):63-73. doi: 10.1007/s00394-014-0824-7.
14. Moskaug JO, Carlsen H, Myhrstad MC, Blomhoff R. Polyphenols and glutathione synthesis regulation. Am J Clin Nutr. 2005;81(1 Suppl):277S-283S. doi: 10.1093/ajcn/81.1.277S.
15. Aggarwal BB, Shishodia S. Molecular targets of dietary agents for prevention and therapy of cancer. Biochem Pharmacol. 2006;71(10):1397-421.
16. Sporn MB, Suh N. Chemoprevention of cancer. Carcinogenesis. 2000;21(3):525-30.doi:10.1093/carcin/21.3.525.
17. Sihvo EI, Salminen JT, Rantanen TK, et al. Oxidative stress has a role in malignant transformation in Barrett's oesophagus. Int J Cancer. 2002;102(6):551-5. doi: 10.1002/ijc.10755
18. Halliwell B, Zhao K, Whiteman M. The gastrointestinal tract: a major site of antioxidant action? Free Radic Res. 2000;33(6):819-30.
19. Puchau B, Zulet MA, de Echavarri AG, Hermsdorff HH, Martinez JA. Dietary total antioxidant capacity: a novel indicator of diet quality in healthy young adults. J Am Coll Nutr. 2009;28(6):648-56.
20. Floegel A, Kim DO, Chung SJ, Song WO, Fernandez ML, Bruno RS, et al. Development and validation of an algorithm to establish a total antioxidant capacity database of the US diet. Int J Food Sci Nutr. 2010;61(6):600-23. doi: 10.3109/09637481003670816.
21. Stedile N, Canuto R, Col CD, Sene JS, Stolfo A, Wisintainer GN, et al. Dietary total antioxidant capacity is associated with plasmatic antioxidant capacity, nutrient intake and lipid and DNA damage in healthy women. Int J Food Sci Nutr. 2016;67(4):479-88. doi: 10.3109/09637486.2016.1164670.
22. Prior RL, Wu X, Schaich K. Standardized methods for the determination of antioxidant capacity and phenolics in foods and dietary supplements. J Agric Food Chem. 2005;53(10):4290-302.
23. Panic N, Leoncini E, de Belvis G, Ricciardi W, Boccia S. Evaluation of the endorsement of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement on the quality of published systematic review and meta-analyses. PLoS One. 2013;8(12):e83138. doi: 10.1371/journal.pone.0083138.
24. Wells G, Shea B, O'Connell D, Peterson J, Welch V. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000 Available from: http://www.evidencebasedpublichealth.de/download/Newcastle_Ottowa_Scale_Pope_Bruce.pdf 2014. Accessed Jan 20, 2014.
25. Shao C, Bai LP, Qi ZY, Hui GZ, Wang Z. Overweight, obesity and meningioma risk: a meta-analysis. PLoS One. 2014;9(2):e90167. doi: 10.1371/journal.pone.0090167.
26. Lanza A, Ravaud P, Riveros C, Dechartres A. Comparison of estimates between cohort and case-control studies in meta-analyses of therapeutic interventions: a meta-epidemiological study. PLoS One. 2016;11(5):e0154877. doi: 10.1371/journal.pone.0154877.
27. Mekary RA, Wu K, Giovannucci E, Sampson L, Fuchs C, Spiegelman D, et al. Total antioxidant capacity intake and colorectal cancer risk in the Health Professionals Follow-up Study. Cancer Causes Control. 2010;21(8):1315-21. doi: 10.1007/s10552-010-9559-9.
28. Praud D, Parpinel M, Serafini M, Bellocco R, Tavani A, Lagiou P, et al. Non-enzymatic antioxidant capacity and risk of gastric cancer. Cancer Epidemiol. 2015;39(3):340-5. doi: 10.1016/j.canep.2015.04.003.
29. Lucas AL, Bosetti C, Boffetta P, Negri E, Tavani A, Serafini M, et al. Dietary total antioxidant capacity and pancreatic cancer risk: an Italian case-control study. Br J Cancer. 2016;115(1):102-7. doi: 10.1038/bjc.2016.114.
30. Serafini M, Jakszyn P, Luján-Barroso L, Agudo A, Bas Bueno-de-Mesquita H, van Duijnhoven FJ, et al. Dietary total antioxidant capacity and gastric cancer risk in the European prospective investigation into cancer and nutrition study. Int J Cancer. 2012;131(4):E544-54. doi: 10.1002/ijc.27347.
31. La Vecchia C, Decarli A, Serafini M, Parpinel M, Bellocco R, Galeone C, et al. Dietary total antioxidant capacity and colorectal cancer: a large case-control study in Italy. Int J Cancer. 2013;133(6):1447-51. doi: 10.1002/ijc.28133.
32. Vece MM, Agnoli C, Grioni S, Sieri S, Pala V, Pellegrini N, et al. Dietary total antioxidant capacity and colorectal cancer in the Italian EPIC Cohort. PLoS One. 2015;10(11):e0142995. doi: 10.1371/journal.pone.0142995.
33. Zamora-Ros R, Fedirko V, Trichopoulou A, González CA, Bamia C, Trepo E, et al. Dietary flavonoid, lignan and antioxidant

capacity and risk of hepatocellular carcinoma in the European prospective investigation into cancer and nutrition study. Int J Cancer. 2013;133(10):2429-43. doi: 10.1002/ijc.28257.
34. Lanza A, Ravaud P, Riveros C, Dechartres A. Comparison of estimates between cohort and case-control studies in meta-analyses of therapeutic interventions: a meta-epidemiological study. PLoS One. 2016;11(5):e0154877. doi: 10.1371/journal.pone.0154877.
35. Gnagnarella P, Gandini S, La Vecchia C, Maisonneuve P. Glycemic index, glycemic load, and cancer risk: a meta-analysis. Am J Clin Nutr. 2008;87(6):1793-801.
36. Karimi Z, Bahadoran Z, Abedini S, Houshyar-Rad A, Rashidkhani B. Dietary total antioxidant capacity and the risk of breast cancer: a case-control study. East Mediterr Health J. 2015;21(8):564-71.
37. Rossi M, Tavani A, Ciociola V, Ferraroni M, Parpinel M, Serafini M, et al. Dietary total antioxidant capacity in relation to endometrial cancer risk: a case-control study in Italy. Cancer Causes Control. 2016;27(3):425-31. doi: 10.1007/s10552-016-0719-4.
38. Vance TM, Wang Y, Su LJ, Fontham ET, Steck SE, Arab L, et al. Dietary total antioxidant capacity is inversely associated with prostate cancer aggressiveness in a population-based study. Nutr Cancer. 2016;68(2):214-24. doi: 10.1080/01635581.2016.1134596.
39. Urquiaga I, Echeverria G, Dussaillant C, Rigotti A. Origin, components and mechanisms of action of the Mediterranean diet. Rev Med Chil. 2017;145(1):85-95. doi: 10.4067/S0034-98872017000100012.
40. Pitsavos C, Panagiotakos DB, Tzima N, Chrysohoou C, Economou M, Zampelas A, et al. Adherence to the Mediterranean diet is associated with total antioxidant capacity in healthy adults: the ATTICA study. Am J Clin Nutr. 2005;82(3):694-9.
41. Chen Y, Wu Y, Du M, Chu H, Zhu L, Tong N, et al. An inverse association between tea consumption and colorectal cancer risk. Oncotarget. 2017;8(23):37367-37376. doi: 10.18632/oncotarget.16959.
42. Schmit SL, Rennert HS, Rennert G, Gruber SB. Coffee Consumption and the Risk of Colorectal Cancer. Cancer Epidemiol Biomarkers Prev. 2016;25(4):634-9. doi: 10.1158/1055-9965.EPI-15-0924.
43. Nascimento-Souza MA, Paiva PG, Martino HSD, Ribeiro AQ. Dietary total antioxidant capacity as a tool in health outcomes in middle-aged and older adults: A systematic review. Crit Rev Food Sci Nutr. 2018;58(6):905-912. doi: 10.1080/10408398.2016.1230089.
44. Bahadoran Z, Golzarand M, Mirmiran P, Shiva N, Azizi F. Dietary total antioxidant capacity and the occurrence of metabolic syndrome and its components after a 3-year follow-up in adults: Tehran Lipid and Glucose Study. Nutr Metab (Lond). 2012;9(1):70. doi: 10.1186/1743-7075-9-70.
45. Bahadoran Z, Carlstrom M, Ghasemi A, Mirmiran P, Azizi F, Hadaegh F. Total antioxidant capacity of the diet modulates the association between habitual nitrate intake and cardiovascular events: A longitudinal follow-up in Tehran Lipid and Glucose Study. Nutr Metab (Lond). 2018;15:19. doi: 10.1186/s12986-018-0254-2.
46. Bjelakovic G, Nikolova D, Simonetti RG, Gluud C. Antioxidant supplements for prevention of gastrointestinal cancers: a systematic review and meta-analysis. Lancet. 2004;364(9441):1219-28.
47. Schatzkin A, Lanza E, Corle D, Lance P, Iber F, Caan B, et al. Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. Polyp Prevention Trial Study Group. N Engl J Med. 2000;342(16):1149-55.
48. Rossi M, Rosato V, Bosetti C, Lagiou P, Parpinel M, Bertuccio P, et al. Flavonoids, proanthocyanidins, and the risk of stomach cancer. Cancer Causes Control. 2010;21(10):1597-604. doi: 10.1007/s10552-010-9588-4.
49. de Sousa Moraes LF, Sun X, Peluzio M, Zhu MJ. Anthocyanins/Anthocyanidins and Colorectal Cancer: What Is Behind the Scenes? Crit Rev Food Sci Nutr. 2019;59(1):59-71. doi: 10.1080/10408398.2017.1357533.
50. Han X, Li J, Brasky TM. Antioxidant intake and pancreatic cancer risk: the Vitamins and Lifestyle (VITAL) Study. Cancer. 2013;119(7):1314-20. doi: 10.1002/cncr.27936.
51. Devore EE, Feskens E, Ikram MA, den Heijer T, Vernooij M, van der Lijn F, et al. Total antioxidant capacity of the diet and major neurologic outcomes in older adults. Neurology. 2013;80(10):904-10. doi: 10.1212/WNL.0b013e3182840c84.
52. Puchau B, Zulet MA, de Echavarri AG, Hermsdorff HH, Martinez JA. Dietary total antioxidant capacity is negatively associated with some metabolic syndrome features in healthy young adults. Nutrition. 2010;26(5):534-41. doi: 10.1016/j.nut.2009.06.017.
53. Detopoulou P, Panagiotakos DB, Chrysohoou C. Dietary antioxidant capacity and concentration of adiponectin in apparently healthy adults: the ATTICA study. Eur J Clin Nutr. 2010;64(2):161-8. doi: 10.1038/ejcn.2009.130.
54. Goodman M, Bostick RM, Dash C, Flanders WD, Mandel JS. Hypothesis: oxidative stress score as a combined measure of pro-oxidant and antioxidant exposures. Ann Epidemiol. 2007;17(5):394-9.
55. Li X, Fang P, Mai J, Choi ET, Wang H, Yang XF. Targeting mitochondrial reactive oxygen species as novel therapy for inflammatory diseases and cancers. J Hematol Oncol. 2013;6:19. doi: 10.1186/1756-8722-6-19.
56. Smith KS, Yadav VK, Pedersen BS. Signatures of accelerated somatic evolution in gene promoters in multiple cancer types. Nucleic Acids Res. 2015;43(11):5307-17. doi: 10.1093/nar/gkv419.
57. Sena LA, Chandel NS. Physiological roles of mitochondrial reactive oxygen species. Mol Cell. 2012;48(2):158-67. doi: 10.1016/j.molcel.2012.09.025.
58. Foksinski M, Gackowski D, Rozalski R, Siomek A, Guz J, Szpila A, et al. Effects of basal level of antioxidants on oxidative DNA damage in humans. Eur J Nutr. 2007;46(3):174-80. doi: 10.1007/s00394-006-0642-7.
59. Nyren O, Adami HO. Stomach cancer. In: Adami HO, Adami HO, Hunter D, Trichopoulos D, eds ed. Textbook of Cancer Epidemiology. UK: Oxford Scholarship Online 2008; 2: 239-274.
60. Steinmetz KA, Potter JD. Vegetables, fruit, and cancer prevention: a review. J Am Diet Assoc. 1996;96(10):1027-39. doi: 10.1016/S0002-8223(96)00273-8.

© 2019 The Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.