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Dietary total antioxidant capacity and risk of cancer: a systematic review and meta-analysis on observational studies

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ABSTRACT

Background: Recent studies have shown that dietary total antioxidant capacity (D-TAC) may affect risk of cancer; however, findings are conflicting. Hence, we aimed to summarize the current evidence on the association between D-TAC and risk of cancer.

Methods: We searched the online databases of PubMed, ISI Web of Science, Scopus, ProQuest, Science Direct and Embase until October 2018 using relevant keywords. To pool data, fixed- or random-effects models were used where appropriate.

Results: In total, 19 studies including 8 prospective and 11 case-control studies with 721429 individuals and 16159 cases of cancer were included in the current systematic review and meta-analysis. Combining 15 effect sizes from 6 prospective and 8 case-control studies revealed a significant inverse association between D-TAC (obtained from ferric reducing antioxidant power (FRAP)) and risk of cancer (combined effect size: 0.86, 95% CI: 0.81-0.92, $P < 0.001$). Such inverse association was also seen for D-TAC obtained from other methods including trolox equivalence antioxidant capacity (TEAC) (combined effect size: 0.80, 95% CI: 0.70–0.90, $P < 0.001$), total radical trapping antioxidant parameter (TRAP) (combined effect size: 0.69, 95% CI: 0.62–0.78, $P < 0.001$) and oxygen radical absorbance capacity (ORAC) (combined effect size: 0.72, 95% CI: 0.52–1.00, $P = 0.04$). In addition, a significant non-linear association was found between D-TAC (based on FRAP and TRAP) and cancer risk (P-nonlinearity < 0.001). Based on linear dose-response meta-analysis, a-10 mmol/day increase in FRAP and a-5 mmol/day increase in TRAP and TEAC were associated with 9%, 17% and 14% reduction in risk of cancer, respectively. Furthermore, D-TAC was inversely associated with risk of colorectal (combined effect size: 0.82, 95% CI: 0.75-0.89, $P < 0.001$), gastric (combined effect size: 0.63, 95% CI: 0.53-0.73, $P < 0.001$), and endometrial cancer (combined effect size: 0.78, 95% CI: 0.69-0.89, $P < 0.001$).

Conclusions: Diet with high antioxidant capacity might have protective effects against cancer.

1. Introduction

The prevalence of cancer has been increasing at an alarming rate in the recent decades (Ferlay et al., 2015). This chronic disease is associated with a high economic burden, disability, and early mortality (Lortet-Tieulent et al., 2016). In 2015, cancer was the second leading

Abbreviation: D-TAC, dietary total antioxidant capacity; FRAP, ferric reducing antioxidant power; TRAP, total radical trapping antioxidant parameter; TEAC, trolox equivalence antioxidant capacity; ORAC, oxygen radical absorbance capacity; OR, odds ratio; RR, relative risk; HR, hazard ratio; FFQ, food frequency questionnaire

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cause of death behind cardiovascular diseases and caused over 8.7 million deaths globally (Fitzmaurice et al., 2017). Therefore, appropriate strategies are required to decrease the incidence of this disorder.

Several risk factors for different types of cancer have been identified. Among them, researchers have focused on the association between diet and risk of cancer (Barak and Fridman, 2017; Schadler et al., 2017). Based on previous studies, dietary intakes of fruits, vegetables, coffee, chocolate, berries, red wine, whole grains and other foods rich in antioxidants have been associated with decreased odds of several common cancers, particularly those affecting digestive tract (Chen et al., 2016; Jiang et al., 2010; Li et al., 2014; Nakagawa-Senda et al., 2017; Vieira et al., 2016; Xu et al., 2015). Recently, it has been shown that total antioxidant capacity of diet might affect risk of cancer (Amiano et al., 2018; Chang et al., 2007; Cui et al., 2011; Gifkins et al., 2012a, b; Holtan et al., 2012; Karimi et al., 2015; Vecchia et al., 2013; Lucas et al., 2016; Mekary et al., 2010; Pantavos et al., 2015; Praud et al., 2015; Rossi et al., 2016; Russnes et al., 2016, 2014; Serafini et al., 2002, 2012; Vece et al., 2015; Ros et al., 2013). It has been proposed that dietary antioxidants are protective against cancer mainly due to their ability to reduce DNA damage caused by reactive oxygen and nitrogen species (Seifried et al., 2003). Dietary total antioxidant capacity (D-TAC) evaluates the single antioxidant activity in addition to the synergistic interactions of the redox molecules available in complex matrixes, giving an insight into the assessment of the non-enzymatic antioxidant network (Serafini et al., 2006).

Several methods were developed recently for the assessment of total antioxidant capacity of foods and beverages (Pellegrini et al., 2003, 2006); ferric reducing-antioxidant power (FRAP) that measures in vitro the reduction of the Fe^{3+} (ferric ion) to Fe^{2+} (ferrous ion) in the presence of antioxidants, total radical-trapping antioxidant parameter (TRAP) which is measured based on the protection provided by antioxidants on the fluorescence decay of R-phycoerythrin (lag-phase) during a controlled peroxidation reaction, Trolox equivalent antioxidant capacity (TEAC) which is measured based on the ability of antioxidant molecules to quench the long-lived ABTS1 compared with that of 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, Trolox, and oxygen radical absorbance capacity (ORAC) which is measured based on taking the free radical reaction to completion, using biologically relevant free radicals (peroxyl, hydroxyl and Cu^{2+}) (Pellegrini et al., 2003, 2006). These methods are different in their chemistry (generation of different radicals and/or target molecules) and in the way which end points are measured (Pellegrini et al., 2006). Because different antioxidants may act in vivo by different mechanisms, no single method can fully determine the antioxidant capacity of foods.

Several studies have been done on the association between D-TAC and risk of cancer (Mekary et al., 2010; Serafini et al., 2012; Vece et al., 2015); however, findings are conflicting. Some studies reported an inverse association between total antioxidant capacity of diet and risk of cancer (Pantavos et al., 2015; Ros et al., 2013), while others failed to find any significant association (Gifkins et al., 2012b; Karimi et al., 2015). Until now, no study has summarized findings on the association between D-TAC and risk of cancer. Therefore, current study aimed to summarize the current evidence in this regard.

2. Material and methods

Current systematic review and meta-analysis was designed, conducted and reported in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page and Moher, 2017).

2.1. Search strategy

The databases including PubMed, ISI Web of Science, Scopus, ProQuest, Science Direct and Embase were searched for all years of record until October 2018. A combination of the following keywords in English was used: “oxygen radical absorbance capacity” OR “trolox equivalence antioxidant capacity” OR “oxygen radical absorbance capacity” OR “trolox equivalence antioxidant capacity” OR “total antioxidant capacity” OR “dietary TAC” OR “total dietary antioxidant capacity” OR “nonenzymatic antioxidant capacity” OR “non-enzymatic antioxidant capacity” OR “ferric reducing antioxidant power” OR “total radical trapping antioxidant parameter” OR “vitamin C equivalent antioxidant capacities” AND “neoplasms” OR “carcinoma” OR “cancer”. The literature search was conducted by two independent researchers (MP and AS). Time of publication and language were not restricted. Furthermore, the reference lists of the related papers were screened to avoid missing any study. In the search strategy, unpublished studies were not included. To facilitate the screening process of papers from databases, all literature searches were downloaded into an EndNote library (version X7, for Windows, Thomson Reuters, Philadelphia, PA, USA).

2.2. Selection criteria

In this meta-analysis, relevant studies were selected based on the following criteria: 1) all studies that were observational with case-control or nested case-control or cohort or cross-sectional design; 2) those that assessed the association between D-TAC and risk of cancer; 3) studies that evaluated D-TAC using common methods including FRAP, TRAP, TEAC and ORAC; and 4) those that reported odds ratio (ORs) or relative risks (RRs) or hazard ratios (HRs) along with 95% confidence intervals for the association between D-TAC and risk of cancer. If ≥ 2 publications drew from the same population, only the paper with higher quality and more complete information or findings was included in the current systematic review and meta-analysis.

2.3. Exclusion criteria

In the current review, we excluded letters, case reports, ecological studies, dissertations, books, animal studies, short communications, reviews, and those unrelated to the subject of the review. In total, 598 articles were detected in our initial search. After removing duplicates (n = 60), we excluded 468 papers by screening on the basis of title and abstract. Of 69 remaining articles, 51 were excluded due to the following reasons: 1) studies that assessed intake of single food group such as fruits and vegetables in relation to risk of cancer (n = 31), 2) those that evaluated the association between single nutrient intake and risk of cancer (n = 11), 3) studies that determined the risk of cancer mortality in relation to D-TAC (n = 2) (Agudo et al., 2007; Kim et al., 2017), 4) studies that assessed the association between serum or plasma level of TAC and cancer (n = 6), 5) those that evaluated the association between D-TAC and severity of cancer, not risk (n = 1) (Vance et al., 2016). In addition, out of 19 remained studies, 2 were done on population of the Health Professionals Follow-up Study (HPFS) (Mekary et al., 2010; Russnes et al., 2014). However, both were included due to assessment of different types of cancer, but to include in the meta-analysis, the risk estimates of both studies were combined to avoid double-counting data. Furthermore, 3 other studies were conducted on the same population in the framework of European Prospective Investigation into Cancer (EPIC) study (Serafini et al., 2012; Vece et al., 2015; Ros et al., 2013). These studies assessed different types of cancer and used different methods for assessment of D-TAC, and therefore all were included. In total, 19 studies (8 prospective (Chang et al., 2007; Cui et al., 2011; Mekary et al., 2010; Pantavos et al., 2015; Russnes et al., 2014; Serafini et al., 2012; Vece et al., 2015; Ros et al., 2013) and 11 case-control studies (Amiano et al., 2018; Gifkins et al., 2012a, b; Holtan et al., 2012; Karimi et al., 2015; Vecchia et al., 2013; Lucas et al., 2016; Praud et al., 2015; Rossi et al., 2016; Russnes et al., 2016; Serafini et al., 2002)) were included in this systematic review and meta-analysis. The details of the study selection process are shown in Fig. 1.

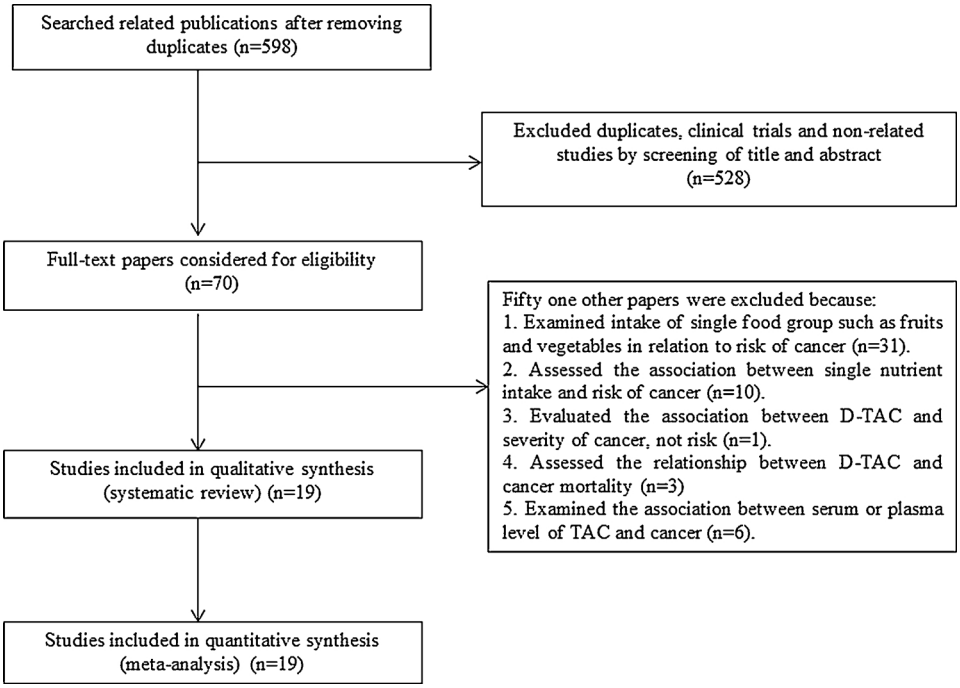

Fig. 1. Flow diagram of study selection.

2.4. Data extraction

Study selection in addition to data extraction from each eligible study was conducted independently by two researches (MP and AS), and any disagreements were resolved by discussion. In prospective studies, the presence or absence of participants across categories of D-TAC in the beginning of study was the key exposure variable. In addition, incidence of different types of cancer during the follow-up was the key outcome variable. In both prospective and case-control studies, any reported effect sizes including ORs or HRs or RRs for cancer among individuals in the highest category of D-TAC (obtained from different methods including TEAC, FRAP, TRAP and ORAC) compared with those in the lowest category or reference group, were extracted. In some included studies, intake of antioxidants from supplements was considered in total amount of D-TAC, and therefore the related effect sizes were not extracted. In two case-control studies, risk estimates were reported across categories of total phenolic intake (Gifkins et al., 2012a,b). Due to the total dietary phenol is a part of D-TAC, not total, the related risk estimates were not extracted. In some studies, risk estimates were reported based on one standard deviation (SD) or one-unit increase in TEAC, FRAP or TRAP (Vecchia et al., 2013; Praud et al., 2015; Rossi et al., 2016; Serafini et al., 2012). Mentioned estimates were also extracted. The following information were extracted from each eligible study: first author, year of publication, country of origin, age range (at study baseline for prospective studies) and mean or age range (for case-control studies), gender, number of subjects (cases, controls or cohort size), duration of follow-up for prospective studies, methods used for assessing dietary intakes and D-TAC, methods applied to diagnosis of cancer and variables controlling as confounder. Details in this regard are shown in Table 1 and 2. In studies presenting gender-stratified analysis, we considered these as two separate studies. If some papers provided no required risk estimates, we computed mentioned estimates through standard methods.

2.5. Quality assessment

The quality of prospective and case-control studies was assessed using Newcastle Ottawa Scale (NOS) (Wells et al., 2015), known as a common method for quality assessment of studies in systematic reviews and meta-analyses. Based on this scale, a maximum of nine points might be given to each prospective or case-control study according to following parameters: four for selection, two for comparability, and three for assessment of outcomes (nine was considered as the highest quality). In the current systematic review and meta-analysis, studies with score of 6 or more were considered as high quality (Supplementary Table 1).

2.6. Statistical analysis

Firstly, we calculated the log RRs and their standard errors using related ORs, RRs and HRs and corresponding 95% confidence intervals (CIs) reported for the association between D-TAC and different types of cancers. Then, the overall effect sizes were calculated using fixed-effects model. Overall effect sizes were separately calculated for different methods used to assess D-TAC including TEAC, FRAP, TRAP and ORAC. If between-study heterogeneity was significant, random-effects model was also done to take between-study variation into account. To assess between-study heterogeneity, I^2 value and its p-value (P-heterogeneity) were used. In the current study, I^2 values of 50% or more were considered as between-study heterogeneity (Higgins and Green, 2011). We also conducted subgroup analysis to find probable sources of heterogeneity. This analysis was done according to pre-defined criteria including study design (prospective vs. case-control), gender (males, females, both genders), geographical region (US vs. non-US countries), methods used for diagnosis of cancer (Histopathological methods vs. using medical records) and use of energy-adjusted D-TAC in statistical analysis (used vs. not-used). In addition, subgroup analysis was done based on follow-up duration ($\geq$15 vs. $<$ 15 years) and sample size ($\geq$10,000 vs. $<$ 10,000 individuals) among prospective studies and according to variables matched between cases and controls (age and sex vs. age matched) among case-control studies. In all subgroup analyses, fixed-effects model was applied. To find dependency of the overall estimate on the effect size from a single study, sensitivity analysis was applied according to main exposure and main outcome. If this was the case, data were re-analyzed by excluding that study. To assess potential publication bias, in addition to visual inspection of funnel plot, we used

Table 1
The association between D-TAC and risk of cancer based on included prospective studies.

Authors (year)	Country	Age range (y)	Sample size	Cases	Follow-up (y)	Exposure	Exposure assessment	Outcome	Outcome assessment	Categorical or continuous	OR, RR or HR (95%CI)	Adjustment[†]
Vece et al., 2015	Italy	35-70	M/F: 45194	434 325 109	11	TEAC	FFQ: Interview	Colorectal cancer Colon cancer Rectal cancer	Medical records	T3 vs. T1 (≥7.2 vs. < 5.2 mmol/d)	HR: 0.88 (0.65–1.19) HR: 0.63 (0.44–0.89) HR: 2.48 (1.32–4.66)	1,2,3,5,6,7,8,9,16,17,18,19,20,22
Mekary et al., 2010	USA	40-75	M: 47339	286 195 66	8	FRAP	FFQ: Self-reported	Colorectal cancer Colon cancer Rectal cancer	Medical records	Q5 vs. Q1 (> 13.9 vs. ≤ 7.3 mmol/d)	RR: 0.98 (0.78-1.23) RR: 1.20 (0.90-1.61) RR: 0.58 (0.35-0.96)	1,4,6,7,8,11,16,17,18,22,23,24,29,41,42
Pantavos et al., 2015	Netherlands	≥55	F: 3209	199	17	FRAP	FFQ: Interview	Breast cancer	Nationwide registries	T3 vs. T1 (≥22.2 vs. < 18.0 mmol/d)	HR: 0.68 (0.49-0.96)	1,3,6,8,11,17,20,21,30,32,39
Russnes et al., 2014	USA	40-75	M: 47896	5656	22	FRAP	FFQ: Self-reported	Prostate cancer	Medical records	Q5 vs. Q1 (N/R)	RR: 0.91 (0.83-1.00)	1,4,5,6,7,8,12,16,17,22,28,43
Serafini et al., 2012	10 European countries	35-70	M: 143721	255	14	FRAP TRAP	FFQ, diet history and food record: Interview	Gastric cancer	Nationwide registries	Q5 vs. Q1 (≥16.9 vs. ≤ 6.7 mmol/d) Q5 vs. Q1 (≥6.4 vs. ≤ 2.1 mmol/d)	HR: 0.68 (0.43-1.08) HR: 0.72 (0.46-1.14)	2, 3, 6, 8, 16, 18
						FRAP TRAP				Per log_2 increase	HR: 0.85 (0.69-1.04) HR: 0.90 (0.76-1.06)	
			F: 339579	189	14	FRAP TRAP	FFQ, diet history and food record: Interview	Gastric cancer	Nationwide registries	Q5 vs. Q1 (≥15.7 vs. ≤ 6.3 mmol/d) Q5 vs. Q1 (≥5.9 vs. ≤ 2.0 mmol/d)	HR: 0.52 (0.28-0.95) HR: 0.62 (0.34-1.12)	
						FRAP TRAP				Per log_2 increase	HR: 0.78 (0.60-1.00) HR: 0.83 (0.63-1.02)	
Ros et al., 2013	10 European countries	35-70	M/F: 477206	191	11.4	FRAP TRAP	FFQ or diet history: Interview	Hepatocellular cancer	Nationwide registries	T3 vs. T1 (> 70.1 vs. < 31.7 mmol/d) T3 vs. T1 (> 32.8 vs. < 14.1 mmol/d)	HR: 0.50 (0.31-0.81) HR: 0.49 (0.31-0.79)	1,2,3,6,7,8,9,12,16,17,20,25
						FRAP TRAP				Per log_2 increase	HR: 0.74 (0.63-0.86) HR: 0.76 (0.67-0.87)	
Chang et al., 2007	USA	20-85	F: 97275	280	8.1	TEAC	FFQ: Self-reported	Ovarian cancer	Medical records	Q5 vs. Q1 (> 24.8 vs. ≤ 8.2 mmol/d)	RR: 1.40 (0.92-2.14)	1,4,7,16,17,34,36,39,40
Cui et al., 2011	USA	30-55	F: 68070	669	26	FRAP	FFQ: Self-reported	Endometrial cancer	Medical records	Q5 vs. Q1 (N/R)	RR: 0.97 (0.75-1.24)	6,8,12,13,16,31,34,35,39,40

Abbreviation: D-TAC: dietary total antioxidant capacity, FRAP: ferric reducing antioxidant power, TRAP: total radical trapping antioxidant parameter, TEAC: trolox equivalence antioxidant capacity, ORAC: oxygen radical absorbance capacity, RR: relative risk, HR: hazard ratio, FFQ: food frequency questionnaire, M: males, F: females.

[†] Adjustment: age (1), sex (2), education (3), race (4), height (5), BMI (6), physical activity (7), smoking (8), study center (9), year of interview (10), family history of cancer (11) and diabetes mellitus (12), hypertension (13), life satisfaction (14), number of meals per day (15), dietary intake of energy (16), alcohol (17), red meat (18), processed meat (19), fiber (20), fat (21), calcium (22), folate (23), vitamin D (24), coffee (25), TAC from coffee (26), salt (27), alpha-linolenic acid (28), antioxidant supplements (29), multivitamin supplements (30), age at menarche (31), reproductive history (32), age at first pregnancy (33), number of full pregnancies (34), age at menopause (35), menopausal status (36), tubal ligation (37), use of brassiere (38), hormone therapy (39), oral contraceptive (40), aspirin (41), previous endoscopy (42) and PSA testing in previous period (43).

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A dose-dependent meta-analysis was used to compute the trend from the correlated log OR/RR/HR estimates across D-TAC categories according to the method proposed by Greenland, Longnecker and Orsini et al (Greenland and Longnecker, 1992; Orsini et al., 2006). For this purpose, publications that categorized D-TAC (at least 3 categories), reported number of participants in each D-TAC category, reported number of patients with cancer in total population and in each D-TAC category, and calculated the OR, RR and HR with related 95% confidence interval for cancer in each category, were used. The midpoint of the D-TAC category was considered as the corresponding OR/RR/HR estimate, while, the open-ended categories were considered as same width as the neighboring categories. Non-linear relationship between D-TAC and risk of cancer was explored using the two-stage random-effects dose–response meta-analysis. To this purpose, we used D-TAC modeling and restricted cubic splines with 3 knots at fixed percentiles of 10%, 50%, and 90% of the distribution (Harre et al., 1988). A restricted cubic spline model was calculated using generalized least square regression taking into account the correlation within each set of published ORs/RRs/HRs (Jackson et al., 2010). Then, the restricted maximum likelihood method was used to combine the study-specific estimates in a multivariate random-effects meta-analysis (Jackson et al., 2010). The null hypothesis considered the coefficient of the second spline equal to 0. In addition, a linear dose-response relation of D-TAC with risk of cancer was estimated using the two-stage generalized least squares trend estimation (Berlin et al., 1993; Greenland and Longnecker, 1992; Orsini et al., 2006). To estimate an overall average slope, the study-specific slope lines were estimated, then combined with studies in which the slopes were directly reported (Orsini et al., 2006). All statistical analyses were conducted using Stata, version 11.2 (Stata Corp, College Station, TX). P values were considered significant at the level of < 0.05.

3. Results

3.1. Findings from systematic review

In total, 19 studies including 8 prospective (Chang et al., 2007; Cui et al., 2011; Mekary et al., 2010; Pantavos et al., 2015; Russnes et al., 2014; Serafini et al., 2012; Vece et al., 2015; Ros et al., 2013) and 11 case-control studies (Amiano et al., 2018; Gifkins et al., 2012a, b; Holtan et al., 2012; Karimi et al., 2015; Vecchia et al., 2013; Lucas et al., 2016; Praud et al., 2015; Rossi et al., 2016; Russnes et al., 2016; Serafini et al., 2002) were included in the current systematic review. Details on the characteristics of included studies are shown in Table 1 and 2. The population of mentioned studies was different varying from 3209 to 483,300 among prospective studies (total: 699,750), and 275 to 6107 among case-control studies (total: 21,679). Totally, 721,429 individuals aged 20 years and more were included in the current systematic review. Included studies had been published between 2002 and 2018. Out of 19 mentioned studies, 7 were done in the US (Chang et al., 2007; Cui et al., 2011; Gifkins et al., 2012a, b; Holtan et al., 2012; Mekary et al., 2010; Russnes et al., 2014), 11 in Europe (Amiano et al., 2018; Vecchia et al., 2013; Lucas et al., 2016; Pantavos et al., 2015; Praud et al., 2015; Rossi et al., 2016; Russnes et al., 2016; Serafini et al., 2002, 2012; Vece et al., 2015; Ros et al., 2013) and one in Iran (Karimi et al., 2015). In addition, three studies were conducted on males (Mekary et al., 2010; Russnes et al., 2016, 2014), seven on females (Chang et al., 2007; Cui et al., 2011; Gifkins et al., 2012a, b; Karimi et al., 2015; Pantavos et al., 2015; Rossi et al., 2016) and nine on both genders (Amiano et al., 2018; Holtan et al., 2012; Vecchia et al., 2013; Lucas et al., 2016; Praud et al., 2015; Serafini et al., 2002, 2012; Vece et al., 2015; Ros et al., 2013). In prospective studies, mean duration of follow-up varied from 8 to 21 years.

Dietary intakes had been assessed using food frequency questionnaire (FFQ) in seventeen studies (Amiano et al., 2018; Chang et al., 2007; Cui et al., 2011; Gifkins et al., 2012a, b; Holtan et al., 2012; Karimi et al., 2015; Vecchia et al., 2013; Lucas et al., 2016; Mekary et al., 2010; Pantavos et al., 2015; Praud et al., 2015; Rossi et al., 2016; Russnes et al., 2016, 2014; Serafini et al., 2002; Vece et al., 2015) and a combination of FFQ, diet history and food record in two other studies (Serafini et al., 2012; Ros et al., 2013). Furthermore, mentioned questionnaires were fulfilled self-reported in ten studies (Amiano et al., 2018; Chang et al., 2007; Cui et al., 2011; Gifkins et al., 2012a, b; Holtan et al., 2012; Mekary et al., 2010; Rossi et al., 2016; Russnes et al., 2016, 2014) and by interviewers in other nine studies (Karimi et al., 2015; Vecchia et al., 2013; Lucas et al., 2016; Pantavos et al., 2015; Praud et al., 2015; Serafini et al., 2002, 2012; Vece et al., 2015; Ros et al., 2013). In some prospective studies, in addition to the assessment of dietary intakes and measurement of D-TAC at the study baseline, these had been repeated during the follow-up period (Cui et al., 2011; Russnes et al., 2014), but all prospective studies, even those that had assessed D-TAC during the follow-up, had categorized subjects based on the baseline value of D-TAC. Among included studies, D-TAC was assessed by different methods including TEAC, FRAP, TRAP and ORAC. Of 19 included studies, five assessed D-TAC by FRAP (Cui et al., 2011; Mekary et al., 2010; Pantavos et al., 2015; Russnes et al., 2016, 2014), one by TRAP (Serafini et al., 2002), two by TEAC (Chang et al., 2007), two by ORAC (Holtan et al., 2012; Karimi et al., 2015), two using both FRAP and TRAP (Serafini et al., 2012; Ros et al., 2013), two using both FRAP and ORAC (Gifkins et al., 2012a, b) and five through three methods including FRAP, TRAP and TEAC (Amiano et al., 2018; Vecchia et al., 2013; Lucas et al., 2016; Praud et al., 2015; Rossi et al., 2016). Among all included studies, one calculated only D-TAC of fruits and vegetables (Serafini et al., 2002). Due to the fruits and vegetables provide the most amount of D-TAC (Russnes et al., 2014), the related effect sizes were included in the current study. Four studies had evaluated D-TAC in relation to colon, rectal and colorectal cancer (Amiano et al., 2018; Vecchia et al., 2013; Mekary et al., 2010; Vece et al., 2015), three in relation to gastric cancer (Praud et al., 2015; Serafini et al., 2002, 2012), two in relation to breast cancer (Karimi et al., 2015; Pantavos et al., 2015), three in relation to endometrial cancer (Cui et al., 2011; Gifkins et al., 2012a; Rossi et al., 2016), one in relation to prostate cancer (Russnes et al., 2016, 2014), two in relation to ovarian cancer (Chang et al., 2007; Gifkins et al., 2012b), one in relation to hepatocellular carcinoma (Ros et al., 2013), one in relation to pancreatic cancer (Lucas et al., 2016) and one in relation to non-Hodgkin lymphoma (Holtan et al., 2012). Data on incidence of cancer were collected using medical records in five studies (Chang et al., 2007; Cui et al., 2011; Mekary et al., 2010; Russnes et al., 2014; Vece et al., 2015) and using electronic discharge registers in 3 studies (Pantavos et al., 2015; Serafini et al., 2012; Ros et al., 2013). In addition, cancer was diagnosed based on pathological and histological methods in 11 other studies (Amiano et al., 2018; Gifkins et al., 2012a, b; Holtan et al., 2012; Karimi et al., 2015; Vecchia et al., 2013; Lucas et al., 2016; Praud et al., 2015; Rossi et al., 2016; Russnes et al., 2016; Serafini et al., 2002).

Among all included studies, 8 had assessed the risk of cancer across quintiles of D-TAC (Amiano et al., 2018; Chang et al., 2007; Cui et al., 2011; Vecchia et al., 2013; Mekary et al., 2010; Russnes et al., 2016, 2014; Serafini et al., 2012), four evaluated this risk across quartiles of D-TAC (Holtan et al., 2012; Karimi et al., 2015; Rossi et al., 2016; Serafini et al., 2002) and 7 remained studies examined this risk across tertiles of D-TAC (Gifkins et al., 2012a, b; Lucas et al., 2016; Pantavos et al., 2015; Praud et al., 2015; Vece et al., 2015; Ros et al., 2013). The reference group in all included studies was participants in the lowest category D-TAC. In addition, five studies had reported risk of cancer based on one-SD or one-unit increase in D-TAC (Amiano et al., 2018; Vecchia et al., 2013; Praud et al., 2015; Rossi et al., 2016; Serafini et al., 2012). All studies had reported adjusted risk estimates for the association between D-TAC and cancer. Out of 19 studies, 13 used energy-adjusted D-TAC in relation to cancer (Amiano et al., 2018; Chang et al.,

Table 2
The association between D-TAC and risk of cancer based on included case-control studies.

Authors (year)	Country	Cases (n)	Controls (n)	Age[a] (cases)	Age[a] (controls)	Exposure	Exposure assessment	Outcome	Outcome assessment	Categorical or continues	OR (95%CI)	Matching factors	Adjustment[†]
Amiano et al., 2018	Spain	M: 1097	M: 1717	20-85	20-85	FRAP	FFQ: Self-reported	Colorectal cancer	Histological methods	Q5 vs. Q1 (> 16.6 vs. < 7.8 mmol/d)	1.08 (0.71-1.65)	Age, sex, study center	1,2,3,6,7,8,9,11,16,17,18,19,20,22,39,41
						TRAP				Q5 vs. Q1 (> 5.3 vs. < 2.1 mmol/d)	0.90 (0.61-1.33)		
						TEAC				Q5 vs. Q1 (> 5.8 vs. < 2.5 mmol/d)	0.93 (0.62-1.40)		
						FRAP				Per 1 mmol/d increase	1.00 (0.97-1.03)		
						TRAP					0.98 (0.92-0.99)		
						TEAC					0.97 (0.90-1.05)		
		F: 621	F: 1595			FRAP	FFQ: Self-reported	Colorectal cancer	Histological methods	Q5 vs. Q1 (> 14.3 vs. < 7.0 mmol/d)	0.67 (0.37-1.21)	Age, sex, study center	
						TRAP				Q5 vs. Q1 (> 4.1 vs. < 1.9 mmol/d)	0.89 (0.52-1.54)		
						TEAC				Q5 vs. Q1 (> 5.1 vs. < 2.3 mmol/d)	0.79 (0.46-1.35)		
						FRAP				Per 1 mmol/d increase	1.00 (0.95-1.05)		
						TRAP					0.94 (0.80-1.09)		
						TEAC					0.99 (0.87-1.11)		
		M/F: 1169	MF: 3312			FRAP	FFQ: Self-reported	Colon cancer	Histological methods	Q5 vs. Q1 (> 15.8 vs. < 7.4 mmol/d)	0.94 (0.65-1.36)	Age, sex, study center	
						TRAP				Q5 vs. Q1 (> 4.8 vs. < 2.0 mmol/d)	0.88 (0.62-1.23)		
						TEAC				Q5 vs. Q1 (> 5.5 vs. < 2.4 mmol/d)	0.79 (0.55-1.13)		
						FRAP				Per 1 mmol/d increase	1.00 (0.97-1.03)		
						TRAP					0.98 (0.91-1.05)		
						TEAC					0.97 (0.90-1.04)		
		M/F: 533	M/F: 3312			FRAP	FFQ: Self-reported	Rectal cancer	Histological methods	Q5 vs. Q1 (> 15.7 vs. < 7.4 mmol/d)	0.99 (0.58-1.68)	Age, sex, study center	
						TRAP				Q5 vs. Q1 (> 4.8 vs. < 2.0 mmol/d)	0.97 (0.60-1.56)		
						TEAC				Q5 vs. Q1 (> 5.5 vs. < 2.4 mmol/d)	1.07 (0.64-1.76)		
						FRAP				Per 1 mmol/d increase	0.99 (0.96-1.04)		
						TRAP					0.97 (0.88-1.07)		
						TEAC					0.97 (0.87-1.08)		

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Table 2 (*continued*)

Authors (year)	Country	Cases (n)	Controls (n)	Age[a] (cases)	Age[a] (controls)	Exposure	Exposure assessment	Outcome	Outcome assessment	Categorical or continues	OR (95%CI)	Matching factors	Adjustment[†]
Gifkins et al. 2012.b	USA	F: 205	F: 391	≥21	≥21	ORAC	FFQ: Self-reported	Ovarian cancer	Histological methods	T3 vs. T1 (> 16.0 vs. < 9.7 mmol/100 g food)	1.09 (0.62-1.94)	Age	1,3,4,6,7,8,16,29,31,34,35,36,37,39,40
						FRAP				T3 vs. T1 (> 6.4 vs. < 3.9 mmol/100 g food)	1.07 (0.62-1.86)		
Karimi et al., 2015	Iran	F: 100	F: 175	46.2	45.9	ORAC	FFQ: Interview	Breast cancer	Histological methods	Q4 vs. Q1 (> 1.7 vs. < 1.3 mmol/100 g food)	0.43 (0.11-1.12)	Age	1,6,7,11,14,16,31,33,34,36,38,40
Lucas et al., 2016	Italy	M/F: 326	M/F: 652	63	63	TEAC	FFQ: Interview	Pancreatic cancer	Histopathological methods	T3 vs. T1 (> 4.7 vs. < 3.6 mmol/d)	0.61 (0.39-0.94)	Age, sex, study center	1,2,3,6,8,9,10,12,16,17
						TRAP				T3 vs. T1 (> 5.0 vs. < 3.4 mmol/d)	0.78 (0.49-1.24)		
						FRAP				T3 vs. T1 (> 12.2 vs. < 9.1 mmol/d)	0.63 (0.41-0.99)		
Rossi et al., 2016	Italy	F: 454	F: 908	60	61	FRAP	FFQ: Self-reported	Endometrial cancer	Histological methods	Q4 vs. Q1 (> 28.6 vs. < 15.8 mmol/d)	0.69 (0.47-1.00)	Age, study center	1,3,6,7,9,10,12,31,34,35,39,40
						TEAC				Q4 vs. Q1 (> 9.1 vs. < 5.2 mmol/d)	0.68 (0.46-0.99)		
						TRAP				Q4 vs. Q1 (> 13.3 vs. < 6.9 mmol/d)	0.68 (0.47-0.98)		
						FRAP				Per one-SD increase	0.86 (0.75-0.98)		
						TEAC					0.86 (0.75-0.98)		
						TRAP					0.87 (0.76-0.99)		
Vecchia et al., 2013	Italy	M/F: 1953	M/F: 4154	N/R	N/R	FRAP	FFQ: Interview	Colorectal cancer	Histological methods	Q5 vs. Q1 (> 14.3 vs. < 7.9 mmol/d)	0.75 (0.61-0.93)	Age, study center	1,2,3,6,7,9,11,16,17,26
						TEAC				Q5 vs. Q1 (> 5.5 vs. < 3.1 mmol/d)	0.76 (0.61-0.93)		
						TRAP				Q5 vs. Q1 (> 5.9 vs. < 2.8 mmol/d)	0.71 (0.57-0.89)		
						FRAP				Per one-SD increase	0.88 (0.81-0.97)		
						TEAC					0.88 (0.81-0.96)		
						TRAP					0.89 (0.82-0.97)		
						FRAP	FFQ: Interview	Colon cancer	Histological methods	Q5 vs. Q1 (> 14.3 vs. < 7.9 mmol/d)	0.81 (0.63-1.05)	Age, study center	
										Q5 vs. Q1 (> 5.5 vs. < 3.1 mmol/d)	0.86 (0.67-1.10)		
						TEAC				Q5 vs. Q1 (> 5.9 vs. < 2.8 mmol/d)	0.77 (0.62-1.00)		
						TRAP							
						FRAP	FFQ: Interview	Rectal cancer	Histological methods	Q5 vs. Q1 (> 14.3 vs. < 7.9 mmol/d)	0.69 (0.51-0.94)	Age, study center	
										Q5 vs. Q1 (> 5.5 vs. < 3.1 mmol/d)	0.64 (0.48-0.87)		
						TEAC				Q5 vs. Q1 (> 5.9 vs. < 2.8 mmol/d)	0.65 (0.48-0.89)		
						TRAP							

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Table 2 (*continued*)

Authors (year)	Country	Cases (n)	Controls (n)	Age[a] (cases)	Age[a] (controls)	Exposure	Exposure assessment	Outcome	Outcome assessment	Categorical or continues	OR (95%CI)	Matching factors	Adjustment[†]
Praud et al., 2015 Praud et al., 2015et al., 2015	Italy	M/F: 230	M/F: 457	63	63	TEAC	FFQ: Interview	Gastric cancer	Histological methods	T3 vs. T1 (> 4.2 vs. < 2.9 mmol/d)	0.54 (0.33-0.88)	Age, sex, study center	1,2,3,6,8,10, 11,16
						FRAP				T3 vs. T1 (> 10.7 vs. < 7.3 mmol/d)	0.67 (0.42-1.07)		
						TRAP				T3 vs. T1 (> 4.0 vs. < 2.6 mmol/d)	0.57 (0.36-0.90)		
						TEAC				Per one-SD increase	0.87 (0.71-1.06)		
						FRAP					0.91 (0.75-1.10)		
						TRAP					0.90 (0.75-1.08)		
Serafini et al., 2002	Sweden	M/F: 505	M/F: 1116	67.6	66.8	TRAP	FFQ: Interview	Gastric cancer	Pathological methods	Q4 vs. Q1 (> 1.3 vs. < 0.8 mmol/d)	0.65 (0.48-0.89)	Age, sex	1,2,6,15,16,27
Holtan et al., 2012	USA	M/F: 603	M/F: 1007	60.9	60.1	ORAC	FFQ: Self-reported	Non-Hodgkin lymphoma	Pathological methods	Q4 vs. Q1 (> 12.9 vs. < 5.4 mmol/d)	0.61 (0.44-0.84)	Age, sex, study center	1,2,16
Russnes et al., 2016	Sweden	M: 1489	M: 1112	66.8	67.7	FRAP	FFQ: Self-reported	Prostate cancer	Histopathological methods	Q5 vs. Q1 (N/R)	1.05 (0.82-1.36)	Age, study center	1,3,6,8,9,16
Gifkins et al. 2012a	USA	F: 417	F: 395	≥21	≥21	ORAC FRAP	FFQ: Self-reported	Endometrial cancer	Histological methods	T3 vs. T1 (> 16.2 vs. 10.0 mmol/100 g food)	0.87 (0.56–1.36)	Age, Study center	1,3,4,6,7,8,16,17,21,29,31,34,35,36,39,40
										T3 vs. T1 (> 6.6 vs. 4.0 mmol/100 g food)	0.84 (0.54–1.33)		

Abbreviation: D-TAC: dietary total antioxidant capacity, FRAP: ferric reducing antioxidant power, TRAP: total radical trapping antioxidant parameter, TEAC: trolox equivalence antioxidant capacity, ORAC: oxygen radical absorbance capacity, OR: odds ratio, RR: relative risk, HR: hazard ratio, FFQ: food frequency questionnaire, M: males, F: females.

[a] Presented as mean or range.

[†] Adjustment: age (1), sex (2), education (3), race (4), height (5), BMI (6), physical activity (7), smoking (8), study center (9), year of interview (10), family history of cancer (11) and diabetes mellitus (12), hypertension (13), life satisfaction (14), number of meals per day (15), dietary intake of energy (16), alcohol (17), red meat (18), processed meat (19), fiber (20), fat (21), calcium (22), folate (23), vitamin D (24), coffee (25), TAC from coffee (26), salt (27), alpha-linolenic acid (28), antioxidant supplements (29), multivitamin supplements (30), age at menarche (31), reproductive history (32), age at first pregnancy (33), number of full pregnancies (34), age at menopause (35), menopausal status (36), tubal ligation (37), use of brassiere (38), hormone therapy (39), oral contraceptive (40), aspirin (41), previous endoscopy (42) and PSA testing in previous period (43).

2007; Cui et al., 2011; Holtan et al., 2012; Karimi et al., 2015; Vecchia et al., 2013; Lucas et al., 2016; Mekary et al., 2010; Pantavos et al., 2015; Rossi et al., 2016; Russnes et al., 2016, 2014; Ros et al., 2013). Furthermore, in 17 from 19 included studies, BMI was considered as a covariate (Amiano et al., 2018; Cui et al., 2011; Gifkins et al., 2012a, b; Karimi et al., 2015; Vecchia et al., 2013; Lucas et al., 2016; Mekary et al., 2010; Pantavos et al., 2015; Praud et al., 2015; Rossi et al., 2016; Russnes et al., 2016, 2014; Serafini et al., 2002, 2012; Vece et al., 2015; Ros et al., 2013). According to NOS, all studies were of high quality (Supplementary Table 1).

Among 14 included studies that assessed the association between D-TAC (based on FRAP) and cancer (Amiano et al., 2018; Cui et al., 2011; Gifkins et al., 2012a, b; Vecchia et al., 2013; Lucas et al., 2016; Mekary et al., 2010; Pantavos et al., 2015; Praud et al., 2015; Rossi et al., 2016; Russnes et al., 2016, 2014; Serafini et al., 2012; Ros et al., 2013), 5 prospective (Mekary et al., 2010; Pantavos et al., 2015; Russnes et al., 2014; Serafini et al., 2012; Ros et al., 2013) and 2 case-control studies (Vecchia et al., 2013; Lucas et al., 2016) reported a significant inverse association and others failed to find any significant association. In terms of D-TAC based on TRAP, five (Vecchia et al., 2013; Praud et al., 2015; Rossi et al., 2016; Serafini et al., 2002; Ros et al., 2013) from eight studies (Amiano et al., 2018; Vecchia et al., 2013; Lucas et al., 2016; Praud et al., 2015; Rossi et al., 2016; Serafini et al., 2002, 2012; Ros et al., 2013) had shown similar inverse association. Furthermore, two prospective (Chang et al., 2007; Vece et al., 2015) and five case-control studies (Amiano et al., 2018; Vecchia et al., 2013; Lucas et al., 2016; Praud et al., 2015; Rossi et al., 2016) had evaluated the association between D-TAC based on TEAC and risk of cancer that among them, 3 had reported a significant inverse association (Vecchia et al., 2013; Lucas et al., 2016; Praud et al., 2015) and 4 other studies had shown no significant relationship (Amiano et al., 2018; Chang et al., 2007; Rossi et al., 2016; Vece et al., 2015). The association between D-TAC (based on ORAC) and cancer was assessed in four case-control studies (Gifkins et al., 2012a, b; Holtan et al., 2012; Karimi et al., 2015) than only one showed a significant inverse association (Holtan et al., 2012).

3.2. Findings from meta-analysis

All studies included in the systematic review, were also considered in the current meta-analysis. To avoid double-counting data, the effect sizes of 2 prospective studies which done on the same population (one about risk of colorectal cancer and another about risk of prostate cancer), were combined before entering in the meta-analysis (Mekary et al., 2010; Russnes et al., 2014). We could not calculate the overall

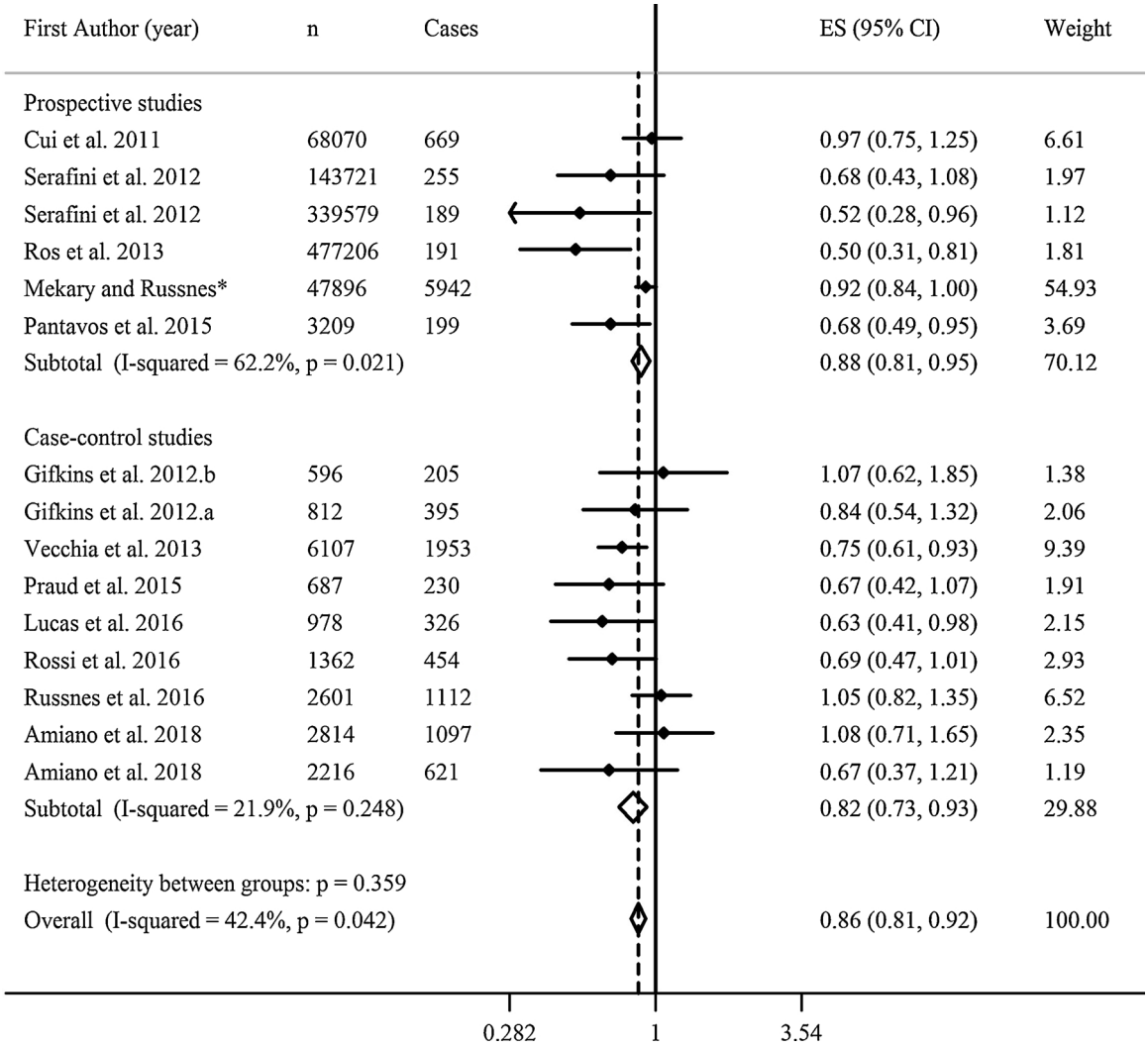

Fig. 2. Forest plot for the association between D-TAC (based on FRAP) and risk of cancer, stratified by study design (prospective versus case-control studies), comparing the highest category of D-TAC to the lowest category. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from fixed-effects analysis. Combining 15 effect sizes from 14 studies revealed that higher D-TAC (based on FRAP) was associated with lower risk of cancer. Such association was also seen in prospective and case-control studies. *Note: Effect sizes from Mekary and Russnes studies were combined because they were done on the same population. ES: effect size, D-TAC: dietary total antioxidant capacity, FRAP: ferric reducing antioxidant power.

estimate about effect sizes reported based on one-SD or one-unit increase in D-TAC because of different values of SD and different methods used to assess D-TAC. Overall, 721429 individuals with 16159 cases of cancer (including 4391 cases of colorectal cancer, 7145 cases of prostate cancer 1540 cases of endometrial cancer, 1179 cases of gastric cancer, 603 cases of non-Hodgkin lymphoma, 485 cases of epithelial ovarian cancer, 326 cases of pancreatic cancer, 299 cases of breast cancer and 191 cases of hepatocellular cancer) were included in the current meta-analysis. In the current meta-analysis, the association between D-TAC and risk of cancer was analyzed separately according to methods used to assess D-TAC.

3.2.1. D-TAC based on FRAP and cancer

The association between D-TAC (based on FRAP) and risk of cancer is presented in Fig. 2. Combining 15 effect sizes from 6 prospective (Cui et al., 2011; Mekary et al., 2010; Pantavos et al., 2015; Russnes et al., 2014; Serafini et al., 2012; Ros et al., 2013) and 8 case-control studies (Amiano et al., 2018; Gifkins et al., 2012a, b; Vecchia et al., 2013; Lucas et al., 2016; Praud et al., 2015; Rossi et al., 2016; Russnes et al., 2016) revealed a significant inverse association between D-TAC (based on FRAP) and risk of cancer (combined effect size: 0.86, 95% CI: 0.81-0.92, $P < 0.001$) with no between-study heterogeneity ($I^2 = 42.4\%$). Subgroup analysis based on study design showed such relationship either in prospective (combined effect size: 0.87, 95% CI: 0.81-0.95, $P = 0.001$) or case-control studies (combined effect size: 0.82, 95% CI: 0.73-0.93, $P = 0.001$). However, between-study heterogeneity was significant among prospective studies ($I^2 = 62.2\%$). Due to mentioned heterogeneity, random-effects analysis was also done. This analysis resulted in no change on observed significant associations (Supplementary Fig. 1).

Subgroup analysis based on gender (males/females/both), geographical region (US vs. non-US countries), methods used for diagnosis of cancer (pathological or histological methods vs. using medical records) and use of energy-adjusted D-TAC in statistical analysis (used vs. not-used) as well as follow-up duration (≥15 vs. < 15 years) and sample size (≥10,000 vs. < 10,000 individuals) among prospective studies, and variables matched between cases and controls among case-control studies (age and sex vs. age matched) revealed a significant inverse association between D-TAC (based on FRAP) and risk of cancer in all subgroups except in studies done on males, those that performed in US countries and case-control studies that matched age and sex variables between cases and controls (Table 3). Furthermore, dividing studies by gender, geographical region, follow-up duration and variables matched between cases and controls disappeared between-study heterogeneity ($I^2 < 50$).

Out of 14 studies that assessed the association between D-TAC (based on FRAP) and risk of cancer, 9 had enough data for inclusion in dose-response analysis (Amiano et al., 2018; Vecchia et al., 2013; Lucas et al., 2016; Mekary et al., 2010; Pantavos et al., 2015; Praud et al., 2015; Rossi et al., 2016; Serafini et al., 2012; Ros et al., 2013). A significant non-linear association was found between D-TAC (based on FRAP) and risk of cancer (P-nonlinearity < 0.001) (Supplementary Fig. 2). In terms of linear dose-response meta-analysis, a-5 mmol/day increment in D-TAC (based on FRAP) was associated with 9% reduction in risk of cancer (combined effect size: 0.91, 95% CI: 0.88-0.94, $P < 0.001$) with no between-study heterogeneity ($I^2 = 42.7\%$) (Supplementary Fig. 3). After dividing studies by design, such inverse association was also seen either in prospective (combined effect size: 0.92, 95% CI: 0.88-0.96, $P < 0.001$) or case-control (combined effect size: 0.89, 95% CI: 0.84-0.94, $P < 0.001$) studies. However, a moderate between-study heterogeneity was seen among prospective studies ($I^2 = 52.8\%$). After doing random-effects analysis, this inverse association remained significant among prospective studies (combined effect size: 0.89, 95% CI: 0.82-0.97, $P = 0.008$) (Supplementary Fig. 4).

3.2.2. D-TAC based on TRAP and cancer

Overall, combining ten effect sizes form 2 prospective (Serafini et al., 2012; Ros et al., 2013) and 6 case-control studies (Amiano et al., 2018; Vecchia et al., 2013; Lucas et al., 2016; Praud et al., 2015; Rossi et al., 2016; Serafini et al., 2002) revealed that diet with high TAC (based on TRAP) was associated with decreased risk of cancer (combined effect size: 0.69, 95% CI: 0.62-0.78, $P < 0.001$) (Fig. 3). No between-study heterogeneity was seen ($I^2 = 0\%$). This inverse association was also seen among both prospective (combined effect size: 0.60, 95% CI: 0.45-0.80, $P = 0.001$) and case-control studies (combined effect size: 0.72, 95% CI: 0.63-0.82, $P < 0.001$) with no between-study heterogeneity ($I^2 = 0\%$). In subgroup analyses, such significant inverse association was observed in all subgroups except in studies that were done on males (Table 3). No between-study heterogeneity was seen in these analyses ($I^2 = 0\%$). However, due to low variation and limited number of studies, we could not do subgroup analysis based on geographical region, follow-up duration and sample size.

All studies in terms of TRAP and risk of cancer were included in dose-response meta-analysis (Serafini et al., 2012; Ros et al., 2013; Amiano et al., 2018; Vecchia et al., 2013; Lucas et al., 2016; Praud et al., 2015; Rossi et al., 2016; Serafini et al., 2002). A significant inverse non-linear association was seen between D-TAC (based on TRAP) and risk of cancer (P-nonlinearity < 0.001) (Supplementary Fig. 5). Based on linear dose-response analysis, a-5 mmol/day increments in TRAP was associated with 11% lower risk of cancer (combined effect size: 0.89, 95% CI: 0.86-0.93, $P < 0.001$). There was moderate evidence of between-study heterogeneity in this regard ($I^2 = 59\%$) (Supplementary Figure 6). When we did random-effects analysis, the inverse association remained significant (Supplementary Figure 7); such that an increase of 5 mmol/day D-TAC (based on TRAP) was associated with 17% decreased risk of cancer (combined effect size: 0.83, 95% CI: 0.76-0.91, $P < 0.001$). When we divided studies by design, such inverse association was also seen in prospective and case-control studies.

3.2.3. D-TAC based on TEAC and cancer

Combined effect sizes on the association between D-TAC (based on TEAC) and risk of cancer are shown in Fig. 4. After combining 8 effect sizes from 2 prospective (Chang et al., 2007; Vece et al., 2015) and 5 case-control studies (Amiano et al., 2018; Vecchia et al., 2013; Lucas et al., 2016; Praud et al., 2015; Rossi et al., 2016), we found a significant inverse association between D-TAC (based on TEAC) and risk of cancer (combined effect size: 0.80, 95% CI: 0.70-0.90, $P < 0.001$) without significant between-study heterogeneity ($I^2 = 44\%$). After excluding two effect sizes from prospective studies and keeping only those from case-control studies, such relationship remained significant (combined effect size: 0.73, 95% CI: 0.63-0.84, $P < 0.001$). Findings from subgroup analysis revealed a significant inverse association between D-TAC (based on TEAC) and risk of cancer for studies done on both males and females (combined effect size: 0.74, 95% CI: 0.64-0.87, $P < 0.001$), those performed in non-US countries (combined effect size: 0.76, 95% CI: 0.66-0.86, $P < 0.001$), studies that used energy-adjusted D-TAC in statistical analysis (combined effect size: 0.81, 95% CI: 0.70-0.93, $P = 0.003$) and those that applied pathological or histological methods for diagnosis of cancer (combined effect size: 0.73, 95% CI: 0.63-0.84, $P < 0.001$) (Table 3). In mentioned subgroups, between-study heterogeneity was not significant ($I^2 < 50\%$). Further analyses based on other variables were not possible due to limited number of studies.

All studies in this part were included in dose-response meta-analysis. We found no significant non-linear relation between D-TAC (based on TEAC) and risk of cancer (P-nonlinearity = 0.12). However, a significant reduction in risk of cancer was seen when increasing TEAC from low levels to ≤5 mmol/day (P-nonlinearity = 0.01) (Supplementa1 Figure 8). In terms of linear dose-response analysis, no significant association was found between D-TAC (based on TEAC) and risk of cancer (combined effect size: 0.96, 95% CI: 0.91–1.01, $P = 0.08$)

Table 3
Subgroup analysis based on fixed-effects model for the association between D-TAC and risk of cancer.

		effect sizes (n)	I^2	$P_{-heterogeneity}$	Combined effect size (95%CI)	$P_{between}$
FRAP						
Overall		15	42.4	0.04	0.86 (0.81-0.92)	
Gender						0.003
	Male	4	6.3	0.36	0.93 (0.86-1.01)	
	Female	7	15.7	0.31	0.80 (0.69-0.93)	
	Both	4	0	0.47	0.69 (0.58-0.81)	
Geographical region						0.004
	US countries	4	0	0.89	0.93 (0.85-1.00)	
	Non-US countries	11	35.1	0.11	0.76 (0.68-0.85)	
Using energy-adjusted D-TAC						0.163
	Used	10	52	0.02	0.88 (0.82-0.94)	
	Not-used	5	0	0.46	0.74 (0.59-0.93)	
Cancer diagnosis						0.072
	Histopathological methods	10	27.5	0.19	0.88 (0.82-0.95)	
	Use of medical records	5	53.7	0.07	0.75 (0.64-0.89)	
Sample size, *n* (Prospective studies)						0.199
	< 10,000	10	21.9	0.25	0.82 (0.73-0.93)	
	≥10,000	5	63	0.03	0.89 (0.82-0.97)	
Follow-up, *y* (Prospective studies)						0.007
	< 10	12	21	0.24	0.82 (0.74-0.92)	
	≥10	3	37.3	0.21	0.91 (0.84-0.98)	
Matching (Case-control studies)						0.354
	Age matched	4	0	0.59	0.77 (0.66-0.91)	
	Age and sex matched	5	43.7	0.13	0.88 (0.74-1.05)	
TRAP						
Overall		10	0	0.74	0.69 (0.62-0.78)	
Gender						0.436
	Male	2	0	0.46	0.82 (0.61-1.10)	
	Female	3	0	0.63	0.71 (0.54-0.94)	
	Both	5	0	0.58	0.66 (0.57-0.77)	
Geographical region						0
	US countries	0	0	0	0	
	Non-US countries	10	0	0.74	0.69 (0.62-0.78)	
Using energy-adjusted D-TAC						0.374
	Used	6	0	0.45	0.72 (0.62-0.84)	
	Not-used	4	0	0.91	0.64 (0.52-0.79)	
Cancer diagnosis						0.283
	Histopathological methods	7	0	0.74	0.72 (0.63-0.82)	
	Use of medical records	3	0	0.51	0.60 (0.45-0.80)	
Matching (Case-control studies)						0.540
	Age matched	2	0	0.84	0.70 (0.58-0.85)	
	Age and sex matched	5	0	0.50	0.73 (0.61-0.88)	
TEAC						
Overall		8	44	0.08	0.80 (0.70-0.90)	
Gender						0.306
	Male	1	0	0	0.93 (0.62-1.40)	
	Female	3	69.2	0.04	0.91 (0.71-1.17)	
	Both	4	17.7	0.30	0.74 (0.64-0.87)	
Geographical region						0.006
	US countries	1	0	0	1.40 (0.92-2.14)	
	Non-US countries	7	0	0.54	0.76 (0.66-0.86)	
Using energy-adjusted D-TAC						0.758
	Used	6	48.2	0.08	0.81 (0.70-0.93)	
	Not-used	2	63.8	0.09	0.77 (0.59-1.00)	
Cancer diagnosis						0.018
	Histopathological methods	6	0	0.57	0.73 (0.63-0.84)	
	Use of medical records	2	67.4	0.08	1.03 (0.81-1.32)	
Matching (Case-control studies)						0.058
	Age matched	2	0	0.61	0.74 (0.62-0.89)	
	Age and sex matched	4	14.1	0.32	0.71 (0.57-0.90)	
ORAC						
Overall		4	66.1	0.03	0.67 (0.58-0.78)	
Gender						0.009
	Male	0	0	0	0	
	Female	3	4.2	0.35	0.84 (0.67-1.06)	
	Both	1	0	0	0.57 (0.47-0.69)	
Geographical region						0.44
	US countries	1	0	0	0.43 (0.13-1.37)	
	Non-US countries	3	75.8	0.01	0.68 (0.58-0.78)	
Using energy-adjusted D-TAC						0.005
	Used	2	0	0.63	0.57 (0.47-0.68)	
	Not-used	2	0	0.39	0.87 (0.69-1.09)	
Cancer diagnosis						0
	Histopathological methods	4	66.1	0.03	0.67 (0.58-0.78)	

(*continued on next page*)

Table 3 (*continued*)

	effect sizes (n)	I^2	$P_{heterogeneity}$	Combined effect size (95%CI)	$P_{between}$
Use of medical records	0	0	0	0	
Matching (Case-control studies)					0.009
Age matched	3	4.2	0.35	0.84 (0.67-1.06)	
Age and sex matched	1	0	0	0.57 (0.47-0.69)	

Abbreviation: D-TAC: dietary total antioxidant capacity, FRAP: ferric reducing antioxidant power, TRAP: total radical trapping antioxidant parameter, TEAC: trolox equivalence antioxidant capacity, ORAC: oxygen radical absorbance capacity.

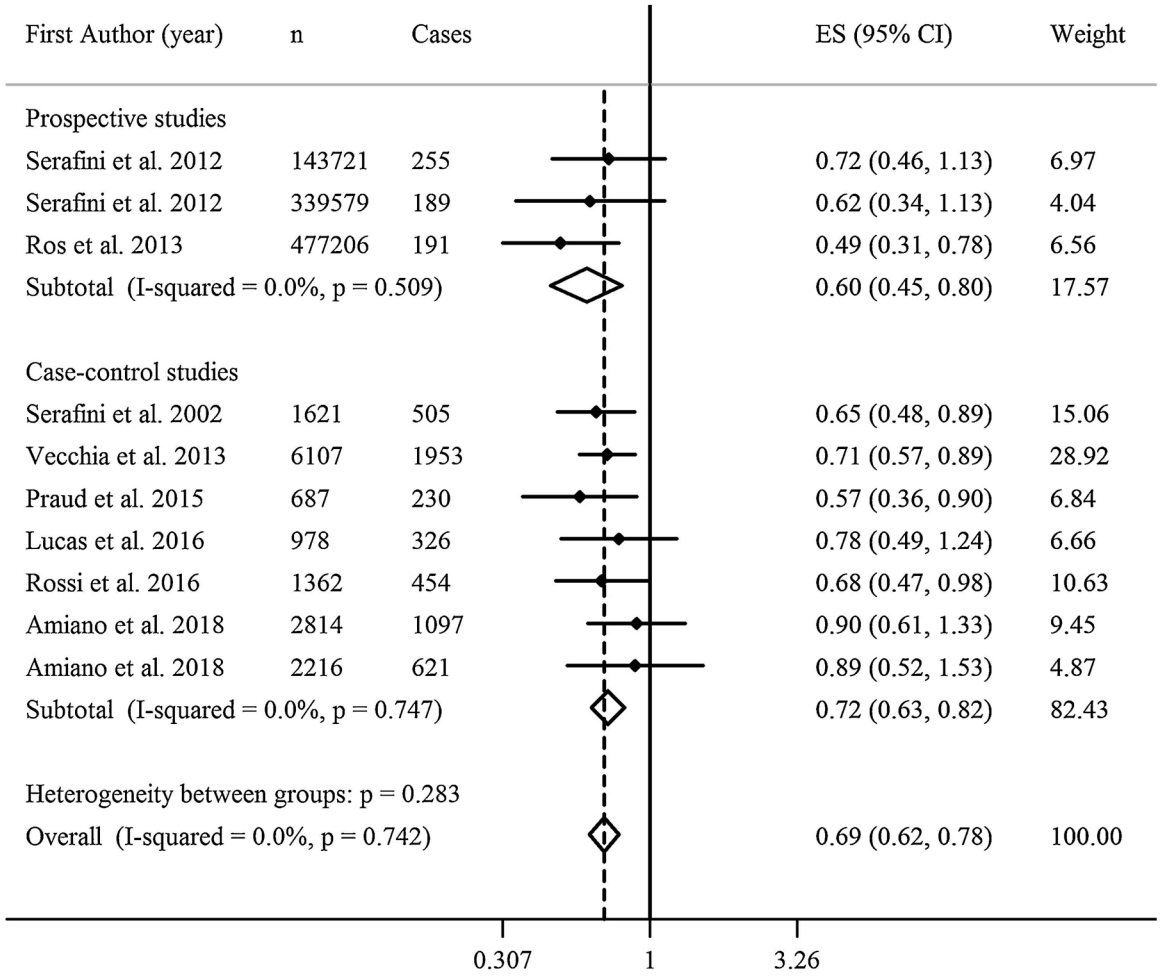

Fig. 3. Forest plot for the association between D-TAC (based on TRAP) and risk of cancer, stratified by study design (prospective versus case-control studies), comparing the highest category of D-TAC to the lowest category. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from fixed-effects analysis. Combining 10 effect sizes from 8 studies revealed that higher D-TAC (based on TRAP) was associated with lower risk of cancer. Such association was also seen in prospective and case-control studies. ES: effect size, D-TAC: dietary total antioxidant capacity, TRAP: total radical trapping antioxidant parameter.

(Supplementary Figure 9). However, between-study heterogeneity was significant (I^2 = 69.8%). When we did random-effects analysis, mentioned association became significant; such that a-5 mmol/day increase in D-TAC (based on TEAC) was associated with 14% decreased risk of cancer (combined effect size: 0.86, 95% CI: 0.76-0.97, P = 0.01) (Supplementary Figure 10). After dividing studies by design, between-study heterogeneity disappeared completely (I^2 = 0). In addition, a significant inverse association was found among case-control studies; such that a-5 mmol/day increase in D-TAC (based on TEAC) was associated with 21% reduction in risk of cancer (combined effect size: 0.79, 95% CI: 0.72-0.87, P < 0.001).

3.2.4. D-TAC based on ORAC and cancer

Overall, 4 case-control studies had assessed D-TAC with ORAC method in relation to cancer (Gifkins et al., 2012a, b; Holtan et al., 2012; Karimi et al., 2015). After combining 4 effect sizes, a significant inverse association was observed between D-TAC (based on ORAC) and risk of cancer (combined effect size: 0.67, 95% CI: 0.58-0.78, P < 0.001) (Fig. 5). However, between-study heterogeneity was significant (I^2 = 66.1%). When we did random-effects analysis, this association attenuated and became marginally significant (combined effect size: 0.72, 95% CI: 0.52–1.00, P = 0.04) (Supplementary Figure 11). To find probable source of heterogeneity, subgroup analysis was done (Table 3). Doing mentioned analysis based on gender, use of energy-adjusted D-TAC in statistical analysis and variables matched between cases and controls explained between-study heterogeneity. In addition, an inverse association was seen between D-TAC (based on ORAC) and cancer for studies done in US countries (combined effect size: 0.68, 95% CI: 0.58-0.78, P < 0.001), and those that used energy-adjusted D-TAC in statistical analysis (combined effect size: 0.57, 95% CI: 0.47-0.68,

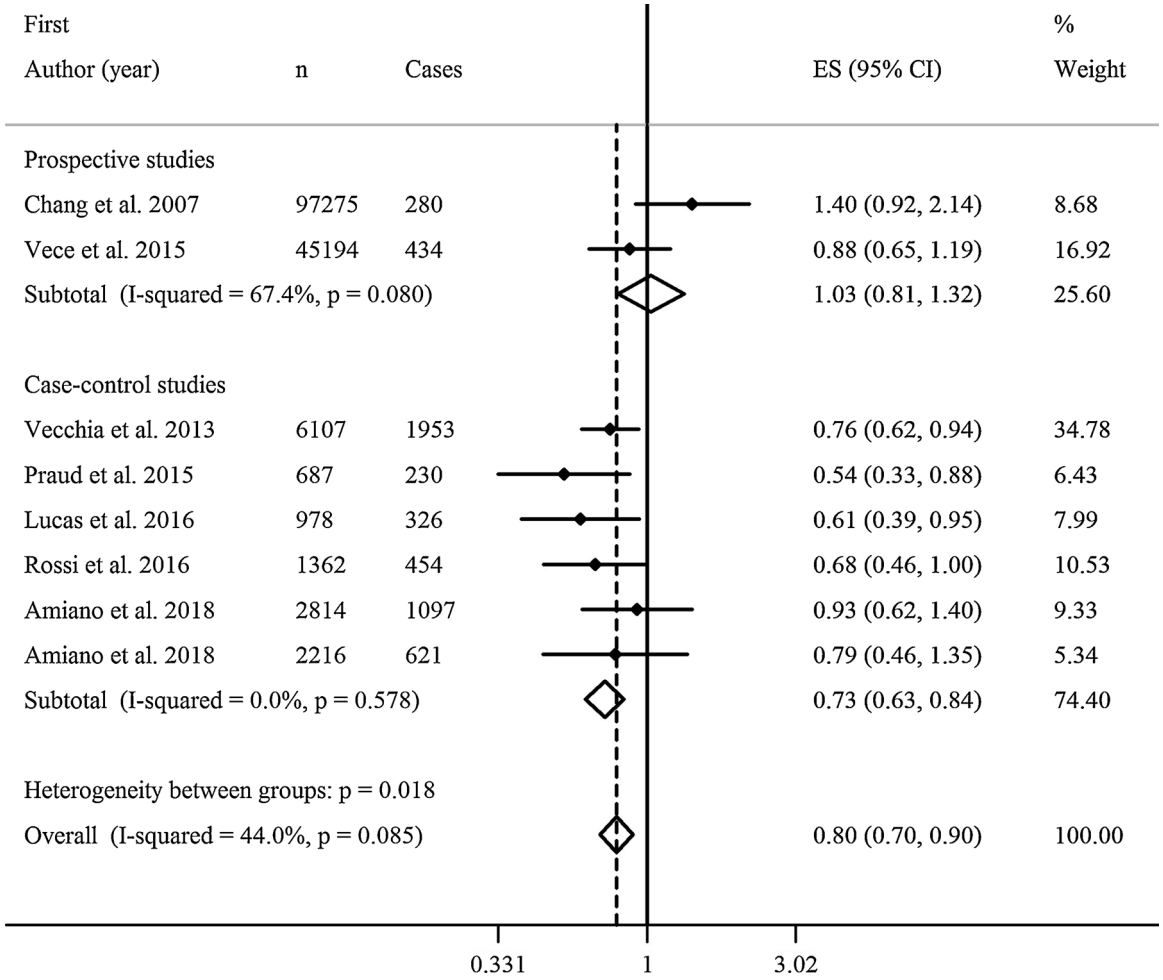

Fig. 4. Forest plot for the association between D-TAC (based on TEAC) and risk of cancer, stratified by study design (prospective versus case-control studies), comparing the highest category of D-TAC to the lowest category. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from fixed-effects analysis. Combining 8 effect sizes from 7 studies revealed that higher D-TAC (based on TEAC) was associated with lower risk of cancer. Such association was also seen in case-control studies. ES: effect size, D-TAC: dietary total antioxidant capacity, TEAC: trolox equivalence antioxidant capacity.

$P < 0.001$). Because of limited number of studies, subgroup analysis based on other variables was not possible. In addition, due to lack of necessary data, we could not examine dose-response relation between D-TAC (based on ORAC) and cancer risk.

3.2.5. D-TAC and different types of cancer (Table 4)

In this part, we considered different methods, used for assessment of D-TAC, as same because of limited number of studies. Some studies assessed D-TAC by different methods in relation to one type of cancer. To avoid double-counting data, in this case, we first combined effect sizes for different methods and then, combined effect size was included in the meta-analysis. Overall, combining 5 effect sizes for colorectal cancer, 4 for colon cancer, 4 for rectal cancer, 4 for gastric cancer and 3 for endometrial cancer in relation to D-TAC provided from 7 studies (Amiano et al., 2018; Vecchia et al., 2013; Mekary et al., 2010; Praud et al., 2015; Serafini et al., 2002, 2012; Vece et al., 2015), we found a significant inverse association for all mentioned cancers. The overall summary effect size for colorectal cancer was 0.82 (95% CI: 0.75-0.89, $P < 0.001$), for colon cancer was 0.85 (95% CI: 0.76-0.94, $P = 0.002$), for rectal cancer was 0.76 (95% CI: 0.66-0.88, $P < 0.001$), for gastric cancer was 0.63 (95% CI: 0.53-0.73, $P < 0.001$), and for endometrial cancer was 0.78 (95% CI: 0.69-0.89, $P < 0.001$). There was a moderate evidence of between-study heterogeneity in the case of colon ($I^2 = 65.4\%$) and rectal cancer ($I^2 = 85.9\%$). When we did random-effects analysis, the inverse association for colon and rectal cancer became non-significant. Because of the limited number of studies, further analyses including subgroup analysis based on study design (prospective vs. case-control) and dose-response analysis were not possible.

3.2.6. Publication bias and sensitivity analysis

Based on visual inspection of funnel plots and also according to results of Begg's test ($P > 0.10$), we found no evidence of publication bias (Supplementary Figure 12). In addition, sensitivity analysis showed that overall estimates, obtained for the associations between D-TAC and risk of cancer, did not depend on a particular study or group of studies.

4. Discussion

In the current study, we found that D-TAC obtained from different methods including FRAP, TRAP, TEAC and ORAC was inversely associated with risk of cancer. Such relationship was also seen for D-TAC based on FRAP and TRAP in either prospective or case-control studies. Furthermore, mentioned inverse association was observed for D-TAC based on TEAC and ORAC in case-control studies. In addition, we found that D-TAC was inversely associated with risk of colorectal, gastric and endometrial cancer. Dose-response meta-analysis provided a significant non-linear association between D-TAC (based on FRAP and TRAP) and cancer risk (P-nonlinearity < 0.001). Based on linear dose-response meta-analysis, a-10 mmol/day increase in FRAP and a-5 mmol/day

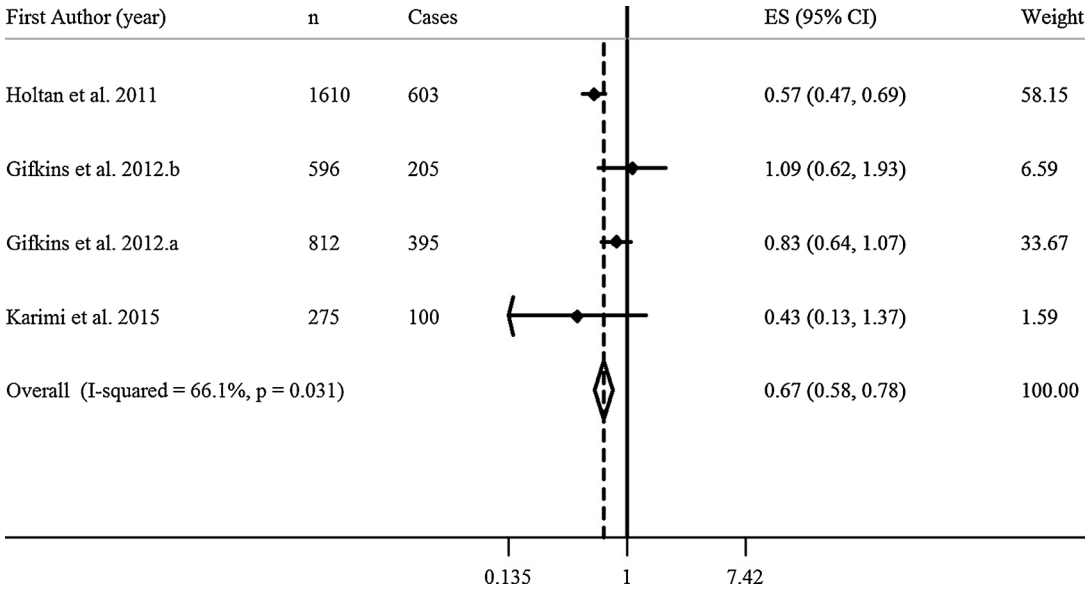

Fig. 5. Forest plot for the association between D-TAC (based on ORAC) and risk of cancer among case-control studies comparing the highest category of D-TAC to the lowest category. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from fixed-effects analysis. Combining 4 effect sizes from 4 studies revealed that higher D-TAC (based on ORAC) was associated with lower risk of cancer. ES: effect size, D-TAC: dietary total antioxidant capacity, ORAC: oxygen radical absorbance capacity.

increase in TRAP and TEAC were associated with 9%, 17% and 14% reduction in risk of cancer, respectively. To the best of our knowledge, current study is the first to summarize earlier studies on the association between D-TAC and risk of cancer.

Cancer is a common chronic disorder that is associated with a high burden, morbidity and mortality (Ferlay et al., 2015, 2013). A large number of studies have been done to determine factors involved in the etiology of cancer (Carreras-Torres et al., 2017; Hung et al., 2015; Ma et al., 2013; Sieri et al., 2014; Sundstrom et al., 2015). Diet is a most important factor known in this regard (Eriksen et al., 2017; Jiao et al., 2018; Thomson et al., 2014). Earlier studies have shown that dietary intakes of antioxidants are associated with lower odds of cancer (Davies et al., 2006; Lin et al., 2009). Recently, it has been shown that considering total antioxidant capacity of diet in relation to cancer is better than assessment of a single antioxidant of food rich in antioxidant (Mekary et al., 2010). There are some antioxidants in foods which have not been identified. D-TAC considers both known and unknown antioxidants in foods and therefore, reflects total antioxidant capacity of diet. Some studies evaluated the association between D-TAC and cancer (Chang et al., 2007; Cui et al., 2011; Gifkins et al., 2012a, b; Holtan et al., 2012; Karimi et al., 2015; Vecchia et al., 2013; Lucas et al., 2016; Mekary et al., 2010; Pantavos et al., 2015; Praud et al., 2015; Rossi et al., 2016; Russnes et al., 2016, 2014; Serafini et al., 2002, 2012; Vece et al., 2015; Ros et al., 2013); however, findings in this regard are conflicting.

Based on findings in the current systematic review and meta-analysis, D-TAC was inversely associated with risk of cancer, particularly with colorectal, gastric and endometrial cancer. In line with our findings, Ben et al., reported that consumption of fruits which are rich in different types of antioxidants had a significant protective effect on colorectal adenoma (A.M.A. Archives of DermatologyBen et al., 2015). Findings from a systematic review and meta-analysis done by Wang et al., suggested an inverse association between citrus fruit intake and esophageal cancer risk (Wang et al., 2015). Another review in this regard revealed that consumption of both fruits and vegetables that are contained of high amount of antioxidants was inversely associated with risk of lung cancer (Vieira et al., 2016). In contrast, Peng et al., reported no significant association between consumption of foods rich in antioxidants and prognosis of breast cancer (Peng et al., 2017). In addition, some observational studies failed to find any significant association between intake of antioxidants or foods rich in antioxidants with risk of cancer (Jung et al., 2013; Peng et al., 2017). Finding no significant association in mentioned studies might be due to assessing the dietary intake of a single antioxidant or a group of antioxidant foods, whereas in the studies included in the current review, total antioxidant capacity of diet was assessed as the exposure. In addition, some studies included in the current review reported no significant association between D-TAC and risk of cancer. This non-significant association might be explained by different methods used to assess D-TAC. The most studies that reported an inverse association between D-TAC and cancer, used FRAP to determine D-TAC (Vecchia et al., 2013; Lucas et al., 2016; Mekary et al., 2010; Pantavos et al., 2015; Russnes et al., 2014; Serafini et al., 2012; Ros et al., 2013). Earlier studies have shown that FRAP is better method to determine D-TAC than other methods (Halvorsen et al., 2002). Furthermore, it must be kept in mind that studies which reached a significant inverse association between D-TAC and cancer had mostly large sample size and were prospective compared with those reported no significant relationship. For example, out of 7 studies reported significant inverse association between D-TAC (based on FRAP) and cancer, 5 had been prospective (Mekary et al., 2010; Pantavos et al., 2015; Russnes et al., 2014; Serafini et al., 2012; Ros et al., 2013) and 4 had included more than 10,000 participants (Mekary et al., 2010; Russnes et al., 2014; Serafini et al., 2012; Ros et al., 2013). While one study (Cui et al., 2011), out of six that reported no significant association (Cui et al., 2011; Gifkins et al., 2012a, b; Praud et al., 2015; Rossi et al., 2016; Russnes et al., 2016), was prospective and five other studies included less than 10,000 individuals (Gifkins et al., 2012a, b; Praud et al., 2015; Rossi et al., 2016; Russnes et al., 2016).

We found that a-10 mmol/day increase in FRAP was associated with 9% reduction in risk of cancer. Based on Pellegrini et al. (2003) study in which content of foods' antioxidants was measured, a-200 g of blackberry (a fruit with very high antioxidant capacity) is equivalent to 10.3 mmol Fe^{2+} for FRAP which means one should consume 200 g of blackberry daily to reduce 9% in the risk of cancer development. Another example is spinach with the highest antioxidant capacity among vegetables (Pellegrini et al., 2003). Consuming a-200 g spinach (is equal to 5.38 mmol Fe^{2+} for FRAP) per day can reduce the risk of cancer by 4.5%. Overall, considering foods rich in antioxidants such as fruits

Table 4
The association between D-TAC and some common types of cancer based on fixed-and random-effects models.

Type of cancer	effect sizes (n)	I^2	$P_{heterogeneity}$	RR (95% CI)	P-value
Colorectal cancer					
Fixed-effects model	5	43.4	0.132	0.82 (0.75-0.89)	< 0.001
Random-effects model	5	43.4	0.132	0.85 (0.74-0.97)	0.016
Colon cancer					
Fixed-effects model	4	65.4	0.034	0.85 (0.76-0.94)	0.002
Random-effects model	4	65.4	0.034	0.86 (0.71-1.05)	0.133
Rectal cancer					
Fixed-effects model	4	85.9	0.000	0.76 (0.66-0.88)	< 0.001
Random-effects model	4	85.9	0.000	0.93 (0.59-1.48)	0.766
Gastric cancer					
Fixed-effects model	4	0	0.812	0.63 (0.53-0.73)	< 0.001
Random-effects model	4	0	0.812	0.63 (0.53-0.73)	< 0.001
Endometrial cancer					
Fixed-effects model	3	55.5	0.106	0.78 (0.69-0.89)	< 0.001
Random-effects model	3	55.5	0.106	0.79 (0.66-0.96)	0.017

Abbreviation: D-TAC: dietary total antioxidant capacity.

and vegetables in food choices may have a benefit for reducing the risk of cancer.

In the current meta-analysis, different methods for calculating D-TAC including FRAP, TRAP, TEAC and ORAC were assessed in relation to cancer. We found similar findings for these methods, but findings from dose-response analyses were different. Unlike FRAP and TRAP, we found no significant non-linear association for TEAC in relation to cancer. Furthermore, as shown in the systematic review, the effect sizes from some studies were quite different for different methods used to assess D-TAC. Differences in chemical mechanisms of these methods may be a reason for this different finding. For example, FRAP method directly measures antioxidants or reductants in a sample through measuring the reduction of Fe^{3+} (ferric iron) to Fe^{2+} (ferrous iron) (Jones et al., 2017). In contrast, other methods are mostly indirect because they measure the inhibition of reactive species (free radicals) generated in the reaction mixture, and these results also depend strongly on the type of reactive species used (Halvorsen et al., 2002; Kobayashi et al., 2012). Furthermore, the other methods, except FRAP, use a lag phase type of measurement that is difficult to standardize in previous experiments and generates varying results among different laboratories (Halvorsen et al., 2002). Therefore, it seems that FRAP is more accurate than other methods for estimating of D-TAC.

In the current study, given the observed inverse association between D-TAC and risk of colorectal cancer, we expected to see such association for colon and rectal cancers, but we found non-significant associations for them. Previous studies have shown that etiologic factors for incidence of cancer in different segments of intestinal tract differ because these segments derive from different parts of embryonic intestinal tract (Hjartaker et al., 2013; Wei et al., 2004). In addition, segments of large bowel differ in function, pH, and exposure to fecal matter (Hjartaker et al., 2013; Iacopetta, 2002; Wei et al., 2004). Furthermore, type and amount of bacterial hydrolytic and reductive enzymes are different regionally within the large bowel (McBain and Macfarlane, 1998). These enzymes are involved in the production of mutagenic metabolites (McBain and Macfarlane, 1998). Therefore, these differences contribute to different effects of D-TAC on intestinal tract.

Diet with high total antioxidant capacity provides an adequate and efficient protection against oxidative stress can result in DNA damage and mutations (Serafini et al., 2006). Antioxidants are scavengers of free radicals, which can cause oxidative damage to DNA, proteins, and lipids (Seifried et al., 2003). Having a meal high in lipids and energy increases the postprandial oxidative and inflammatory stress, mediated by proinflammatory cytokines including tumor necrosis factor-α, interleukin-6 and oxidized lipids (Adibhatla et al., 2008; Serafini et al., 2009). The presence of foods rich in antioxidants along with a high-fat meal might provide a battery of exogenous antioxidants, able to quench radical species produced at the gastric level, synergizing with endogenous antioxidants and providing a more efficient protection against oxidative stress (Gorelik et al., 2008; Lamb and Goldstein, 2008). Furthermore, for cells or DNA that have already been mutated, higher intakes of antioxidants might also protect them from excessive oxidant toxicity and apoptosis (Cui et al., 2011). Diet with high total antioxidant capacity has anti-inflammatory properties (Valtuena et al., 2008). Inflammation is a known risk factor for cancer (Chen et al., 2017; Prevete et al., 2018).

In addition to cancer risk, dietary intake of antioxidant can affect different clinical outcomes in patients suffering from cancer. Genkinger et al reported that greater intake of fruits and vegetables or diet with high antioxidant capacity was associated with lower risk of mortality from cancer (Genkinger et al., 2004). In a cohort study, intake of fresh fruit, root vegetables, and fruiting vegetables was associated with lower risk of cancer mortality, probably as a result of their high content of vitamin C, pro-vitamin A carotenoids, and lycopene (Agudo et al., 2007). In a meta-analysis, adherence to a low-fat diet with high content of antioxidants was associated with better prognosis in patients with breast cancer (Hauner et al., 2011). Overall, it seems that diet rich in antioxidants can favorably affect both prevention and treatment of cancer.

There are some limitations in the current study. Although we assessed the association between D-TAC and risk of cancer, but due to the limited number of studies, assessment of this association for other common types of cancer such as prostate, lung and breast cancer was not possible. Furthermore, studies included in the current review were different in terms of statistical analyses (logistic vs. Cox proportional hazards regression) and methods used to assess D-TAC. However, statistical analysis in the current meta-analysis was separately done for methods of D-TAC assessment. In addition, cases and controls in case-control studies were matched based on age or sex or both, while other important factors such as BMI were not considered in this regard. However, most of mentioned studies considered BMI as a covariate. In some included studies, energy-adjusted D-TAC was not used to assess the association between D-TAC and cancer. However, energy was considered as a covariate. Earlier studies have shown that using energy-adjusted dietary intakes are better than considering energy as a covariate for the assessment of diet-disease relationships.

5. Conclusion

We found that D-TAC obtained from different methods including FRAP, TRAP, TEAC and ORAC was inversely associated with risk of cancer. This protective effect of D-TAC was also seen for some common types of cancer including colorectal, gastric and endometrial cancer.

Declarations of interest

None.

Conflict of interest

All authors in this study have no conflict of interest to report.

Authors' contribution

OS, AS, MP, SRK, AM and MK contributed in conception, design, statistical analyses, data interpretation and manuscript drafting. OS and MN contributed in data analysis, data interpretation and manuscript drafting. All authors approved the final manuscript for submission.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.critrevonc.2019.04.003.

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