ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ

ΙΑΤΡΙΚΗ ΣΧΟΛΗ

ΘΕΡΑΠΕΥΤΙΚΗ ΚΛΙΝΙΚΗ ΝΟΣ. ΑΛΕΞΑΝΔΡΑ

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

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Διευθυντής

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"Olive oil intake and gastrointestinal and urogenital cancer incidence: a systematic review and meta-analysis"

Όνομα: Μάρκελλος Χρήστος

Αριθμός Μητρώου: 20180658

Ιδιότητα: Ειδικευόμενος Παθολογικής Ογκολογίας, ΓΝΑ Αλεξάνδρα

Επιβλέπουσα καθηγήτρια ΜΔΕ Θεοδώρα Ψαλτοπούλου, Καθηγήτρια Θεραπευτικής-Επιδημιολογίας-Προληπτικής Ιατρικής, Ιατρική Σχολή ΕΚΠΑ

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<u>Τα Μέλη της Εξεταστικής Επιτροπής</u>

1. Θεοδώρα Ψαλτοπούλου, Καθηγήτρια Θεραπευτικής-Επιδημιολογίας-Προληπτικής Ιατρικής, Ιατρική Σχολή ΕΚΠΑ
2. Μαρία Γαβριατοπούλου, Επίκουρη Καθηγήτρια Θεραπευτικής Κλινικής, Νοσοκομείο «Αλεξάνδρα», Ιατρική Σχολή ΕΚΠΑ
3. Θεόδωρος Ν. Σεργεντάνης, Ακαδημαϊκός Υπότροφος Θεραπευτικής Κλινικής, Νοσοκομείο «Αλεξάνδρα», Ιατρική Σχολή ΕΚΠΑ

ΑΘΗΝΑ 2021

Πίνακας περιεχομένων

Κατανάλωση ελαιολάδου και επίπτωση γαστρεντερικού και ουρογεννητικού καρκίνου: συστηματική ανασκόπηση και μετα-ανάλυση

Περίληψη

ΥΠΟΒΑΘΡΟ: Διάφορες επιδημιολογικές μελέτες υποστηρίζουν ότι το ελαιόλαδο θα μπορούσε να συμβάλλει στη μείωση του κινδύνου εμφάνισης καρκίνου. Για το σκοπό της παρούσας εργασίας πραγματοποιήσαμε μια συστηματική ανασκόπηση και μετα-ανάλυση με στόχο τη διερεύνηση της συσχέτισης μεταξύ της κατανάλωσης ελαιολάδου και της επίπτωσης καρκίνου του γαστρεντερικού και ουρογεννητικού συστήματος.

ΜΕΘΟΔΟΙ: Μια συστηματική αναζήτηση πραγματοποιήθηκε στις βάσεις δεδομένων PubMed, EMBASE και Google Scholar (καταληκτική ημερομηνία αναζήτησης: 10 Μαΐου 2020). Εκτιμήθηκε ο συγκεντρωτικός σχετικός κίνδυνος (RR) και τα διαστήματα εμπιστοσύνης 95% (95% CIs) με μοντέλα τυχαίων επιδράσεων (DerSimonian-Laird). Πραγματοποιήθηκαν επίσης αναλύσεις υποομάδων, ανάλυση ευαισθησίας και ανάλυση μετα-παλινδρόμησης.

ΑΠΟΤΕΛΕΣΜΑΤΑ: 15 μελέτες για γαστρεντερικό καρκίνο συμπεριλήφθηκαν στη μετα-ανάλυση: 13 ήταν ασθενών-μαρτύρων και 2 ήταν κοόρτης. Υψηλότερη κατανάλωση ελαιολάδου συσχετίστηκε με 23% μικρότερη πιθανότητα ανάπτυξης καρκίνου του μαστού (RR=0.77, 95%CI: 0.66-0.89). Αναφορικά με το ουρογεννητικό σύστημα, συνθετική ανάλυση 6 μελετών ασθενών-μαρτύρων έδειξε μείωση κινδύνου κατά 54% (RR=0.46, 95%CI: 0.29-0.72). Σημαντικές προστατευτικές επιδράσεις παρατηρήθηκαν τόσο σε υποομάδες ανάλογα με τη θέση της κακοήθειας, σε Μεσογειακούς όσο και μη Μεσογειακούς πλυθησμούς, μελέτες με μόνο- και πολυμεταβλητή ανάλυση και σε όλες τις υποομάδες βάσει της ποιότητας της μελέτης.

ΣΥΜΠΕΡΑΣΜΑΤΑ: Η κατανάλωση ελαιολάδου φαίνεται να έχει ευεγερτικές επιδράσεις στην πρόληψη του καρκίνου του γαστρεντερικού και του ουρογεννητικού συστήματος. Επιπρόσθετες προοπτικές μελέτες κοόρτης, όπως και ελεγχόμενες τυχαιοποιημένες κλινικές δοκιμές, είναι ωστόσο επιθυμητές.

Λέξεις-κλειδιά: Ελαιόλαδο, Καρκίνος, Μετα-ανάλυση, Διατροφή, Μεσογειακή διατροφή

Olive oil intake and gastrointestinal and urogenital cancer incidence: a systematic review and meta-analysis

Abstract

BACKGROUND: Various epidemiological studies have suggested that olive oil component could play a role in decreasing cancer risk. For the scope of the present thesis we conducted a systematic review and meta-analysis aiming at investigating the association between olive oil consumption and incidence of gastrointestinal and urogenital cancer.

METHODS: A systematic search was conducted in PubMed, EMBASE and Google Scholar databases (end-of-search: May 10, 2020). Pooled relative risk (RR) and 95% confidence intervals (95% CIs) were estimated with random-effects (DerSimonian-Laird) models. Subgroup analyses, sensitivity analysis and meta-regression analysis were also performed.

RESULTS: 15 studies on gastrointestinal cancer were included in the meta-analysis; 13 were case-control and 2 were cohort studies. Highest olive oil consumption was associated with 23% lower likelihood of developing breast cancer (RR=0.77, 95%CI: 0.66-0.89). Concerning the urogenital cancers, pooled analysis of 6 case-control studies showed a cancer risk reduction of 54% (RR=0.46, 95%CI: 0.29-0.72). Effect remained significant in subanalysis on different tumour sites, Mediterranean and non-Mediterranean participants, studies presenting a multivariate and a univariate analysis and subgroups by study quality.

CONCLUSIONS: Olive oil consumption seems to exert favourable actions in terms of gastrointestinal and urogenital cancer prevention. Additional prospective cohort studies, as well as large randomized trials, seem desirable.

Keywords: Olive oil, Cancer, Meta-analysis, Nutrition, Mediterranean diet

Abbreviations: CB1; cannabinoid receptor type 1 (CB1), CI:; confidence interval, d; day, EVOO; extra virgin olive oil, g; grams, gpd; grams per day, gpw; grams per week, HER2; human epidermal growth factor receptor 2, I^2; inconsistency index, lpm; liters per month, NC; not calculable, NOS; Newcastle-Ottawa score, PEA3; polyomavirus enhancer activator 3, PRISMA; Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, RR; relative risk, Qn; quintile, Qr; quartile, spw; servings per week , T; tertile, tabspy; tablespoon per year, tpm; times per month, tpw; times per weeak

1. Introduction

Cancer is accountable for an estimated 9.6 million deaths in 2018, being the second leading cause of death globally, only after cardiovascular diseases [1]. The economic burden of cancer on patients and healthcare systems is substantial and increasing, with a worldwide annual economic toll in 2010 estimated at approximately US$ 1.16 trillion [1]. The role of diet as an important, potentially modifiable factor in cancer prevention has been highlighted [2–4]. According to the World Cancer Research Fund (WCRF), 40% of cancer cases can be prevented by appropriate diet, nutrition and physical activity [5]. However, the attributable detrimental impact of diet on cancer incidence seems to be increasing nowadays [6].

Accumulating evidence has pointed to a reduction in the risk of various types of cancer in populations of the Mediterranean basin, largely due to high consumption of olive oil as the main vegetable fat, plant-based foods and fish, as well as to a moderate consumption of white meat, eggs, dairy products and alcohol [7–13]. Olive oil (*Olea europaea, Oleaceae*) is a traditional staple food for Mediterranean people and a fundamental component of the Mediterranean diet, used for both dressing and cooking. It has the highest ratio of monounsaturated to polyunsaturated fatty acids among vegetable oils. Its favorable effects have been attributed to the abundance of valuable nutrients, such as antioxidant phenolic compounds (i.e., hydroxytyrosol and oleuropein), vitamins, lignans, squalene and terpenoids [14–18].

Recent bibliography from *in vitro* and animal nutrigenomics studies suggests that olive oil components act on receptors, signaling kinases and transcription factors associated with cellular stress and inflammation, lipoprotein metabolism and damage, endothelial function and, in general, with pathways responsible for cell cycle regulation and metabolism, exerting a protective role on malignancy development [14,16,19–23]. To date, the relationship between olive oil consumption and cancer risk in humans has been studied in epidemiological studies, most taking place around the Mediterranean region,

where populations consume it in large quantities, reporting equivocal associations [13,24–29]. In our previous meta-analysis of 19 case-control studies, conducted nearly 10 years ago, we observed a significant inverse relationship between olive oil intake and overall cancer risk [30]; nevertheless, a considerable amount of evidence has been accumulated thereafter, allowing further insight in overall and site-specific associations.

For the scope of the present study, we conducted a systematic review and meta-analysis of all the available epidemiological studies that have assessed the association between olive oil consumption and gastrointestinal or urinary cancer risk or prognosis, aiming, ultimately, at establishing the role of olive oil intake in cancer prevention and survival.

2. Material and Methods

Search strategy and eligibility of studies

The present systematic review and meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [31]; the PRISMA Checklist is presented in Supplemental Table 1. The study protocol was discussed and agreed upon in advance by all authors. A systematic search was conducted in PubMed, EMBASE and Google Scholar databases (end-of-search: May 10, 2020). In PubMed and EMBASE, the following search algorithm was used: olive AND oil AND cancer. Only publications concerning gastrointestinal or urinary cancer were considered eligible. As far as publication language is concerned, no restriction was implemented. Reference lists of reviews and eligible articles were systematically searched for relevant articles in a "snowball" procedure. The search in Google Scholar was performed using the keywords "olive oil" and cancer; articles including these words were sorted by best matching and the first 1000 hits were screened.

Eligible articles included randomized controlled trials, case-control, cohort and cross-sectional studies investigating the association between higher *versus* lower intake of olive oil with cancer risk (incidence; mortality) and prognosis. Case series and case reports, reviews, *in vitro* and animal studies were not included in this meta-analysis. In case of overlapping study populations, only the larger study was included. The selection

of studies was performed by two reviewers (CM, MO) working independently and any disagreements were resolved following consultation with a senior author (TNS) and team consensus.

Data abstraction and effect estimates

The abstraction of data encompassed general information (first author's name, study year), study characteristics [study design, time period, geographical region, number of cases and controls (for case–control studies), matching factors (for case–control studies), follow-up period, cohort size and incident cases (for cohort studies)], definition of olive oil intake, categorization of exposure, features of ascertainment for exposure and characteristics of participants [inclusion and exclusion criteria, age of participants (range, mean), percentage of males], as well as adjusting factors regarding multivariate analyses. If the required data for the meta-analysis were not readily available in the published article, the corresponding authors were contacted twice (a reminder e-mail was sent seven days after the first e-mail). Data were independently extracted, analyzed and recorded in a predeveloped data extraction sheet by two reviewers (CM and MO). Final decision was reached after consultation with a senior author (TNS) and team consensus.

The maximally adjusted effect estimates i.e., odds ratios (ORs) for case–control studies, relative risks (RRs) or hazard ratios (HRs) in case of randomized controlled trials and non-randomized cohort studies with their confidence intervals (CIs) were extracted from each study by category of olive oil intake. In case the aforementioned information was not available, crude effect estimates and 95% CIs were calculated by means of 2x2 tables presented in the articles.

Statistical analyses

Statistical analyses included pooling of studies as well as *post hoc* meta-regression and sensitivity analyses. Statistical synthesis was performed in case of two or more eligible study arms. Random-effects (DerSimonian–Laird) models were appropriately used to calculate pooled effect estimates. The category of highest olive oil intake was

compared with the one corresponding to the lowest consumption. Between-study heterogeneity was assessed by estimating Q-test and I^2 [32]. Separate analyses were performed based on cancer site, study design, geographic region (grouped as Mediterranean, mixed Mediterranean and non-Mediterranean studies), degree of adjustment and overall study quality. Meta-regression analysis was performed in cases of 10 or more pooled study arms [32] and aimed to assess whether gender (expressed as percentage of males in the individual studies), age (expressed as the mean age in the individual studies) and publication year modified the association between olive oil consumption and cancer risk. Statistical analysis and meta-regression analysis were performed using STATA/SE version 13 (Stata Corp, College Station, TX, USA).

Assessment of study quality and publication bias

As far as the risk of bias is concerned, the Newcastle-Ottawa Quality scale [34] was used to evaluate the quality of the included non-randomized studies. Regarding the items assessing the completeness (adequacy) of follow-up of cohorts and whether the follow-up period was enough for outcomes to occur, the cut-off values were set *a priori* at 85% response rate and 5 years, respectively. Study quality was considered "low" when the Newcastle-Ottawa score (NOS) ranged between 1-3, "intermediate" for studies with NOS between 4-6 and "high" for those with a score between 7-9. Two independently working reviewers (CM, MO) rated the studies and, in case of disagreement, final decision was reached after consultation with a senior author (TNS) and team consensus.

Publication bias was evaluated in the analyses that included 10 or more study arms [32]; Egger's statistical test [34] was implemented as well as a visual inspection of the funnel plot. For the interpretation of Egger's test, statistical significance was defined as $p<0.1$. The evaluation of publication bias was performed using STATA/SE version 13 (Stata Corp, College Station, TX, USA).

3. Results

Description of eligible studies

A total of 3813 records were identified (998 from Pubmed, 1815 from EMBASE, 1000 from Google Scholar) using the search algorithm. After duplicates were removed, 2413 abstracts were screened; all details pertaining to the successive steps for the selection of eligible studies are provided in the supplemental material (Supplemental Figure 1).

20 articles that resulted in 21 studies and explored the association between olive oil intake and gastrointestinal or urinary cancer risk were finally considered eligible; 19 were case-control and 2 were cohort studies

Overall, 15 studies examined the association between olive oil consumption and the risk of gastrointestinal cancer, three on gastric [38,41,44], six on colorectal [40,42,43,45,46,49], among which two provided data on colon and rectal cancers as well [43,49], one on both gastric and colorectal [39], one on pancreatic [50], and 6 studies examined the association between olive oil consumption and the risk of urinary tract cancers (bladder [37], prostate [36,47,48,51], any site [35]). Study characteristics are extracted in Supplemental Table 2 and 3.

Table 1. Results of the meta-analyses examining the association between olive oil consumption and cancer risk. Bold cells denote statistically significant associations.

	"Highest vs. lowest" comparison		
	n[§]	RR (95%CI:)	Heterogeneity I^2, p
Analysis on gastrointestinal cancer			
Overall analysis	15	**0.77 (0.66-0.89)**	40.6%, 0.052
Subgroups by study			

design			
Case-control studies	13	**0.72 (0.61-0.85)**	38.5%, 0.077
Cohort studies	2	0.97 (0.75-1.24)	21.4%, 0.259
Subgroups by geographic region			
Mediterranean	9	**0.77 (0.67-0.88)**	39.9%, 0.101
Mixed Mediterranean	1	1.15 (0.78-1.69)	NC
Non-Mediterranean	5	0.60 (0.35-1.03)	24.1%, 0.261
Subgroups by degree of adjustment			
Adjustment	10	**0.76 (0.63-0.90)**	56.3%, 0.015
No adjustment	5	0.76 (0.57-1.01)	0.0%, 0.602
Subgroups by site			
Colorectal	7	0.90 (0.79-1.03)	0.0%, 0.906
Esophageal	3	**0.47 (0.24-0.93)**	61.5%, 0.074
Gastric	4	0.75 (0.53-1.05)	62.0%, 0.048
Pancreatic	1	**0.58 (0.35-0.97)**	NC

Subgroups by overall study quality			
Low (NOS 1-3)	0	No studies	
Intermediate (NOS 4-6)	3	1.02 (0.75-1.38)	0.0%, 0.609
High (NOS 7-9)	12	**0.73 (0.62-0.86)**	45.5%, 0.043
Analysis on urinary cancer			
Overall analysis	6	**0.46 (0.29-0.72)**	72.9%, 0.002
Subgroups by study design			
Case-control studies	6	**0.46 (0.29-0.72)**	72.9%, 0.002
Cohort studies	0	No studies	
Subgroups by geographic region			
Mediterranean	3	**0.33 (0.23-0.48)**	8.6%, 0.335
Mixed Mediterranean	0	No studies	
Non-Mediterranean	3	**0.60 (0.38-0.93)**	52.5%, 0.122
Subgroups by degree of adjustment			
Adjustment	4	**0.59 (0.42-0.83)**	38.8%, 0.179
No adjustment	2	**0.29 (0.20-0.41)**	0.0%, 0.753

Subgroups by site			
Prostate	4	**0.61 (0.40-0.92)**	30%, 0.232
Bladder	1	**0.47 (0.28-0.78)**	NC
Urinary tract, any site	1	**0.29 (0.20-0.42)**	NC
Subgroups by overall study quality			
Low (NOS 1-3)	1	**0.28 (0.20-0.42)**	NC
Intermediate (NOS 4-6)	1	0.80 (0.59-1.08)	NC
High (NOS 7-9)	4	**0.46 (0.32-0.66)**	0.0%, 0.874

[§]number of study arms

Gastrointestinal cancer

The risk for gastrointestinal cancer was found to be 23% lower for those who consumed the highest amounts of olive oil (RR=0.77, 95%CI: 0.66-0.89). When we proceeded with subanalyses per tumor site, an inverse relationship was found between olive oil intake and risk for esophageal (RR=0.47 95%CI: 0.24-0.93) and pancreatic cancer (RR=0.58, 95%CI: 0.35-0.97) (Table 1, Figure 1); no significance was reached in the site-specific analysis on gastric (RR=0.75, 95%CI: 0.53-1.05, four studies) and colorectal cancer (RR=0.90, 95%CI: 0.79-1.03, seven studies). Subgroups that reached significant effects included case-control studies (RR=0.72, 95%CI: 0.61-0.85), studies

within the Mediterranean area (RR=0.77, 95%CI: 0.67-0.88), multivariate analyses (RR=0.76, 95%CI: 0.63-0.90) and high quality studies (RR=0.73, 95%CI: 0.62-0.86). Supplemental Figures 2-9 portray the results on gastrointestinal cancer as a whole. Information on further subgroups per individual cancer type is illustrated in Supplemental Table 6 and Supplemental Figures 10-19.

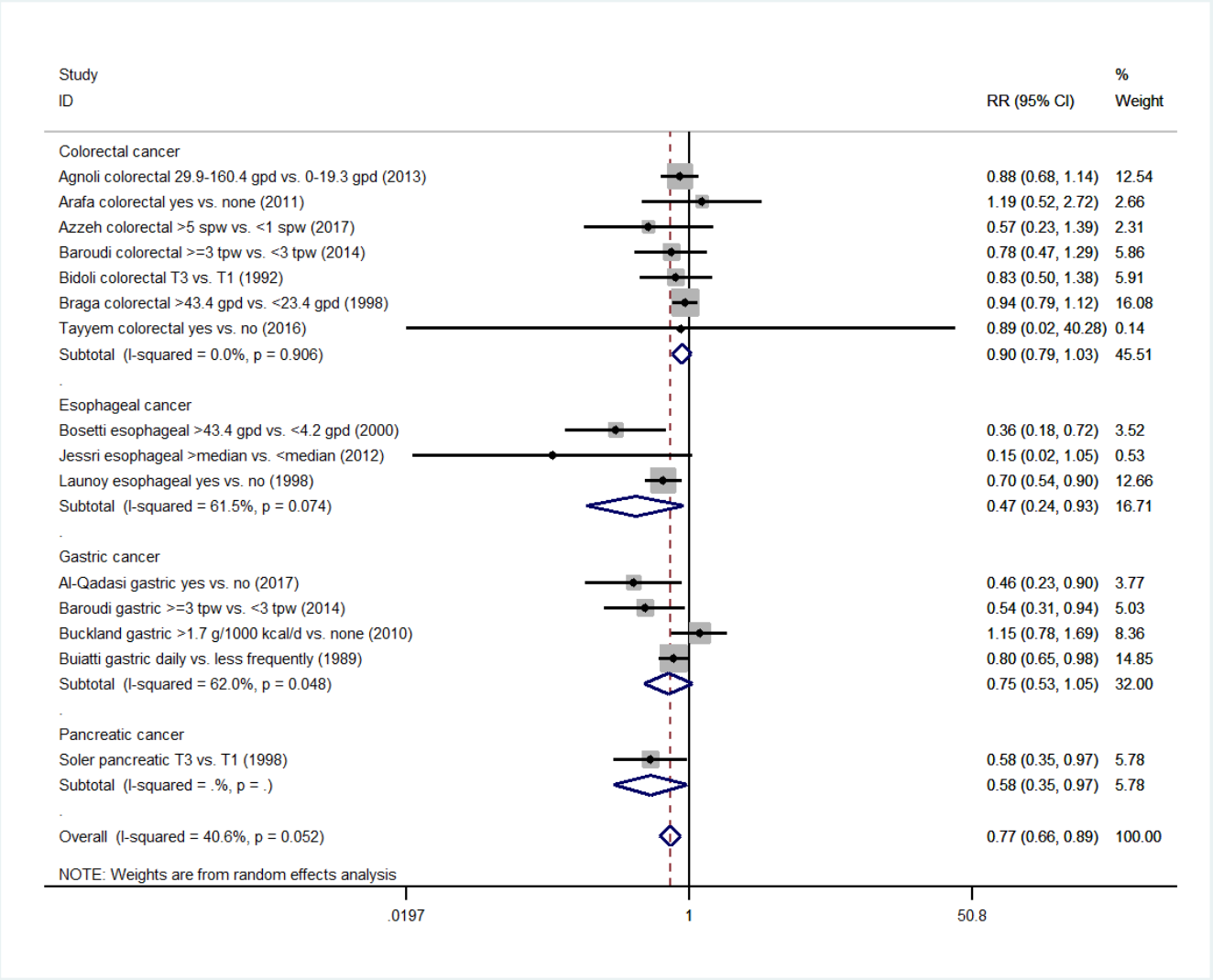

Figure 1. Forest plot describing the association between high olive oil consumption and risk for gastrointestinal cancer. Apart from the overall analysis, the subanalyses per tumor site are presented.

Urinary tract cancers

Remarkably, pooled analysis on urinary tract cancers indicated a relative risk of 0.46 (95%CI: 0.29-0.72) (Table 1); examination of all relevant sites indicated an inverse association with olive oil intake (prostate; RR=0.61, 95%CI: 0.40-0.92), bladder; RR=0.47, 95%CI: 0.28-0.78; urinary tract, any site; RR=0.29, 95%CI: 0.20-0.42) (Table 1, Figure 1). All studies were conducted using a case-control design; the strong protective effects were reproducible on any origin and degree of adjustment, as well as in lowest and highest quality scores (RR=0.28, 95%CI: 0.20-0.42 and RR=0.46, 95%CI: 0.32-0.66, respectively) (Supplemental Figures 20-23). Forest plots and meta-analysis data on prostate study arms are presented in Supplemental Table 6 and Supplemental Figures 24-27.

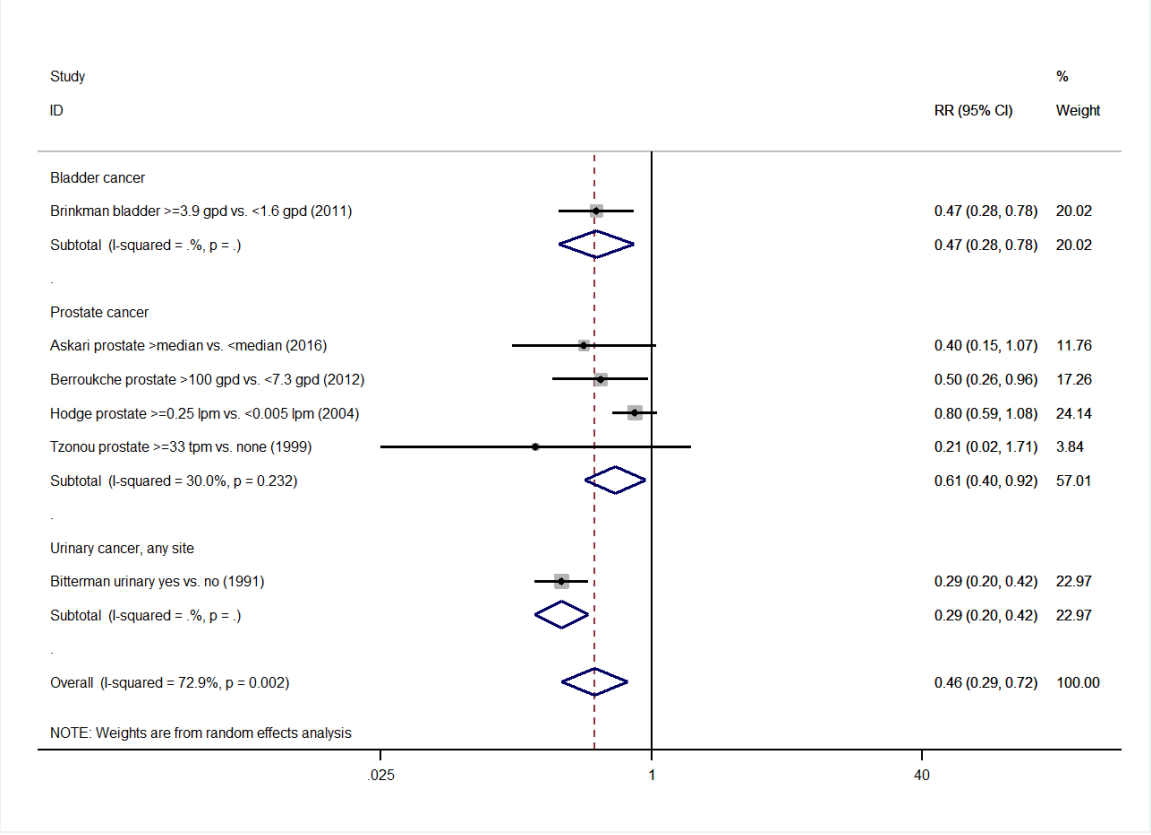

Figure 5. Forest plot describing the association between high olive oil consumption and risk for urinary tract cancer. Apart from the overall analysis, the subanalyses per tumor site are presented.

Meta-regression analysis

Table 2 presents the results of meta-regression analyses. A null effect on gastrointestinal cancer risk was observed when mean age was studied. Similarly, publication year did not modify the decrease in gastrointestinal cancer incidence by olive oil consumption. The protective effects mediated by high olive oil intake in terms of gastrointestinal cancer risk seemed marginally more pronounced among males (exponentiated coefficient = 0.94, 95%CI: 0.89-1.00) (Supplemental Figure 29).

Table 2. Meta-regression analysis examining the role of potential modifiers in the association between cancer risk and olive oil consumption.

Variables	**Category or increment**	**Gastrointestinal cancer**		
		n[§]	**Exponentiated coefficient (95%CI)**	**p**
Percentage of males	10% increase	15	**0.94 (0.89-1.00)**	**0.052**
Mean age of study	10 year increase	14	0.91 (0.58-1.42)	0.639
Publication year	1 year increase	15	1.00 (0.98-1.02)	0.751

[§]number of studies

Evaluation of quality of studies and risk of bias

The evaluation of quality within the eligible studies is presented in Supplemental Tables 4 and 5 for case-control and cohort studies respectively. In case of cohort studies, the quality was mainly compromised by the ascertainment of exposure (self-administered questionnaires) and completeness of follow-up (no information). However, it has to be noted that for all studies, non-exposed individuals were selected from the same population as the exposed ones, at least one confounder was adjusted for in the analysis and follow-up was long enough.

In case-control studies, hospital-based controls often compromised quality. Cases were representative in all 19 studies and were defined adequately in all studies. In terms of exposure, many studies contained no description of non-response rates. Nevertheless, the same method of ascertainment was uniformly guaranteed for both cases and controls in all studies; standardized, validated food frequency questionnaires were used through a structured interview for most studies.

Significant publication bias was detected *via* Egger's test in the analysis on gastrointestinal cancer risk (p=0.048). These results are reflected as asymmetry in the respective funnel plots (Supplemental Figure 28).

4. Discussion

The present systematic review and meta-analysis comprising data from 21 individual studies reveals that, overall, highest *versus* lowest olive oil consumption was associated with 23% lower cancer risk in gastrointestinal and 54% in urinary tract cancer. The overall findings remained consistent when studies were further subgrouped by degree of adjustment and overall study quality, for both Mediterranean and non-Mediterranean populations, whereas they were more prominent for case-control over cohort studies.

Increasing evidence supports that olive oil constituents convey protection against the development of several types of cancer [52,53]. The results of the present work are in agreement with relevant studies in the field. Pelucchi *et al*. in 2011 reported a summary risk ratio of breast cancer of 0.62 (95% CI: 0.44-0.88) for the highest *versus* lowest level of olive oil consumption

after evaluating five case-control and one cohort study [26]. Focusing also on breast cancer risk in 2015, Xin *et al*. reported a pooled effect estimate of nine case-control and three cohort studies of 0.74 (95%CI: 0.60-0.92) [29], with the latter design giving a null association. This level of risk reduction is comparable to the one resulted from our analysis of 14 eligible studies (RR=0.67, 95%CI: 0.52-0.86); it has to be noted though that Xin *et al*. included also articles on the use of monounsaturated fatty acids as well as olive oil combined with frying/liquid oils.

From a mechanistic point of view, our findings comply with several experimental *in vivo* and human *in vitro* studies. The favorable effect of olive oil is largely attributed to its exceptional composition, rich in monounsaturated fatty acids (mainly oleic acid) [54], squalene and phenolic compounds (simple phenols, secoiridoids and lignans) [15,55]. Their strong anti-oxidant properties limit cellular oxidative stress and DNA damage *via* scavenging and influence crucial signaling pathways linked to carcinogenesis [56]. Regarding breast cancer, *in vitro* studies indicated that oleic acid is able to transcriptionally repress Her-2/neu overexpression and to upregulate PEA3, a transcriptional repressor of the HER2 gene [57]. It has been also observed to suppress the fatty acid synthase gene whose levels are usually increased in breast tumors [58]. In human mammary epithelial cells (MCF10A), hydroxytyrosol [59] and squalene [60] were found to reduce reactive oxygen species in the cell and protect from oxidative injury. In an experimental model of mammary cancer, a more beneficial effect was seen for mice that were fed with a diet rich in olive oil compared to a high-corn diet; additionally, the tumors were less aggressive. Underlying mechanisms involved modification of cellular membranes, signaling pathways, gene expression leading to lower proliferation, higher apoptosis and lower DNA damage [61].

Regarding gastrointestinal effects of olive oil, a plethora of preclinical evidence points to a protective role of its components [62]. In human colon cancer cells (Caco-2), extra virgin olive oil stimulated the expression of CNR1 gene encoding for type 1 cannabinoid receptor (CB1) and reduced proliferation. Similar increase in CB1 expression was observed in the colon of rats receiving dietary EVOO supplementation for 10 days [63]. Alu'Datt *et al*. reported that both free and lipid bound phenolic extracts of virgin olive oil exhibited antiproliferative activities against the colorectal cancer cell lines CRC1 and CRC5 [64], whereas in the studies by Hashim *et al*. the extracts limited invasion *in vitro* and metastasis *in vivo* more likely *via* modulation of integrin

expression [65]. Additionally, hydroxytyrosol exerted antiproliferative effects in colon cancer cells by strong inhibition of extracellular signal-regulated kinase (ERK)1/2 phosphorylation and reduction of cyclin D1 expression [66].

Commenting on effects in the urinary tract, EVOO phenolic extract suppressed proliferation and clonogenic ability in a dose-dependent manner in human urinary bladder cancer cells (T24 and 5637) [67]. Oleuropein decreased proliferation and migration of 786-O renal cell adenocarcinoma lines [68] while hydroxytyrosol and oleuropein caused inhibition on the cancer cells of urinary bladder (T-24) [69]. The favorable antitumor effects of oleuropein and hydroxtyrosol have been extensively explored for other types of cancer such as blood, brain, hepatic, skin, cervical and thyroid [70-72].

According to the recent meta-analysis by Schwingshackl *et al*., strongest adherence to a Mediterranean diet was inversely associated with cancer mortality and risk of various cancer types; nevertheless, pooled data about the use of olive oil as a single component pointed to a non-significant effect on overall cancer risk, synthesizing a subset of relevant studies [13]. High olive oil intake may signal a healthier overall dietary pattern, interacting with other beneficial nutrients, such as those involved in the Mediterranean diet. The portions of coexisting individual food groups and, hence, their implication to health status are likely to differ from country to country; nevertheless, the beneficial effects in our meta-analysis spanned Mediterranean and non-Mediterranean countries.

Regarding the limitations of the present meta-analysis, between studies heterogeneity was substantial but in line with previous meta-analyses [29]. Heterogeneity might be due to differences in study design, geographical region, population size, follow-up duration and other factors; in an attempt to trace its origins, we conducted a series of subgroup analyses and meta-regression analyses. Furthermore, considerable publication bias was observed, suggesting that the presence of small studies effect cannot be excluded as a factor of influence on the effect estimates. Other shortcomings pertain to the large number of case-control studies and hospital-based controls susceptible to various sources of bias, including information and selection bias. Regarding cohort studies, concerns entailed missing information on completeness of follow-up as well as the use of self-administered questionnaires for the determination of highest and the lowest category of olive intake that differed across populations. The available data,

encompassing various exposure classification schemes, did not allow for dose-response evaluation; however, pooling highest vs. lowest levels of exposure is a commonly performed practice when conducting a meta-analysis. Next, many were limited to Mediterranean populations, where olive oil is the core of the diet, whereas none was detected in the American area, thus, compromising the generalizability of the results.

Despite the above mentioned limitations, the present work possesses a plethora of important strengths. First of all, our updated search was performed in three online databases that cover the most of biomedical literature and it was not subject to any restriction. Moreover, through strict and meticulous adherence to the PRISMA guidelines [31] as well as a careful, systematic search in reference lists (‘‘snowball’’ procedure) a rather impressive number of studies was achieved. In contrast to previous meta-analyses, the selection procedure included articles that reported solely on olive oil consumption *per se* and not as a source of monounsaturated fatty acids or mixed with other components. Furthermore, available information was depicted on a considerable set of meaningful subanalyses and sensitivity analyses, where the favorable effects of olive oil were frequently persisted.

In conclusion, the results of this meta-analysis represent valuable evidence of the protective effects of olive oil against cancer development. Additional prospective cohort studies on various cancer types, especially in non-Mediterranean regions, as well as large randomized trials, seem desirable in order to provide further insight into the role of olive oil in preventing cancer.

6. References

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Supplemental Material

Abbreviations: CRC; colorectal cancer, d; day, EVOO; extra virgin olive oil, FFQ; food frequency questionnaire, g; grams, gpd; grams per day, gpw; grams per week, I2; inconsistency index, lpm; liters per month, NC; not calculable, NOS; Newcastle-Ottawa score, NR; not reported, PRISMA; Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, Qn; quintile, Qr; quartile, s.e.; standard error, spw; servings per week, T; tertile, tabspy; tablespoon per year, tpm; times per month, tpw; times per week, UADT; upper aerodigestive tract, yrs; years

Supplemental Tables

Supplemental Table 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	p.1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	p. 6

INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	p. 9
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	p. 10
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	p. 10
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	p. 10
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	p. 10
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	p. 10
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	p. 10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	p. 10
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	p. 11
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	p. 11
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	p. 11

Section/topic	#	Checklist item	Reported

			on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	p.12
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	p. 11
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Suppl. fig.1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Suppl. Tables 2-3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	p. 20, Suppl. Tables 5 & 6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	p. 7-8, Figure 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	p. 7-18, Table 1, Figures 1-5, Suppl. Table 7, Suppl. Figures 2-39
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	p. 19

Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	p.17-18
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	p. 19-22
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	p. 19-22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	p. 19-22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	-

Supplemental Table 2. Characteristics of the eligible case-control studies.

First author (Year)	Number of cases	Number of controls	Study period	Region	Males percentage	Mean age	Age range	Definition/features of cases	Definition of controls	Matching factors	Definition of olive oil intake	Categorization of exposure	Features of ascertainment for exposure: e.g. was the questionnaire validated/reproducible?	Adjusting factors
Bitterman (1991)	270	694	1986-1989	Naharija, Israel	NR	56.97±0.761	>18	Adults patients with histologically confirmed urinary tract cancer (bladder, prostate, kidney, testicle), admitted for the first time at the Urological Department of Naharija Hospital between 1986 and 1989	Adult patients suffering from a wide spectrum of benign urologic diseases, randomly selected from among the patients of the urology department	None	A questionnaire of 65 questions covering biographical and dietary details with emphasis on food preparation and spicing and exposure to environmental factors was completed by each participant	Olive oil consumption yes vs. no (Ref.)	NR	None

Buiatti (1989)	1016	1159	June 1985-December 1987	4 Areas in Italy, 2 with high risk (1: Forli, Cremona, Imola; 2: Florence, Sienna) and 2 with low risk (3: Genoa; 4: Cagliari) for GC	61.8 Overall, 63 (cases), 61 (controls)	65	45-75	All patients with histologically confirmed GC first diagnosed between June 1985 and December 1987 among residents in the study areas aged 75 or less. Cases were identified in surgery and gastroenterology departments and outpatient gastroscopic services of private and public hospitals. Ascertainment of cases was compared in each center with the local cancer registry (CR) wherever available	Randomly selected from municipal computerized lists of residents (which existed for 60% of the population) or National Health Service computerized files (for the remaining 40%)	Age (5-year), sex, center	A structured questionnaire, developed and tested during a pilot phase, was used.All cases and controls were interviewed personally. A group of professional interviewers was trained centrally in the use of the questionnaire, which was administered with the aid of an instruction manual and an atlas containing pictures of the more frequently consumed foods represented in 3 portion sizes. Dietary	Olive oil consumption less frequently (Ref.) vs. daily	Structured, developed and tested in a pilot phase	Age, sex, study area, place of residence, migration from the south, socio-economic status, familial history of GC and the Quetelet index

	(Florence, Forli and Genoa) or pathology department files to evaluate completeness of reporting. Slides were sought from each case for review and diagnostic classification according to the system of Lauren (1965) previously utilized in two large histopatholog ic series in these same study areas. Non-epithelial neoplasms of the stomach, primarily lymphomas, were excluded from analysis.	patterns of cases and controls were assessed by asking the usual frequency of intake and portion size (categorized as small, medium or large) of 146 food items and beverages, as consumed in a 12-month period approximatel y 2 years before the interview. For some items it was asked whether foods were consumed preserved or fresh, cooked or raw, and whether they were

											prepared at home or purchased			
Braga (1998)	1953 (1225 Colon, 728 rectal)	4154	January 1992-June 1996	Greater Milan, the provinces of Pordenone and Gorizia, the urban area of Genoa, and the province of Forlı´ in northern Italy; the province of Latina in central Italy; and the urban area of Naples in southern Italy	52.4 (Overall), 57.6 (cases), 49.9 (controls)	62 (cases), 58 (control)	20–74	Patients, diagnosed within 1 year before interview, with incident histologically confirmed colorectal carcinomas who were admitted to the major teaching and general hospitals in the areas under surveillance	No history of cancer, admitted to the same network of hospitals for acute, nonneoplastic conditions unrelated to the digestive tract and requiring no long term modifications of diet	None	An interviewer - administered validated food-frequency questionnaire was developed to assess the usual diet during the 2 years before carcinoma diagnosis or hospital admission (for controls). It included 78 foods, groups of foods, or recipes. Additional questions aimed at assessing seasoning fat	Olive oil consumption tertiles of intake, upper limits (gpd): 23.4 (T1, Ref.), 43.4 (T2), —(T3)	Validated	Study center, quinquennia of age, sex, years of education, alcohol consumption, total energy intake, and the various types of oils and fats simultaneously, total vegetable consumption

	intake patterns were included. These addressed the type of fat used as a condiment for raw and cooked vegetables, to prepare meat dishes, to fry, and to prepare pasta or rice dishes; subjective judgment on the amount of fat used in seasoning (scarce, average) and habits of eating or leaving on the plate the seasoning or sauce. These questions, as well as frequency of consumption and portion size, were

											used to derive estimates of intake of added lipids			
Soler (1998)	362	1552	1983-1992	Greater Milan area, northern Italy	71.6	59 (cases), 55 (controls)	Cases <75, controls NR	Patients aged below 75 years with histologically confirmed incident cancer of the pancreas	Patients admitted to the same network of hospitals for acute, non neoplastic diseases, unrelated to alcohol or tobacco	None	Trained interviewers identified and questioned cases and controls using a structured questionnaire including selected indicator foods. Patients were asked to indicate the frequency of consumption per week of 14 selected indicator foods	Subjective scores (low, intermediate and high) were used to obtain information of fat intake in seasoning including oil (olive oil consumption tertiles of intake): low (T1, Ref.), intermediate (T2), high (T3)	Reproducibility of the questionnaire was satisfactory	Age, sex, education, tobacco consumption and area of residence
Tzonou (1999)	320	246	February 1994-January	Athens, Greece	100	71.1 (cases), 70.4 (con	NR	Newly diagnosed with prostate cancer who were	Selected from the same hospital and interviewed	Residents of same area, approxi	Semi-quantitative food frequency questionaire	Frequency of consumption of olive oil (tpm) 0	Validated	None

	1997	trols)	residents of the Greater Athens area were identified in 6 major hospitals of this area, histologically confirmed cases	in the wards at the same date as the correspondin g case, residents of the Greater Athens area, be of approximatel y the same age as the correspondin g case (+-3 years), never have had cancer or been diagnosed with BPH and have as current diagnosis a minor eye ailment, a minor injury or a minor ear, nose and throat condition	mately the same age ±3y, selecte d from the same hospital and intervie wed at the same date as the corresp onding case	was used. Cases and controls were asked to indicate the average frequency of consumption , over a period of 1 year immediately preceding the recognition of symptoms or signs of the present disease, of about 120 food items or beverage categories per month, per week or per day. For analysis, the frequency of consumption of different food items was quantified approximatel y in terms of the number	(Ref.), 1–8, 9–16, 17–24, 25–32, 33+

											of times per month the food was consumed. Some important items, notably olive oil were considered individually.			
Bosetti (2000)	304	743	1992-1997	Provinces of Milan, Pordenone and Padova in northern Italy	82.9 (Overall), 90.5 (cases), 79.8 (controls)	60 (cases), 60 (controls)	36-77	Admitted to the major teaching and general hospitals in the areas under study with incident, histologically confirmed squamous cell cancer of the esophagus, diagnosed no longer than 1 year before and with no history of cancer of other sites	Admitted to the same hospitals as the cases for a wide spectrum of acute, non-neoplastic conditions, not related to smoking or alcohol consumption and long-term modification of diet.	Age (5–year groups), sex, year of interview and area of residence. A control-to-case ratio of about 5 was chosen for females, as opposed to 2 for males	Food frequency questionnaire including 78 specific foods and beverages, as well as a range of meal recipes, i.e., the most common ones in the Italian diet. Study subjects were asked to indicate the average weekly frequency of consumption during the 2 years prior	Olive oil consumption quintile intake, upper limit (gpd): 4.2 (Qn1, Ref.) 16.4 (Qn2) 27.4 (Qn3) 43.4 (Qn4) – (Qn5)	Satisfactory reproducibility and validity of the FFQ have already been reported	Age, sex, area of residence, education, tobacco smoking, alcohol drinking, non-alcohol energy and all added lipids in the table (specific seed oils, mixed seed oils, butter, margarine), vegetable consumption

					to cancer diagnosis or hospital admission. A commonly used unit or serving size was specified whenever possible. Intakes lower than once a week but at least once a month were coded as 0.5 per week. Several questions aimed to assess the fat intake pattern were also included and used to derive quantitative estimates of intake of various added lipids, such as olive oil

Hodge (2004)	858	905	1994-1997	Melbourne, Sydney and Perth, Australia	100	NR	<70	Diagnosis of clinically important prostate cancer, gleason score >5, diagnosed between 1994 and 1997, aged less than 70 years at diagnosis and were registered to vote	Controls were randomly selected from the current State Electoral Rolls	Controls were frequency matched to the age distribution of the cases in a ratio of one control per case	121-item food frequency questionnaire was used. Olive oil and vegetable oil intakes were based on the estimated monthly household consumption divided by the number of people in the household.	Olive oil consumption (lpm) <0.005 (1, Ref.), 0.005-0.24 (2), >0.25 (3)	NR	State, age group, year, country of birth, socioeconomic group, total energy intake and family history of prostate cancer
Brinkman (2011)	198	377	1999-2004	Belgian province of Limburg	86 (cases), 60 (controls), 69 overall	NR	NR	Incident cases histologically confirmed with transitional cell carcinoma (TCC) of the	Controls were selected through a Belgian authority, Kruispuntbank van de Sociale	None	A standardised food frequency questionnaire (FFQ) was sent by mail to all participants	Olive oil consumption quartiles of intake (gpd): (Qr1) <1.6 (Ref.), (Qr2) 1.6–3.8, (Qr3) ≥3.9	Validated	Age, sex, smoking (status, history and number of cigarettes smoked), occupational exposure

	bladder from the Limburg Cancer Registry (LIKAR) diagnosed in 1996 or later	Zekerheid (Crossroads Bank of Social Security). This was done by stratified random sampling of individuals 50 years of age and older from the province of Limburg according to municipality and social economic status. Individuals were eligible for inclusion as controls in the study if they belonged to the Caucasian race (to minimise differences due to genetic polymorphisms), were	in the study. It contained 322 food items and was linked to the combined contents of three existing food tables supplemented with information on the composition of common recipes from the region. Usual dietary intake was estimated from food frequencies and quantities reported by participants for the 12 months prior to the interview. Dietary information obtained from the	(never vs. ever: polycyclic aromatic hydrocarbons (PAHs), aromatic amines) and calorie intake

		fluent in the Dutch language (spoken and written) and had no previous diagnosis of bladder cancer or any mental impairment which prevented their participation .	FFQ was based on a fixed response format consisting of nine categories for frequency of food consumption . For some food items, alternative response options of five frequency categories were provided. Intake quantity was determined based on standard household measures or, alternatively 1–2, 3–4, 5–6, 7–8, 9 table spoons, etc. and an open-ended response option

										(number of grams/pieces /plates, etc.). Conversion of household units into g/mg etc. and the calculation of average daily intakes of food groups, energy and 29 nutrients was performed using a computer software programme.			
Jessri (2012)	47	96	Kurdistan province of Iran	38 (Cases), 40 (controls)	58	40-75	Esophageal Squamous Cell Carcinoma patients who were diagnosed within the last 6 months of the interview and were admitted to the major	40–75, without history of carcinomas of other sites, who were admitted to the same hospital as the cases for a wide spectrum of acute non-	Age and sex (5-year age groups)	Usual dietary intakes of cases for 1 year before diagnosis and controls for 1 year before interview were collected by trained dietitians in	Olive oil consumption, over/under (Ref.) median value	Validated and reproducible	Age, sex, total energy intake, gastroesophageal reflux disease symptoms, medication use, BMI, smoking, physical activity, and education

								general hospitals under study in the Kurdistan province of Iran	neoplastic conditions that were unrelated to alcohol abuse, smoking and long-term dietary modifications		face-to-face interviews using a valid and reproducible semiquantitative food frequency questionnaire, containing 168 food items.			level
Baroudi (2014)	69 (Gastric cancer), 95 colorectal	185	2009-2010	Salah Azaiez Institute of Oncology in Tunisia	57	57.96 (cases), 46.01 (controls)	20-89	Histopathology confirmed adenocarcinoma colorectal cancer and adenocarcinoma gastric cancer newly diagnosed and considered before any treatment	From Department of Gastroenterology at the Charles Nicole Hospital, without any history of malignancy	Age and sex	Food frequency questionnaire with 10 items including dietary behaviors intake during the period of 3 to 5 years before diagnosis for cases and 3 years before the interview for controls. Subjects were asked to report how many times they consumed	Olive oil consumption <3 tpw (Ref.) vs. ≥3 tpw	Validated	None

										olive oil per week.				
Tayyem (2016)	220	280	January 2010-December 2012	Five largest hospitals in Jordan	52.1 (cases), 57.6 (controls), 54.5 overall	49.5	NR	Diagnosed with colorectal cancer, recruited conveniently from five large Jordanian hospitals, received a confirmatory diagnosis within a year from interview. To be included in the study, volunteers had to be free of cancer other than CRC, diabetes mellitus, liver and renal diseases, and rheumatoid arthritis, aged ≥18 years, of Jordanian nationality and able to	Healthy disease-free controls, recruited from hospital personnel, outpatients and visitors. Control subjects were excluded if any first- or second-degree relatives were diagnosed with CRC	Age, sex, occupation and marital status. Data of participants' socio-demographic variables showed that controls and cases did no differ significantly with respect to age	Food frequency questionnaire was used. The FFQ was developed from the Diet History Questionnaire I (DHQ I) of the National Cancer Institute of the USA and validated for use in the Jordanian setting. Participants were asked about their intake from the food groups before the diagnosis of CRC for the cases, and specifically during the 12 months leading up to	Olive oil consumption, yes vs. no	Validated	None

								communicate verbally. Participants were excluded if they had a critical illness or were currently hospitalised.			the time of the CRC diagnosis for those with the disease, as well as during the 12-month period leading up to the first interview for the control group. A 1-year period was chosen for the FFQ data collected to include seasonal variation in available foods.			
Al-Qadasi (2017)	70	140	May-October 2004	Yemen	70.5	57.9 (cases), 57.6 (controls)	NR	Patients who had histologically confirmed gastric cancer, collected from the National Oncology Centre in Sana'a City	From the two major hospitals in Sana'a City (Al-Thawra and Al-Jomhori). The controls were selected randomly from	Age (±5 years) and gender	Food frequency questionnaire	Olive oil consumption, yes vs. no	Validated	Sociodemographic factors such as education status, occupation, house ownership, history of smoking, tobacco and khat

								outpatient clinics (5.3%) or inpatient departments. The controls were free from any malignant tumours or digestive tract disorders.					chewing, family history of gastric cancer or other cancers, and source of drinking water (treated and untreated water).
Azzeh (2017)	137	164	June 2014-March 2015	Mecca, Saudi Arabia	50.2	56 (cases), 56.7 (controls)	40-75	Patients with colon and/or rectal cancer from King Abdullah Medical City Hospital with Saudi nationality, 40-75yo, not diagnosed with other types of cancer	164 healthy participants, from the same region as cases, patients' visitors and hospital staff	Age and gender	Food frequency questionnaire was used. Participants were educated about the serving size of each food item before beginning the questionnaire.	Olive oil consumption (spw): <1 (Ref.), 1-2, 3-5, >5	Validated	Age (continuous), gender, BMI (continuous), education, income, employment, smoking, marital status, physical activity and family history of CRC
Bidoli (1992)	248 (123 colon, 125 rectal	699	Jan 1986-1990	Pordenone province, north-east Italy	74.5 (Overall), 62.5 (cases), 78.8	57.5 ±12 (colon), 62.1	NR	Histologically confirmed cancer of the intestine diagnosed	Admitted to these hospitals as in-patients for a wide	No individual matching was	A structured questionnaire was used. Further, patients	Frequencies of consumption of various items were	Reproducible	None

canc er)		(control s)	±9.2 (rec tal), 56.4 ±11. 5 (con trols)	within the 6 months preceding interview, colon and rectum (including recto-sigmoid junction)	variety of acute conditions, None of these patients had malignant tumors, digestive-tract disorders or any condition related to alcohol or tobacco consumption , or which might have resulted in long-term modification s of diet.	perfor med and, althoug h an attempt was made to balance cancer cases and control s by age and sex strata, patients with rectal cancer were signific antly older than control s	were asked about their frequency of consumption per week of various food items before the onset of the disease which led to the current admission. Categories of weekly frequency of consumption of different foods and beverages were not defined a priori, but collected as reported by interviewees . The interviewers were aware of the diagnosis which led each patient to the hospital, but not of the hypotheses being tested.	subdivided into 3 levels, each including, as far as possible, the same number of cases and controls combined (approximat e tertiles). Simple subjective scores (low, intermediate, or high) were used as measures of intake were used: Low (T1, Ref.) Intermediate (T2) High (T3)

			Any substantial change in consumption of the same foods during the 10-year period preceding diagnosis was also explored. Changes of diet, however, were infrequent and no significant difference was evident between cases and controls. Thus, for all analytical purposes, only information on recent diet was taken into consideratio n.

Launoy (1998)	208	399	1991-1994	University hospitals of Caen (Normandy, Department of Calvados), Dijon (Burgundy, Department of Coˆte d'Or) and Toulouse (Midi Pyrenees, Department of Haute-Garonne)	100	NR	NR	All males, with histologically proven squamous-cell carcinoma of the esophagus. Adenocarcinoma of the esophagus was excluded from the study	All males, frequency-matched for hospital and age	Hospital and age	Current dietary intakes were assessed through a standardized detailed questionnaire about the previous year's diet following the pattern of meals throughout the day. When the subject finished the description, the interviewer referred to a list of foods and interrogated the subject about each food not mentioned. The same food item	Yes vs. no consumption	Standardized detailed questionnaire	Age, interviewer, smoking, beer, aniseed aperitifs, hot Calvados, whisky, total alcohol, total energy intake and other food groups

		could be recalled at several meals. Foods consumed less than once a month were neglected. For each food item, the subject was asked for usual amount and frequency. The dietician coded the data immediately after the interview to obtain mean weekly intake. Foods were grouped together to form 39 groups. Estimates of weekly mean intake of nutrients from foods were derived by means of

											a specific programme using a European compilation food composition table.			
Arafa (2011)	220	220	February 2008 and through January 2009	Al-Bashir Hospital, a national referral hospital and the principal governmental center for CRC registry and therapy in Jordan	53.6	55.1 (56.3±12.3 years for males and 53.7 ±6.8 years for females)	44-68	Recently diagnosed and histologically confirmed CRC cases within the specified period of the study	The controls were selected from those attending the outpatient departments at the same hospital, eing free of gastrointestinal diseases and have no previous diagnosis of CRC or other types of cancers. All female cases and controls were not currently pregnant or lactating	Age, gender	Semiquantitative FFQ was used where, cases and controls were asked to report the frequency (how often) and portion size for each food item consumed during a period of 12-months prior CRC diagnosis for cases and prior being interviewed for controls. Also, all study subjects were inquired if	Olive oil consumption yes vs. no (Ref.)	Tested for its validity, reliability and reproducibility before conducting the study	None

		they have changed their diet than the usual routine in the last 12 months. To overcome the problem of reverse causality, that cancer patients might change their dietary habits after the diagnosis, only newly diagnosed cases in which diagnosis was confirmed 10-14 days prior to dietary intake questionnaire were included. The FFQ included 9 food groups and was

										adapted according to portion sizes based on commonly used household serving units/utensils in Jordan. Olive oil intake was defined as addition of olive oil to foods.			
Askari (2016)	50	99	2011-2012	Tehran, Iran	100	55.7	40-78	Patients 40-78 admitted to Labafi Nejad hospital with histologically confirmed prostate cancer diagnosed not before 6 months from the interview	Patients sampled randomly from patients admitted to the same hospital as cases during the same time period for acute non neoplastic conditions and not afflicted with diet-related chronic diseases	Frequency-matched according to age and BMI	FFQ containing 168 items commonly consumed in Iran, with standard serving sizes. Subject were asked to report the frequency of intake on a daily, weekly, monthly or yearly basis. These reported	Olive oil consumption over/under median value, Ref. <median	Validated	Age, total energy intake, smoking, bmi, education level

											consumptions were then converted to daily frequencies and the namual for household measures was used to convert intake frequencies to daily grams of food intake.			
Berroukche (2012)	160	160	January 2007-March 2011	Algeria	100	71.6 ±10 (Cases), 68.3 ±9.4 (controls)	50-74 (Cases)	Incident patients, who had a confirmed histological prostate carcinoma. 98 cases were obtained from the Department of Urology of Sidibel-Abbes UHC and 62 cases from the Department of Urology of Saida	Selected from the departments of respiratory diseases, ophthalmology and dermatology of the same hospitals as the cases. Exclusion criteria for controls were having other prostatic diseases or malignant	Controls were matched to cases in frequency of 1:1 by age (±5 years)	Epidemiological and dietary data were obtained using a standard questionnaire. Dietary information was obtained by a quantitative history approach in which subjects were asked about their usual	<7.3 gpd (1, Ref,), 7.3-50.2 gpd (2), 50.3-100 gpd (3), >100 gpd (4)	This questionnaire was not previously validated but was studied regarding its reproducibility	Total energy intake, tobacco smoking and family history of Pca

	Hospital	tumours, being under dietary restriction and patients in critical conditions	frequency of intake and portion size of a list of 20 main food items including beverages, representativ e of usual diet of the Algerian population. For each food item, the patient indicated mean intake frequency and the amount consumed over the past year or the year prior to onset of symptoms. For a more adequate evaluation of quantities consumed, we have used in interview photographs of food

	items in different portion sizes of known quantity

Supplemental Table 3. Characteristics of the eligible cohort studies.

First author (Year)	Cohort size	Cases in cohort	Follow-up (years, median or mean)	Study period	Region	Males percentage	Mean age	Age range	Cohort characteristics	Definition/features of cancer in cohort	Definition of olive oil intake	Categorization of exposure	Features of ascertainment for exposure e.g. was the questionnaire validated/ reproducible?	Adjusting factors
Buckland (2010)	485044	449	8.9	1992-2006	23 Centers from 10 European countries (United Kingdom, France, Denmark, Sweden, Germany, Italy, Spain, the Netherlands, Norway, and Greece)	29.81	52.2 ±10.1	Mostly 35–70	European Prospective Investigation into Cancer and Nutrition study. Most of the participants were from the general population, selected from a defined geographic area, region, or town with exceptions for France (health insurance	GC included cancers coded as C16 from the 10th revision of the International Statistical Classification of Diseases. They were classified according to both anatomic location (cardia and noncardia) and Lauren histologic type (intestinal and diffuse), which were validated	Dietary data were collected at enrollment by using validated country-specific questionnaires (quantitative or semiquantitative) recording the usual diet over the previous 12 mo. Most centers used self-administered questionnaires	Adherence to an rMED was measured by using an 18-point linear scale that incorporated 9 key components of the diet and was a variation of the original Mediterranean diet score. Olive oil in the index was coded by using the median for	Validated country-specific	Adjusted for sex (in overall model), BMI, educational level, smoking status, cigarette smoking intensity, and total energy intake

									members), Utrecht and Florence (participants of breast cancer screening programs), Oxford (mostly vegetarian volunteers), and some centers in Spain and Italy (mostly blood donors). The French and Norwegian cohorts were all women. Subjects with a prevalent cancer at recruitment were excluded at baseline.	and confirmed by a panel of pathologists who reviewed specimen material and pathology reports from each center. Only primary incident GC cases were included in the analysis.	with the number of food items ranging from 88 to 266. The questionnaires in Greece, Spain, and Ragusa were administered during a personal interview. A secondary dietary measurement from a detailed 24-h diet recall was carried out on a random 7.1% subsample of each cohort (36,994 subjects).	consumers: 1.7 g/1000 kcal/d for the total sample (men & women). (Ref.: none, 1: for subjects below the median (calculated only within olive oil consumers), and 2: for subjects equal or above this median)		
Agnoli (2013)	45275	435	11.28	1993-31 December 2006 for Varese,	Italian section of the EPIC cohort	31	50.5	NR	Italian section of the EPIC cohort, Ragusa: Local blood donors association, population-	In Varese, Turin, Florence and Ragusa, incident cases were identified by study cohort linkage to the	Semiquantitative FFQ was designed to capture eating behavior in different regions of Italy: one for	Tertiles of olive oil intake (as one of the Italian Mediterranean Index components, in gpd): T1	Validated	Non-alcoholic energy intake, gender (analysis of entire cohort

	Florence, Naples and Ragusa and on 31 December 2008 for Turin	based recruitment in four towns, local teachers union, and other sources, Florence: Breast cancer screening participants (CSPO), men and women from the general population, Turin: Blood donors, employees, volunteers, medical test users at national health service, Varese: Volunteers from resident general population, mostly an extension of an ongoing study (ORDET). Excluding those with cancer at	databases of the regional cancer registries, which are considered high quality registries with nearly complete cancer registration. In Naples, incident cases were identified through linkage to the regional archive of hospital discharges, and by direct telephone contact where necessary. Colon cancers were primary incident cases, identified by the codes of the International Statistical Classification of Diseases (10th Revision) as follows: proximal (C18.0–18.5);	northern and central Italy (Varese, Turin and Florence), one for Ragusa and one for Naples. The questionnaires contained questions on 188, 217 and 140 food items, respectively, and were designed to investigate dietary habits in the 12 months before enrolment. The food items were then linked, using specifically designed software, to Italian Food Tables to obtain estimates of daily intake of energy, and 37 macro- and micro-	(Ref.): 0–19.3, T2: 19.4–29.8, T3: 29.9–160.4	only), age, BMI, smoking, education and total physical activity; stratified for centre

		recruitment (except non-melanoma skin cancer)	distal (C18.6–C18.7), and overlapping or unspecified sites (C18.8 and C18.9). Rectal cancers were identified by the codes C19 (rectosigmoid junction) and C20 (rectum). Anal cancers were excluded.	nutrients. It was used the Italian Mediterranean Index (calculated from intake of 11 items) by adapting the Greek Mediterranean Index to Italian eating behavior.	

Supplemental Table 4. Evaluation of the eligible case-control studies with Newcastle-Ottawa scale**.**

Study	Selection				Comparability	Exposure			Total
	Adequacy of case definition	**Representativeness of cases**	**Selection of controls**	**Definition of controls**	**Comparability on age and other factors**	**Assessment of exposure**	**Same method of ascertainment for cases and controls**	**Non-response rate**	
Bitterman (1991)	1	1	0	0	0	0	1	0	3
	The population examined consisted of adults patients with histologically confirmed urinary tract cancer (bladder, prostate, kidney, testicle)	Admitted for the first time at the Urological Department of Naharija Hospital	Adult patients suffering from a wide spectrum of benign urologic diseases, randomly selected from among the patients of the urology department	No description	No description	A questionnaire of 65 questions covering biographical and dietary details with emphasis on food preparation and spicing and exposure to environmental factors	Was completed by each participant in this study	No statement on non-response rates	
Buiatti (1989)	1	1	1	0	2	1	1	0	7
	All patients with histologically confirmed GC. Cases were identified in surgery and gastroenterology departments and outpatient gastroscopic services of private and public hospitals. Ascertainment of cases was compared in each	First diagnosed between June 1985 and December 1987 among residents in the study areas aged 75 or less. Cases were identified in surgery and gastroenterology departments and outpatient gastroscopic services of private and	For sampling, municipal computerized lists of residents (which existed for 60% of the population) or National Health Service computerized files (for the remaining 40%) were used. Nor did the cases or controls	No description	Controls were randomly selected from 5-year age and sex strata of the general population of each center, approximately in the ratio of 1 : 1 to the cases in each stratum	A structured questionnaire, developed and tested during a pilot phase, was used (146 food items). A group of professional interviewers was trained centrally in the use of the questionnaire, which was administered with the aid of an instruction	All cases and controls were interviewed personally. Cases were interviewed at the hospital (94.1%) or at their homes (5.9%); controls were interviewed at their homes (63.2%), at the local Health Department	Among the 1159 controls sampled from residents' lists, 140 (12.1%) refused interview and 126 (10.9%) were no longer resident, were deceased, or were unavailable because of mental or other health	

Study	Selection				Comparability	Exposure			Total
	Adequacy of case definition	**Representativeness of cases**	**Selection of controls**	**Definition of controls**	**Comparability on age and other factors**	**Assessment of exposure**	**Same method of ascertainment for cases and controls**	**Non-response rate**	
	center with the local cancer registry (CR) wherever available (Florence, Forli and Genoa) or pathology department files to evaluate completeness of reporting. Slides were sought from each case for review and diagnostic classification according to the system of Lauren (1965) previously utilized in two large histopathologic series in these same study areas	public hospitals	represent selected subsets of the population, since we sought to enroll all patients, and randomly selected controls in the study areas, achieving a high response rate for both			manual and an atlas containing pictures of the more frequently consumed foods represented in 3 portion sizes	(30.2%) or elsewhere (6.6%).	conditions. These subjects were replaced with additional residents randomly selected from the same age and sex stratum, so the total number of interviewed controls was 1159. Of 1229 patients, 50 (4. 1%) refused to participate and 163 (13.2%) had died or were too ill for interview	
Braga (1998)	1	1	0	1	2	1	1	1	8
	Patients, diagnosed within 1 year before interview, with incident	Who were admitted to the major teaching and general hospitals in the	Admitted to the same network of hospitals for acute nonneoplastic	For acute nonneoplastic conditions, no history of cancer	With respect to confounding, we allowed for age and	An interviewer - administered validated food-frequency questionnaire,	During the 2 years before carcinoma diagnosis or hospital	On average, less than 4% of cases and controls refused to	

Study	Selection				Comparability	Exposure			Total
	Adequacy of case definition	**Representativeness of cases**	**Selection of controls**	**Definition of controls**	**Comparability on age and other factors**	**Assessment of exposure**	**Same method of ascertainment for cases and controls**	**Non-response rate**	
	histologically confirmed colorectal carcinomas	areas under surveillance	conditions unrelated to the digestive tract and requiring no long term modifcations of diet		sex in the statistical analysis	including 78 items, was developed to assess the usual diet	admission (for controls)	participate	
Soler (1998)	1	1	0	1	2	1	1	1	8
	Patients aged below 75 years with histologically confirmed incident cancer of the pancreas	The data were derived from a case-control study of various digestive tract neoplasms conducted in the Greater Milan Area, Northern Italy, between 1983-1992	Patients admitted to the same network of hospitals	For acute, non neoplastic diseases, unrelated to alcohol or tobacco	Estimates from multiple logistic regression equations including terms for age, sex, education, tobacco consumption and area of residence	Trained interviewers identified and questioned cases and controls using a structured questionnaire including selected indicator foods. Reproducibility of the questionnaire was satisfactory	Trained interviewers identified and questioned cases and controls using a structured questionnaire including selected indicator foods	Less than 3% of cases and controls approached for interview refused to participate	
Tzonou	1	1	0	1	2	1	1	0	7

Study	Selection				Comparability	Exposure			Total
	Adequacy of case definition	**Representativeness of cases**	**Selection of controls**	**Definition of controls**	**Comparability on age and other factors**	**Assessment of exposure**	**Same method of ascertainment for cases and controls**	**Non-response rate**	
(1999)	There were 372 histologically confirmed cases	During a 3-year period, from February 1994 to January 1997, all men newly diagnosed with PC who were residents of the Greater Athens area were identified in 6 major hospitals of this area	Controls had to be residents of the Greater Athens area, treated in the same hospital as the cases for minor diseases or conditions, be of approximately the same age as the corresponding case (63 years)	Never have had cancer or been diagnosed with BPH and have as current diagnosis a minor eye ailment, a minor injury or a minor ear, nose and throat condition	Residents of same area, approximately the same age ±3y, selected from the same hospital and interviewed at the same date as the corresponding case	Dietary information was elicited through a validated, interviewer-administered, semiquantitative food-frequency questionnaire (of about 120 food items or beverage categories) that was comprehensive enough to allow adjustment for energy intake	This was submitted to cases and controls by the same interviewers under similar conditions	There were 372 histologically confirmed cases. It was not possible to interview 52 patients (14%), so 320 were finally included in the study. Controls were identified for 308 cases with PC, but for 62 of them (20%) a complete interview was not obtained (non-response rate for controls 20.1%)	
Bosetti (2000)	1	1	0	1	2	1	1	0	7
	With incident, histologically confirmed squamous cell cancer of the esophagus,	Cases were individuals admitted to the major teaching and general hospitals in the	Controls were patients admitted to the same hospitals as the cases	For a wide spectrum of acute, non-neoplastic conditions, not related to	Controls were frequency-matched with cases on age (5–year groups), sex,	Trained interviewers administered a structured questionnaire to cases and	Trained interviewers administered a structured questionnaire to cases and	No statement on non-response rate for cases Less than 5%	

Study	Selection				Comparability	Exposure			Total
	Adequacy of case definition	**Representativeness of cases**	**Selection of controls**	**Definition of controls**	**Comparability on age and other factors**	**Assessment of exposure**	**Same method of ascertainment for cases and controls**	**Non-response rate**	
	diagnosed no longer than 1 year before the interview and with no history of cancer of other sites	areas under study		smoking or alcohol consumption and long-term modification of diet	year of interview and area of residence	controls during their hospital stays. A food-frequency questionnaire (FFQ, 78 questions on food items or recipes) was used to assess subjects' habitual diet and to estimate their total energy intake, including 78 specific foods and beverages, as well as a range of meal recipes, i.e., the most common ones in the Italian diet. Satisfactory reproducibility and validity of the FFQ have already been reported	controls during their hospital stays. Study subjects were asked to indicate the average weekly frequency of consumption during the 2 years prior to cancer diagnosis or hospital admission. The questionnaire was submitted to cases and controls by the same interviewers under similar conditions, thus minimizing information bias	of the identified controls refused or were unable to participate. Among other strengths of our study are the high response rate of study participants	
Hodge	1	1	1	0	2	0	1	0	6

Study	Selection				Comparability	Exposure			Total
	Adequacy of case definition	**Representativeness of cases**	**Selection of controls**	**Definition of controls**	**Comparability on age and other factors**	**Assessment of exposure**	**Same method of ascertainment for cases and controls**	**Non-response rate**	
(2004)	Population-based case–control study of 858 men aged <70 years at diagnosis with histologically confirmed prostate cancer of Gleason Grade 5 or greater	Eligible cases were diagnosed between 1994 and 1997, were aged less than 70 years at diagnosis and were registered to vote, in Melbourne, Sydney and Perth, Australia	Controls were randomly selected from the current State Electoral Rolls	No description	OR adjusted for state, age group, year, country of birth, socioeconomic group, total energy intake and family history of prostate cancer	Food frequency questionnaire, 121-item, face to face interviews administered, usually at the man's home	The food frequency questionnaire (FFQ) was administered to the first 964 cases and 911 controls	The response rate was 65% in cases and 50% in controls	
Brinkman (2011)	1 Incident cases histologically confirmed with transitional cell carcinoma (TCC) of the bladder	1 A population based case–control study was conducted in the Belgian province of Limburg between 1999 and 2004. Cases were derived from the Limburg Cancer Registry (LIKAR) and invited to participate in the study by urologists and	1 Controls were selected through a Belgian authority, Kruispuntbank van de Sociale Zekerheid (Crossroads Bank of Social Security). This was done by stratified random sampling of individuals 50 years of age and older from the	1 Individuals were eligible for inclusion as controls in the study if they had no previous diagnosis of bladder cancer	2 Adjustment was made for age, sex, smoking characteristics, occupational exposures and calorie intake	1 A standardized, detailed, validated, population-specific food frequency questionnaire (FFQ, 322 food items) was sent by mail to all participants in the study. Three trained interviewers visited cases and controls at home, checked answers to the	1 Sent by mail to all participants in the study. Three trained interviewers visited cases and controls	0 Reulen 2007 [102]: Ultimately, 202 bladder cancer patients out of the 2230 patients registered with LIKAR agreed to participate in the study (response rate 9%). After selection, controls were sent a letter	8

Study	Selection				Comparability	Exposure			Total
	Adequacy of case definition	**Representativeness of cases**	**Selection of controls**	**Definition of controls**	**Comparability on age and other factors**	**Assessment of exposure**	**Same method of ascertainment for cases and controls**	**Non-response rate**	
		general practitioners	province of Limburg according to municipality and social economic status			FFQ and where necessary clarified and helped participants to answer questions		inviting them to participate in the study. Controls could participate by returning a signed consent form back to the Study Center. In total, 390 controls participated in the study, giving a response rate of 26%	
Jessri (2012)	1	1	0	1	2	1	1	1	8
	50 histologically confirmed incident ESCC patients who were diagnosed within the last 6 months of the interview	And were admitted to the major general hospitals under study in the Kurdistan province of Iran	Controls were 100 patients who were admitted to the same hospital as the cases	For a wide spectrum of acute non-neoplastic conditions	Cases were frequency-matched with controls according to their age and sex (5-year age groups)	Usual dietary intakes of cases for 1 year before diagnosis and controls for 1 year before interview were collected by trained dietitians in face-to-face interviews using a valid and reproducible	We also administered the same questionnaires to both cases and controls using the same interviewer and under the similar conditions in order to reduce the potential for information bias	The probability of selection bias was minimized by high participation rates (94% among cases and 91% among controls)	

Study	Selection				Comparability	Exposure			Total
	Adequacy of case definition	**Representativeness of cases**	**Selection of controls**	**Definition of controls**	**Comparability on age and other factors**	**Assessment of exposure**	**Same method of ascertainment for cases and controls**	**Non-response rate**	
						semiquantitative food frequency questionnaire (FFQ, 168 food items)			
Baroudi (2014)	1	1	0	1	2	1	1	0	7
	All patients presented with histopathology confirmed adenocarcinoma colorectal cancer and adenocarcinoma gastric cancer	68 gastric cancer cases and 95 colorectal cancers were recruited between 2009 and 2010 from the Salah Azaiez Institute of Oncology in Tunisia	One hundred eighty-five healthy controls were recruited from the Department of Gastroenterology at the Charles Nicole Hospital	These controls were considered without any history of malignancy	The healthy controls were matched by age and sex with gastrointestinal patients in our study	After obtaining a written informed consent, all patients were interviewed, and dietary habits were evaluated using a validated food survey which contains a food frequency questionnaire (FFQ)	The survey contains dietary behaviors intake during the period of 3 to 5 years before diagnosis for cases and 3 years before the interview for controls	No statement on non-response rates	
Tayyem (2016)	1	1	0	1	0	1	1	0	5
	Those with CRC must have received a confirmatory diagnosis at most 1 year before the first interview	Participants were enrolled in the study from January 2010 to December 2012. Those diagnosed with CRC were recruited conveniently	The control group was recruited from hospital personnel, outpatients and visitors	Healthy disease-free controls… Control subjects were excluded if any first- or second-degree relatives were diagnosed	An attempt was made to match the two sets of participants by age, sex, occupation and marital status. Data of participants'	Trained research assistants were assigned to collect data via face-to-face interview, where the participants were informed about the purpose of the	Participants were asked about their food intake, especially meats, dairy products and fats, at the time of their first interview. They	No statement on non-response rates	

Study	Selection				Comparability	Exposure			Total
	Adequacy of case definition	**Representativeness of cases**	**Selection of controls**	**Definition of controls**	**Comparability on age and other factors**	**Assessment of exposure**	**Same method of ascertainment for cases and controls**	**Non-response rate**	
		from five large Jordanian hospitals with oncology services		with CRC	socio-demographic variables showed that controls and cases did no differ significantly with respect to age	research. A validated Arabic food frequency questionnaire (FFQ) was used for dietary assessment. The FFQ was developed from the Diet History Questionnaire I (DHQ I) of the National Cancer Institute of the USA and validated for use in the Jordanian setting	were asked about their intake from the food groups before the diagnosis of CRC for the cases, and specifically during the 12 months leading up to the time of the CRC diagnosis for those with the disease, as well as during the 12-month period leading up to the first interview for the control group		
Al-Qadasi (2017)	1	1	0	1	2	1	1	0	7
	The cases were all patients who had histologically confirmed gastric cancer	Collected from the National Oncology Centre in Sana'a City (between May and October 2014), which is a specialized	The controls were collected from the two major hospitals in Sana'a City from where the cases were referred	The controls were free from any malignant tumours	The controls matched to cases for age (± 5 years) and gender	A structured questionnaire was used to collect information through direct interview. Dietary history was collected by	From cases and controls	No statement on non-response rates	

Study	Selection				Comparability	Exposure			Total
	Adequacy of case definition	**Representativeness of cases**	**Selection of controls**	**Definition of controls**	**Comparability on age and other factors**	**Assessment of exposure**	**Same method of ascertainment for cases and controls**	**Non-response rate**	
		centre that receives referrals from hospitals for chemotherapy and radiotherapy				validated questionnaire taken from Cancer Council, Australia and modified for the diet in Yemen			
Azzeh (2017)	1	1	1	1	2	1	1	0	8
	The inclusion criteria for the case group were Saudi nationality and CRC diagnosed in any region of the colon and/or rectum	Patients with colon and/or rectal cancer were recruited from King Abdullah Medical City Hospital (KAMC), Mecca, Saudi Arabia from June 2014 to March 2015	Controls were recruited from patients' visitors and hospital staff	164 healthy participants were recruited in the control group	Both groups were matched for their age and gender	Eligible participants were asked to complete a questionnaire under the supervision of trained registered dietitians that included personal information as well as information regarding nutritional habits. Usual food intakes and nutritional habits were assessed using an existing validated dietary questionnaires	Eligible participants were asked to complete a questionnaire	No statement on non-response rates	

Study	Selection				Comparability	Exposure			Total
	Adequacy of case definition	**Representativeness of cases**	**Selection of controls**	**Definition of controls**	**Comparability on age and other factors**	**Assessment of exposure**	**Same method of ascertainment for cases and controls**	**Non-response rate**	
Bidoli (1992)	1	1	0	1	0	1	1	1	6
	The cases studied were subjects with histologically confirmed cancer of the intestine diagnosed within the 6 months preceding interview	The hospitals in which cases were interviewed include the great majority of the diagnostic and therapeutic facilities available in the study area and therefore the largest proportion of colo-rectal cancers will have been referred there	Controls were admitted to these hospitals as in-patients for a wide variety of acute conditions	None of these patients had malignant tumors	No individual matching was performed and, although an attempt was made to balance cancer cases and controls by age and sex strata, patients with rectal cancer were significantly older than controls	Patients were asked about their frequency of consumption per week of various food items before the onset of the disease which led to the current admission. Categories of weekly frequency of consumption of different foods and beverages were not defined *a priori*, but collected as reported by interviewees. The interviewers were aware of the diagnosis which led each patient to the hospital, but not of the hypotheses being tested	The same interviewers identified and questioned patients admitted to all the hospitals of the area under surveillance for cancers of the intestine and for a wide spectrum of other conditions	Approximately 2% of cases and 3% of controls refused to be interviewed	

Study	Selection				Comparability	Exposure			Total
	Adequacy of case definition	**Representativeness of cases**	**Selection of controls**	**Definition of controls**	**Comparability on age and other factors**	**Assessment of exposure**	**Same method of ascertainment for cases and controls**	**Non-response rate**	
Launoy (1998)	1	1	0	0	2	1	1	1	7
	208 cases, all males, with histologically proven squamous-cell carcinoma of the oesophagus	A multicentre case-control study was conducted between 1991 and 1994 in the university hospitals of Caen, Dijon and Toulouse	Launoy 1997 [103]: The control group consisted of 399 males admitted to the same hospitals during the same period	Launoy 1997 [103]: In the rheumatology or orthopaedics unit for osteoarthritis (n 5 229), lumbago or sciatica (n 5 127), or in the eye unit	Controls were frequency-matched for hospital and age	Data regarding diet, alcohol and tobacco were collected from cases and from controls in face-to-face, 2 hr interviews. Specially trained dieticians (4 in Caen, 2 in Dijon and 1 in Toulouse) conducted interviews in a special room, with no family members present. Current dietary intakes were assessed through a standardized detailed questionnaire about the previous year's diet following the pattern of meals throughout the	Data regarding diet, alcohol and tobacco were collected from cases and from controls in face-to-face, 2 hr interviews. Specially trained dieticians (4 in Caen, 2 in Dijon and 1 in Toulouse) conducted interviews in a special room, with no family members present. Current dietary intakes were assessed through a standardized detailed questionnaire about the previous year's diet following the pattern of meals	223 cases of squamous-cell cancer of the oesophagus were identified. Of these, 5 refused to be interviewed. All controls contacted agreed to be interviewed	

Study	Selection				Comparability	Exposure			Total
	Adequacy of case definition	**Representativeness of cases**	**Selection of controls**	**Definition of controls**	**Comparability on age and other factors**	**Assessment of exposure**	**Same method of ascertainment for cases and controls**	**Non-response rate**	
						day	throughout the day		
Arafa (2011)	1	1	0	1	2	1	1	0	7
	This study included all recently diagnosed and histologically confirmed CRC cases within the specified period of the study. Cases were inquired about date of first complaint and the interval of time between the appearance of first sign and/or symptom and visit to health provider confirming diagnosis. Basis of confirmed diagnosis, staging and diagnostic facility information (hospitals and	This study included all recently diagnosed and histologically confirmed CRC cases within the specified period of the study (February 2008 and through January 2009), at Al-Bashir Hospital, a national referral hospital and the principal governmental center for CRC registry and therapy in Jordan	The controls were selected from those attending the outpatient departments at the same hospital	Being free of gastrointestinal diseases and have no previous diagnosis of CRC or other types of cancers	220 were interviewed based on age and gender matching criteria to CRC cases	In-person interviews were scheduled for study participants (cases and controls). The retrospective dietary intake of the study participants was estimated using a semi-quantitative FFQ (Block et al., 1990) where, cases and controls were asked to report the frequency (how often) and portion size for each food item consumed during a period of 12-months prior CRC diagnosis for cases and prior	In-person interviews were scheduled for study participants (cases and controls). They were asked to complete the study questionnaire included questions related to dietary intake using a food frequency questionnaire (FFQ)	No statement on non-response rates	

Study	Selection				Comparability	Exposure			Total
	Adequacy of case definition	**Representativeness of cases**	**Selection of controls**	**Definition of controls**	**Comparability on age and other factors**	**Assessment of exposure**	**Same method of ascertainment for cases and controls**	**Non-response rate**	
	laboratories) were collected from medical records. Clinical data were collected and coded by following of the International Classification of Diseases for Oncology (ICD-O-3) as a dual classification with coding system for both topography and morphology					being interviewed for controls, this period was chosen to take into account seasonal variation in food consumption. Also, all study subjects were inquired if they have changed their diet than the usual routine in the last 12 months. The FFQ was adapted according to portion sizes based on commonly used household serving units/utensils in Jordan, and was tested for its validity, reliability and reproducibility before			

Study	Selection				Comparability	Exposure			Total
	Adequacy of case definition	**Representativeness of cases**	**Selection of controls**	**Definition of controls**	**Comparability on age and other factors**	**Assessment of exposure**	**Same method of ascertainment for cases and controls**	**Non-response rate**	
						conducting the study			
Askari (2016)	1	1	0	1	2	1	1	0	7
	Patients with histologically confirmed prostate cancer diagnosed not before 6 months from the interview	Patients 40-78 admitted to Labbafi Nejad hospital, in Tehran	Patients sampled randomly from patients admitted to the same hospital as cases during the same time period	For acute non neoplastic conditions and not afflicted with diet-related chronic diseases	Frequency-matched according to age and BMI	Administered reliable and valid FFQ by trained interviewers containing 168 items commonly consumed in Iran	Administered reliable and valid FFQ by trained interviewers containing 168 items commonly consumed in Iran	In total, 52 patients with PCa and 104 controls underwent face-to-face interviews by specifically trained professional interviewers (participation rate 85%)	
Berrouk che (2012)	1	1	0	1	2	1	1	0	7
	Incident patients, who had a confirmed histological prostate carcinoma	98 cases were obtained from the Department of Urology of Sidibel-Abbes UHC and 62 cases from the Department of Urology of Saida Hospital (Algeria, January 2007-March 2011)	Selected from the departments of respiratory diseases, ophthalmology and dermatology of the same hospitals as the cases	Exclusion criteria for controls were having other prostatic diseases or malignant tumours, being under dietary restriction and patients in critical conditions	Controls were matched to cases in frequency of 1:1 by age (±5 years). Logistic regression models with adjustment for total energy intake, tobacco	Epidemiological and dietary data were obtained using a standard questionnaire. Dietary information was obtained by a quantitative history approach in which subjects were asked about their	Epidemiological and dietary data were obtained using a standard questionnaire. Dietary information was obtained by a quantitative history approach in which subjects were asked about	No statement on non-response rates Among a total of 204 incident patients, who had a confirmed histological prostate carcinoma, 44	

Study	Selection				Comparability	Exposure			Total
	Adequacy of case definition	**Representativeness of cases**	**Selection of controls**	**Definition of controls**	**Comparability on age and other factors**	**Assessment of exposure**	**Same method of ascertainment for cases and controls**	**Non-response rate**	
					smoking and family history of Pca	usual frequency of intake and portion size of a list of 20 main food items including beverages, representative of usual diet of the Algerian population. This questionnaire was not previously validated but was studied regarding its reproducibility	their usual frequency of intake and portion size of a list of 20 main food items including beverages, representative of usual diet of the Algerian population	patients could not participate in this study. The final group consisted of 160 Pca cases	

Supplemental Table 5. Evaluation of the eligible cohort studies with Newcastle-Ottawa scale.

Study	**Selection**				**Comparability**	**Outcome**			**Total**
	Representativeness of the exposed	**Selection of non-exposed**	**Ascertainment of exposure**	**Outcome not present at start**	**Comparability on age and other factors**	**Assessment of outcome**	**Long enough follow-up (median ≥5 years)**	**Adequacy (completeness) of follow-up (≥85% response rate)**	
Bucklan d (2010)	1	1	0	1	1	1	1	0	6
	Most of the participants were from the general population, selected from a defined geographic area, region, or town with exceptions for France (health insurance members), Utrecht and Florence (participants of breast cancer screening programs), Oxford (mostly vegetarian volunteers), and some centers in Spain and Italy (mostly	Most of the participants were from the general population, selected from a defined geographic area, region, or town with exceptions for France (health insurance members), Utrecht and Florence (participants of breast cancer screening programs), Oxford (mostly vegetarian volunteers), and some centers in Spain and Italy (mostly	Dietary data were collected at enrollment by using validated country-specific questionnaires (quantitative or semiquantitative) recording the usual diet over the previous 12 mo (31, 32). Most centers used self-administered questionnaires with the number of food items ranging from 88 to 266. The questionnaires in Greece, Spain, and Ragusa were administered during a personal interview.	Subjects with a prevalent cancer at recruitment were excluded at baseline	No adjustment for age; adjustment for other factors. Adjusted for sex (in overall model), BMI, educational level, smoking status, cigarette smoking intensity, and total energy intake	Vital status was obtained through periodic linkage to regional and national mortality registries. Information on cancer status (including a diagnosis of GC) was obtained by linkage with population cancer registries, except for France, Germany, Greece, and Naples, where a combination of different active follow-	Mean follow-up of 8.9 years	No statement on the exact number of participants who were lost to follow-up	

Study	Selection				Comparability	Outcome			Total
	Representativeness of the exposed	**Selection of non-exposed**	**Ascertainment of exposure**	**Outcome not present at start**	**Comparability on age and other factors**	**Assessment of outcome**	**Long enough follow-up (median ≥5 years)**	**Adequacy (completeness) of follow-up (≥85% response rate)**	
	blood donors). The French and Norwegian cohorts were all women	blood donors). The French and Norwegian cohorts were all women				up methods was used. GC included cancers coded as C16 from the 10th revision of the International Statistical Classification of Diseases. They were classified according to both anatomic location (cardia and noncardia) and Lauren histologic type (intestinal and diffuse), which were validated and confirmed by a panel of pathologists who reviewed specimen material and pathology			

Study	Selection				Comparability	Outcome			Total
	Representativeness of the exposed	**Selection of non-exposed**	**Ascertainment of exposure**	**Outcome not present at start**	**Comparability on age and other factors**	**Assessment of outcome**	**Long enough follow-up (median ≥5 years)**	**Adequacy (completeness) of follow-up (≥85% response rate)**	
						reports from each center			
Agnoli (2013)	1	1	0	1	2	1	1	0	7
	Italian section of the EPIC cohort, Volunteers were recruited from five centers <u>Riboli 2002</u> [104]<u>:</u> <u>Ragusa:</u> Local blood donors association, population-based recruitment in four towns, local teachers union, and other sources <u>Florence:</u> Breast cancer screening participants (CSPO), men and women	Italian section of the EPIC cohort, volunteers were recruited from five centers	<u>Riboli 2002</u> [104]<u>:</u> <u>Northern Italy:</u> Extensive self-administrated quantitative dietary questionnaires, containing up to 260 food items and estimating individual average portions systematically, were used <u>Ragusa:</u> performed a face-to-face dietary interview using a computerised dietary program <u>Naples:</u> Semi-quantitative	Excluding those with cancer at recruitment (except non-melanoma skin cancer)	Effect estimate was adjusted for non-alcoholic energy intake, gender (analysis of entire cohort only) and age	In Varese, Turin, Florence and Ragusa, incident cases were identified by study cohort linkage to the databases of the regional cancer registries, which are considered high quality registries with nearly complete cancer registration. In Naples, incident cases were identified through linkage to the regional archive of	Mean follow-up 11.28 years	No statement	

Study	Selection				Comparability	Outcome			Total
	Representativeness of the exposed	**Selection of non-exposed**	**Ascertainment of exposure**	**Outcome not present at start**	**Comparability on age and other factors**	**Assessment of outcome**	**Long enough follow-up (median ≥5 years)**	**Adequacy (completeness) of follow-up (≥85% response rate)**	
	from the general population Turin: Blood donors, employees, volunteers, medical test users at national health service Varese: Volunteers from resident general population, mostly an extension of an ongoing study (ORDET)		food-frequency questionnaires (with the same standard portion(s) assigned to all subjects) were used in Naples			hospital discharges, and by direct telephone contact where necessary			

Supplemental Table 6. Results of the meta-analyses examining the association between olive oil consumption and risk of individual cancer types. Bold cells denote statistically significant associations.

	"Highest vs. lowest" comparison		
	n[§]	RR (95%CI)	Heterogeneity I^2, p
Analysis on colorectal cancer			
Overall analysis	7	0.90 (0.79-1.03)	0.0%, 0.906
Subgroups by study design			
Case-control studies	6	0.91 (0.78-1.06)	0.0%, 0.835
Cohort studies	1	0.88 (0.68-1.14)	NC
Subgroups by geographic region			
Mediterranean	4	0.90 (0.79-1.03)	0.0%, 0.877
Mixed Mediterranean	0	No studies	
Non-Mediterranean	3	0.85 (0.47-1.55)	0.0%, 0.492
Subgroups by degree of adjustment			
Adjustment	3	0.91 (0.79-1.05)	0.0%, 0.534
No adjustment	4	0.86 (0.62-1.19)	0.0%, 0.855
Subgroups by overall study quality			
Low (NOS 1-3)	0	No studies	
Intermediate (NOS 4-6)	2	0.83 (0.51-1.37)	0.0%, 0.974
High (NOS 7-9)	5	0.91 (0.79-1.04)	0.0%, 0.727
Analysis on colon cancer			
Overall analysis	2	0.96 (0.78-1.17)	0.0%, 0.642
Subgroups by study			

design			
Case-control studies	2	0.96 (0.78-1.17)	0.0%, 0.642
Cohort studies	0	No studies	
Analysis on rectal cancer			
Overall analysis	2	0.86 (0.57-1.30)	33.2%, 0.221
Subgroups by study design			
Case-control studies	2	0.86 (0.57-1.30)	33.2%, 0.221
Cohort studies	0	No studies	
Analysis on esophageal cancer			
Overall analysis	3	**0.47 (0.24-0.93)**	61.5%, 0.074
Subgroups by study design			
Case-control studies	3	**0.47 (0.24-0.93)**	61.5%, 0.074
Cohort studies	0	No studies	
Subgroups by geographic region			
Mediterranean	2	0.55 (0.29-1.03)	67.3%, 0.080
Mixed Mediterranean	0	No studies	
Non-Mediterranean	1	0.15 (0.02-1.05)	NC
Subgroups by degree of adjustment			
Adjustment	3	**0.47 (0.24-0.93)**	61.5%, 0.074
No adjustment	0	No studies	
Subgroups by overall study quality			
Low (NOS 1-3)	0	No studies	
Intermediate (NOS 4-6)	0	No studies	
High (NOS 7-9)	3	**0.47 (0.24-0.93)**	61.5%, 0.074
Analysis on gastric cancer			
Overall analysis	4	0.75 (0.53-1.05)	62.0%, 0.048
Subgroups by study design			
Case-control studies	3	**0.65 (0.46-0.93)**	46.2%, 0.156

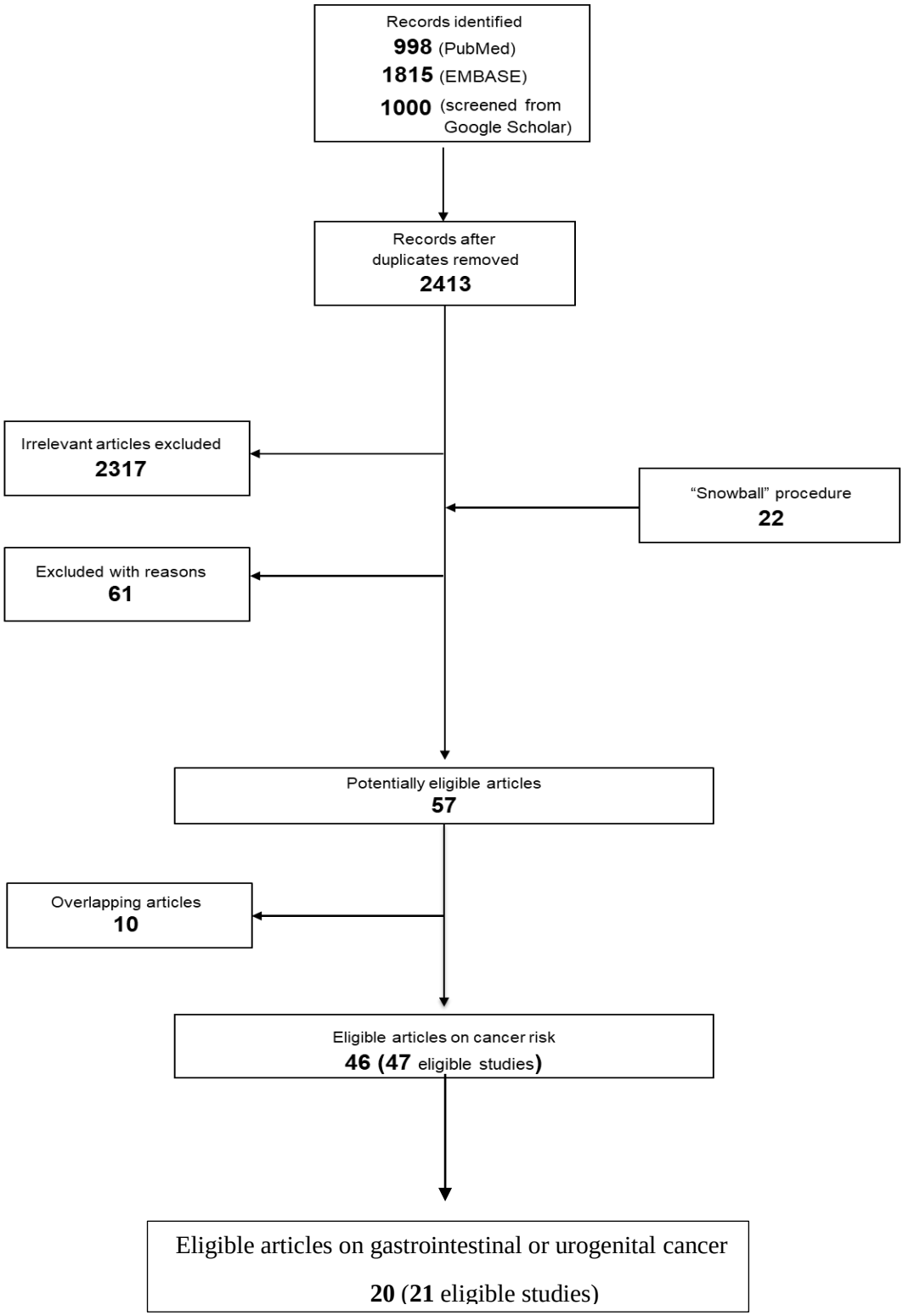
Cohort studies	1	1.15 (0.78-1.69)	NC
Subgroups by geographic region			
Mediterranean	2	0.72 (0.51-1.01)	40.9%, 0.193
Mixed Mediterranean	1	1.15 (0.78-1.69)	NC
Non-Mediterranean	1	**0.46 (0.23-0.90)**	NC
Subgroups by degree of adjustment			
Adjustment	3	0.81 (0.55-1.19)	65.7%, 0.054
No adjustment	1	**0.54 (0.31-0.94)**	NC
Subgroups by overall study quality			
Low (NOS 1-3)	0	No studies	
Intermediate (NOS 4-6)	1	1.15 (0.78-1.69)	NC
High (NOS 7-9)	3	**0.65 (0.46-0.93)**	46.2%, 0.156
Analysis on prostate cancer			
Overall analysis	4	**0.61 (0.40-0.92)**	30.0%, 0.232
Subgroups by study design			
Case-control studies	4	**0.61 (0.40-0.92)**	30.0%, 0.232
Cohort studies	0	No studies	
Subgroups by geographic region			
Mediterranean	2	**0.46 (0.25-0.86)**	0.0%, 0.435
Mixed Mediterranean	0	No studies	
Non-Mediterranean	2	0.67 (0.37-1.21)	42.7%, 0.186
Subgroups by degree of adjustment			
Adjustment	3	**0.64 (0.43-0.96)**	33.8%, 0.221
No adjustment	1	0.21 (0.02-1.71)	NC
Subgroups by overall study quality			
Low (NOS 1-3)	0	No studies	
Intermediate (NOS 4-6)	1	0.80 (0.59-1.08)	NC

High (NOS 7-9)	3	**0.44 (0.26-0.75)**	0.0%, 0.715

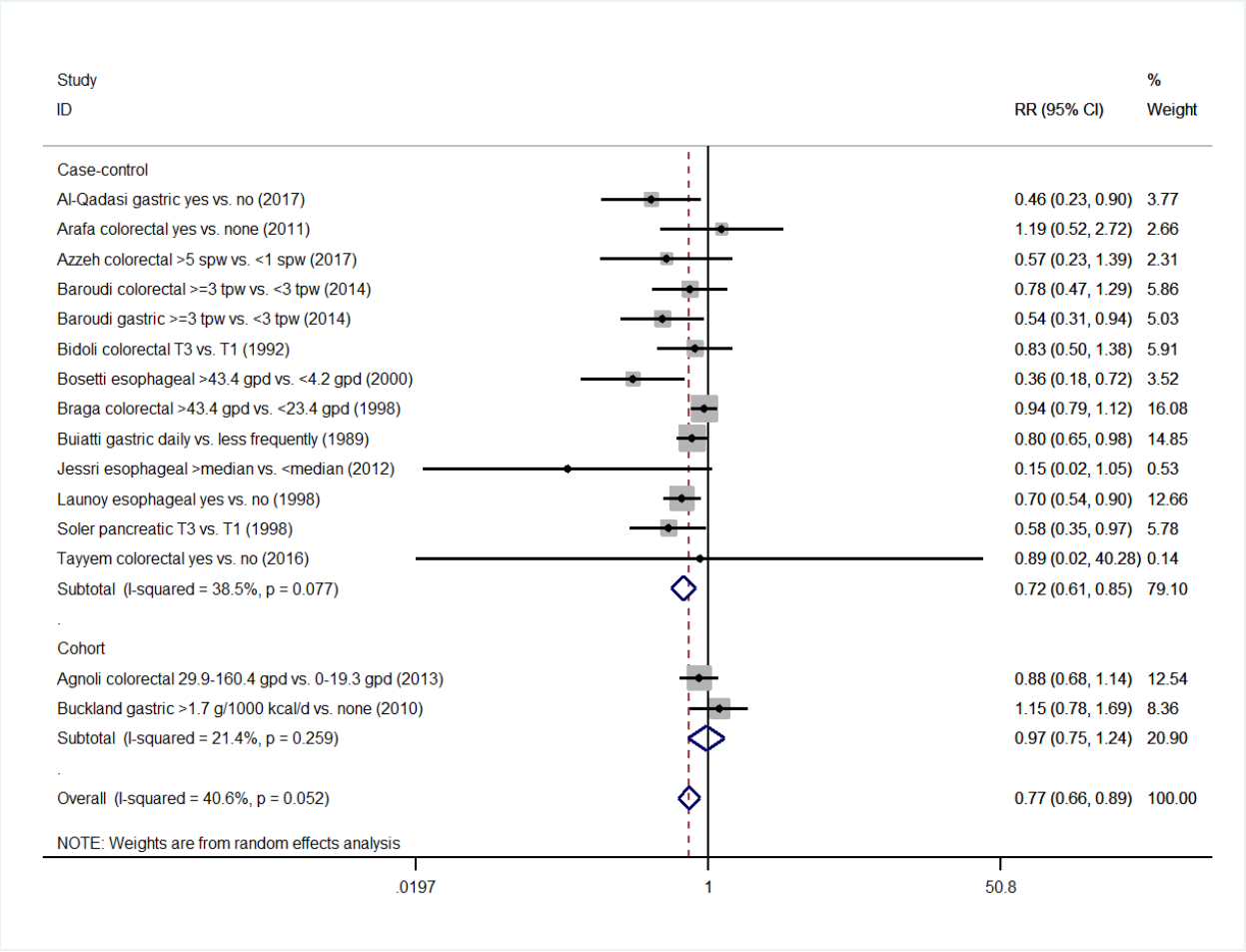
[§]number of study arm

Supplemental Figures

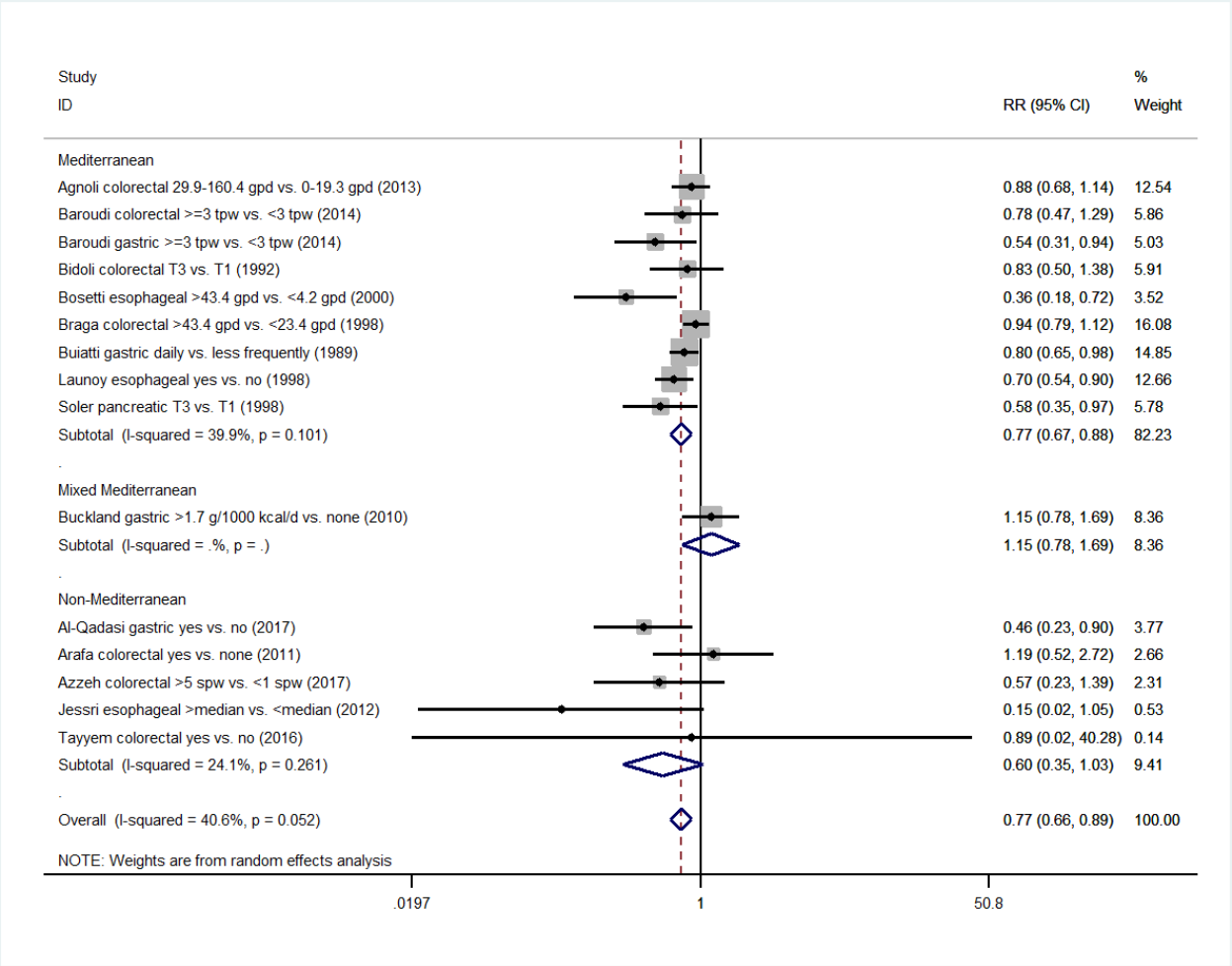
Supplemental Figure 1. Flow chart presenting the successive steps in the selection of eligible studies.



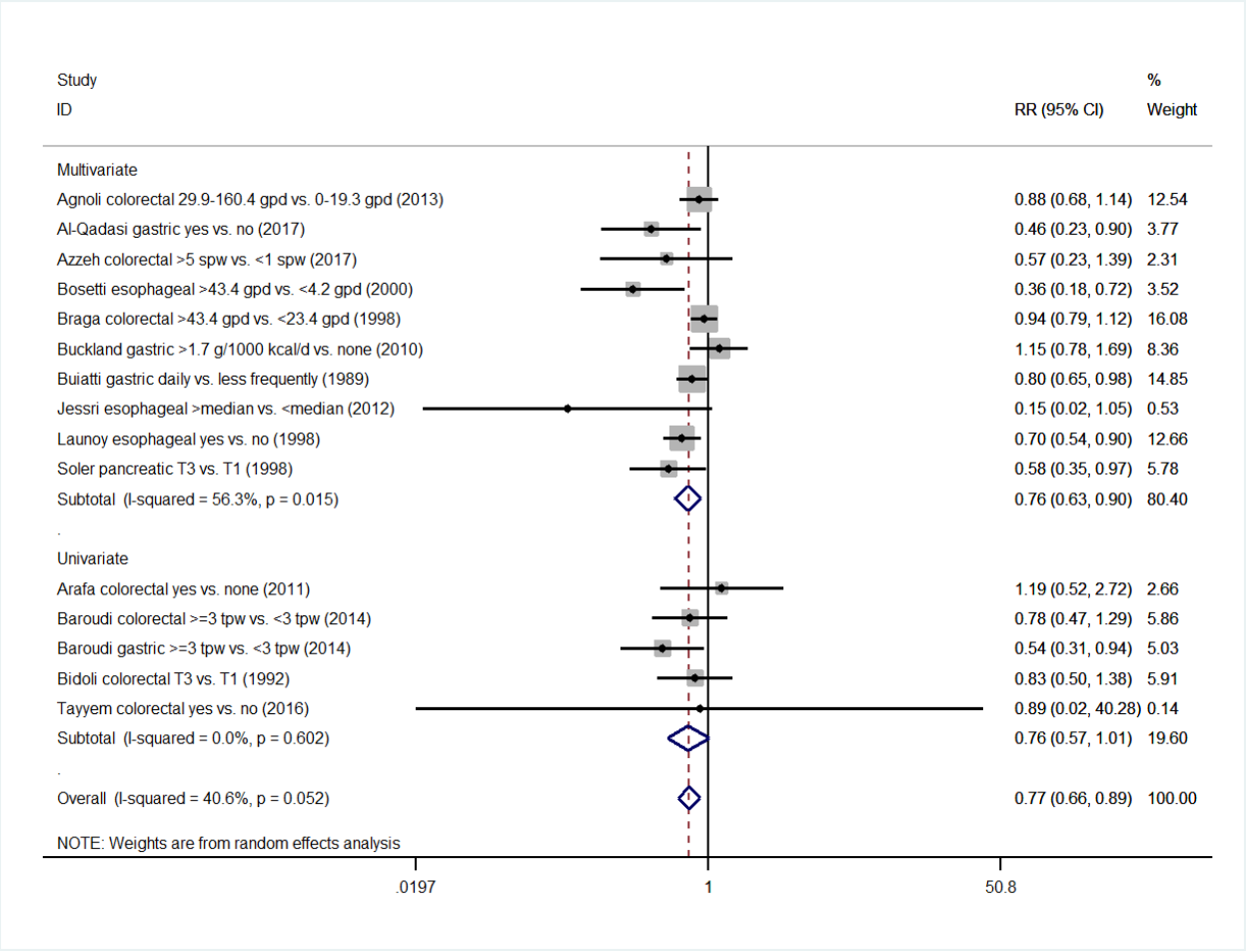
Supplemental Figure 2. Forest plot describing the association between high olive oil consumption and risk for gastrointestinal cancer. Apart from the overall analysis, the subanalyses on study design are presented.



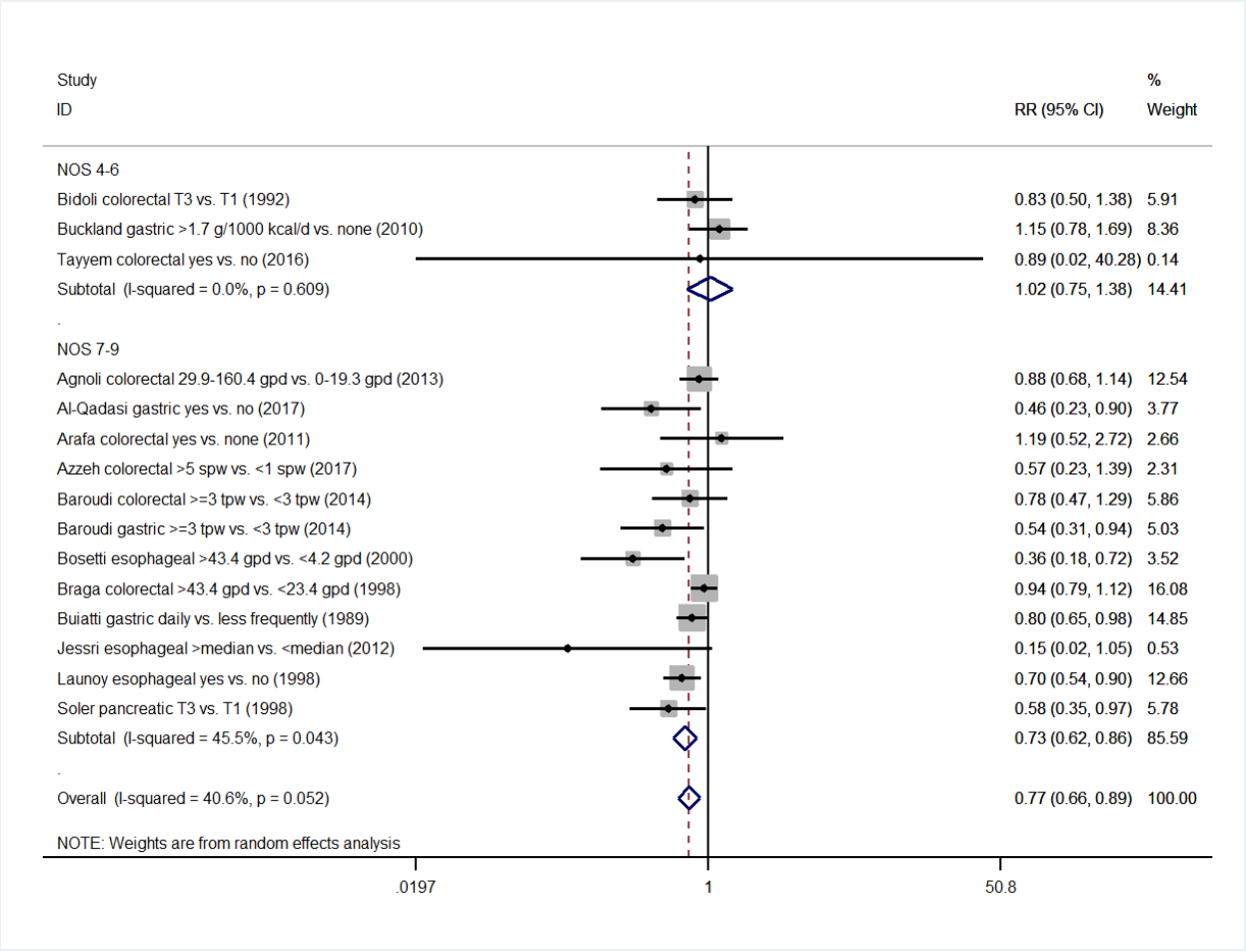
Supplemental Figure 3. Forest plot describing the association between high olive oil consumption and risk for gastrointestinal cancer. Apart from the overall analysis, the subanalyses on study geographic region are presented.



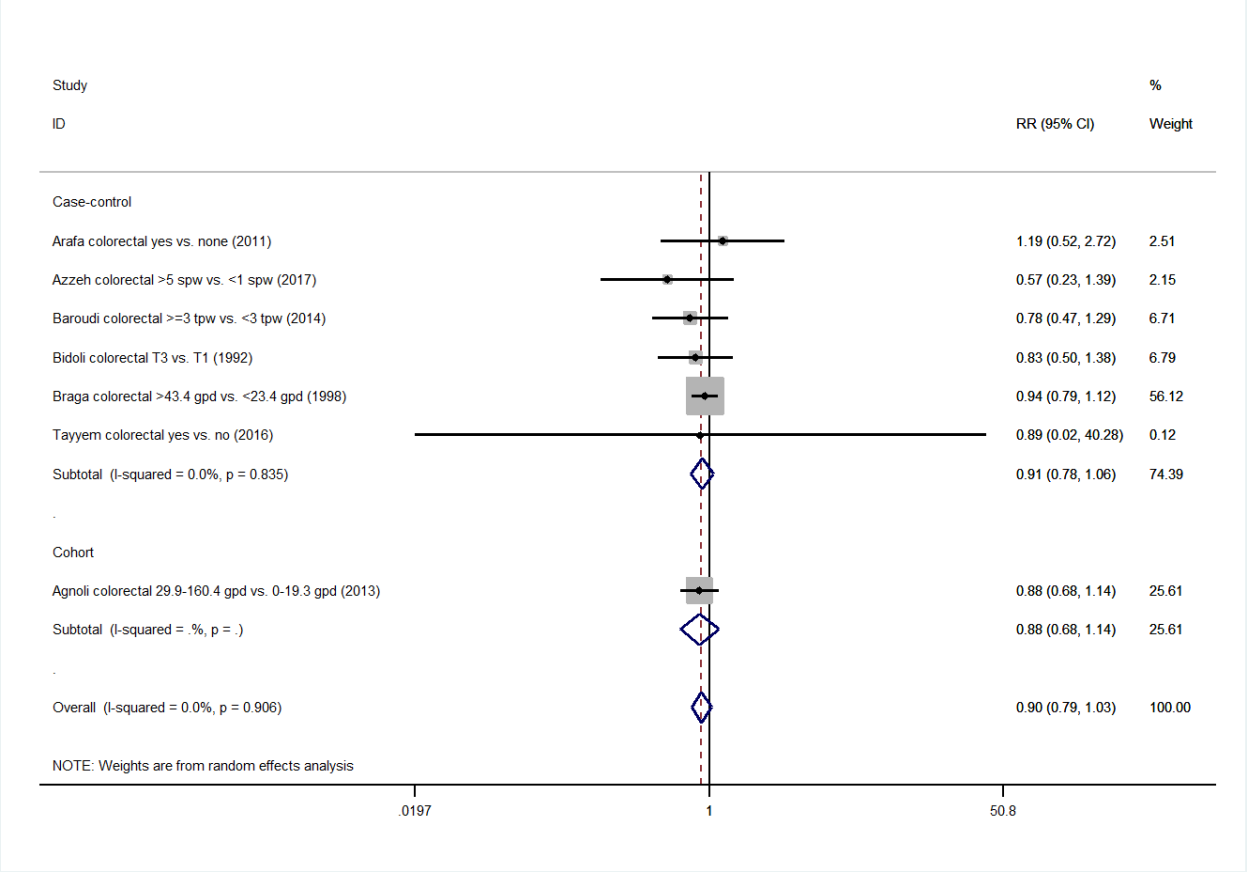
Supplemental Figure 4. Forest plot describing the association between high olive oil consumption and risk for gastrointestinal cancer. Apart from the overall analysis, the subanalyses on degree of adjustment are presented.



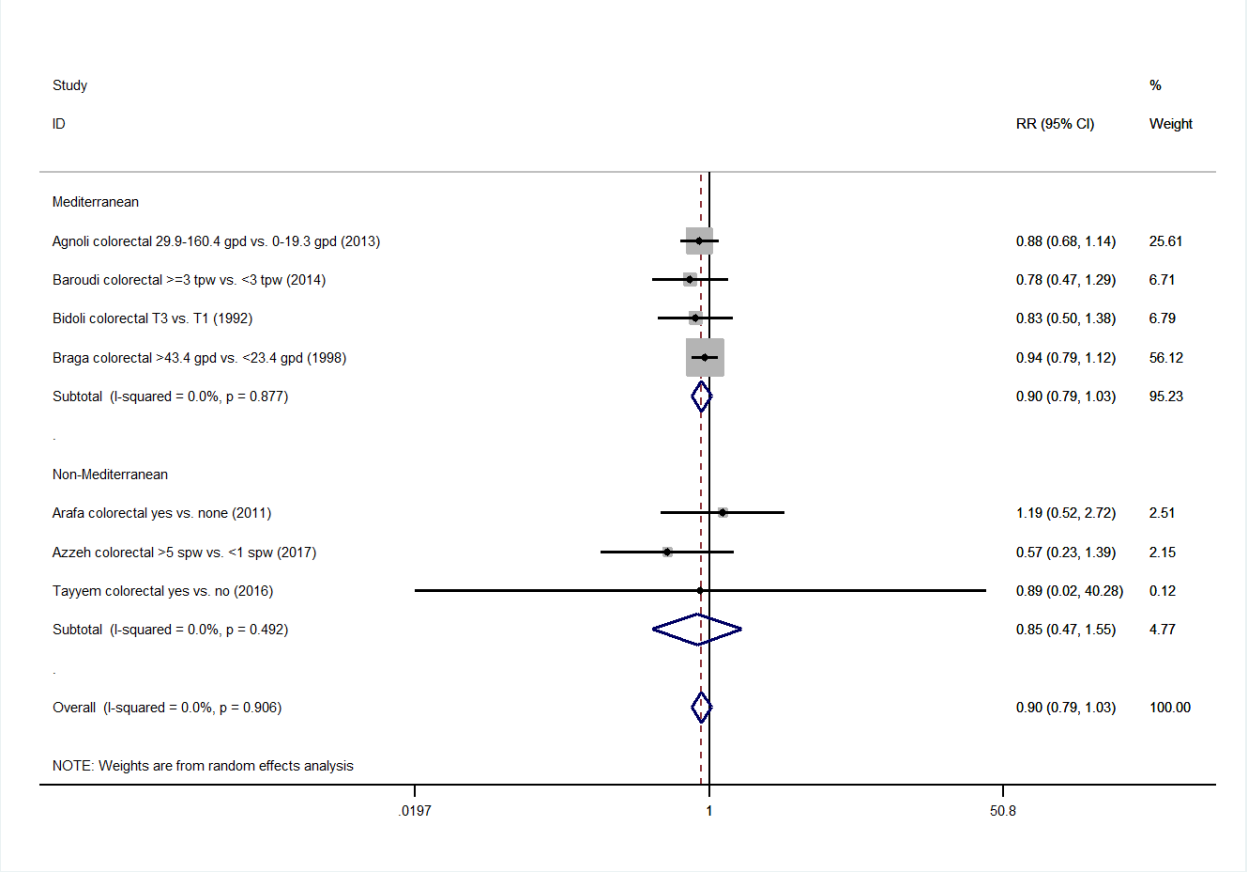
Supplemental Figure 5. Forest plot describing the association between high olive oil consumption and risk for gastrointestinal cancer. Apart from the overall analysis, the subanalyses on overall study quality are presented.



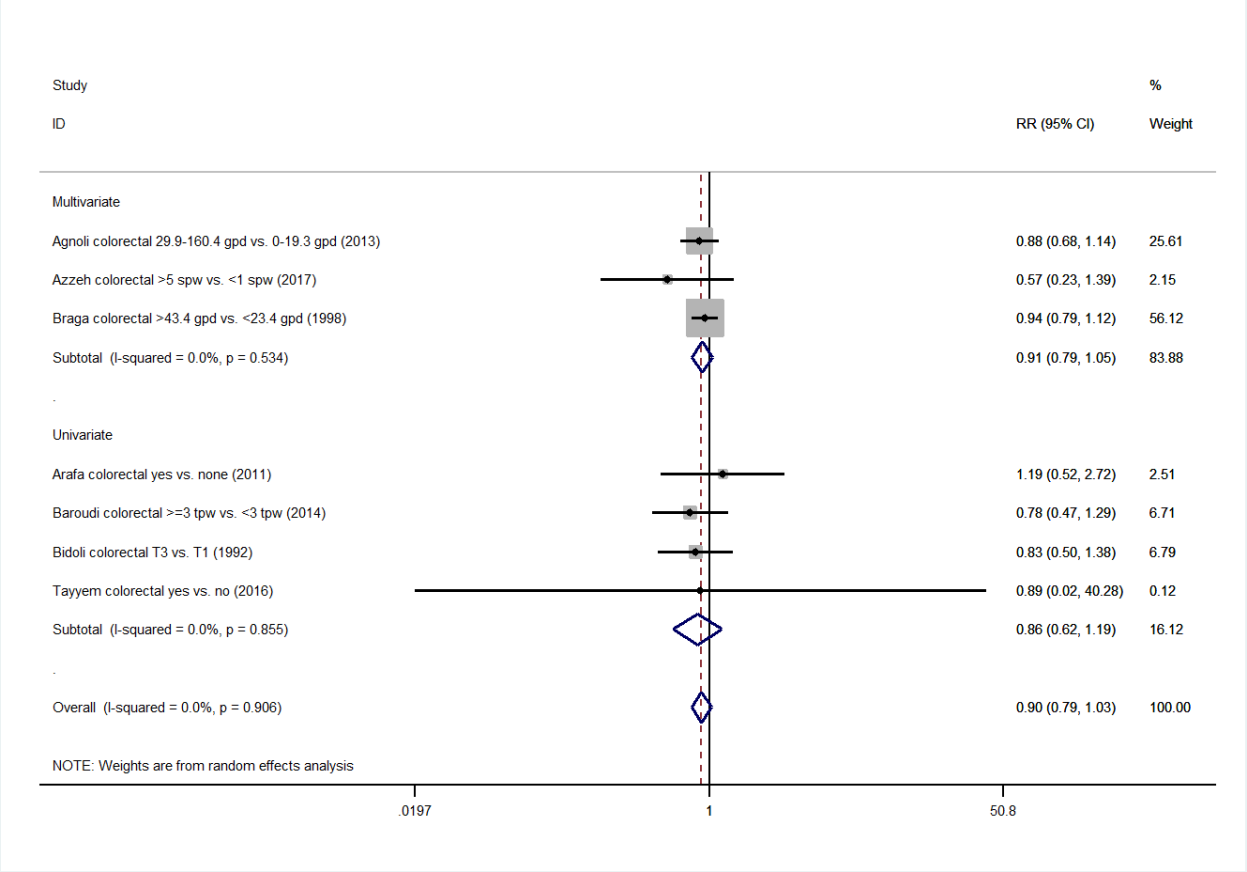
Supplemental Figure 6. Forest plot describing the association between high olive oil consumption and risk for colorectal cancer. Apart from the overall analysis, the subanalyses on study design are presented.



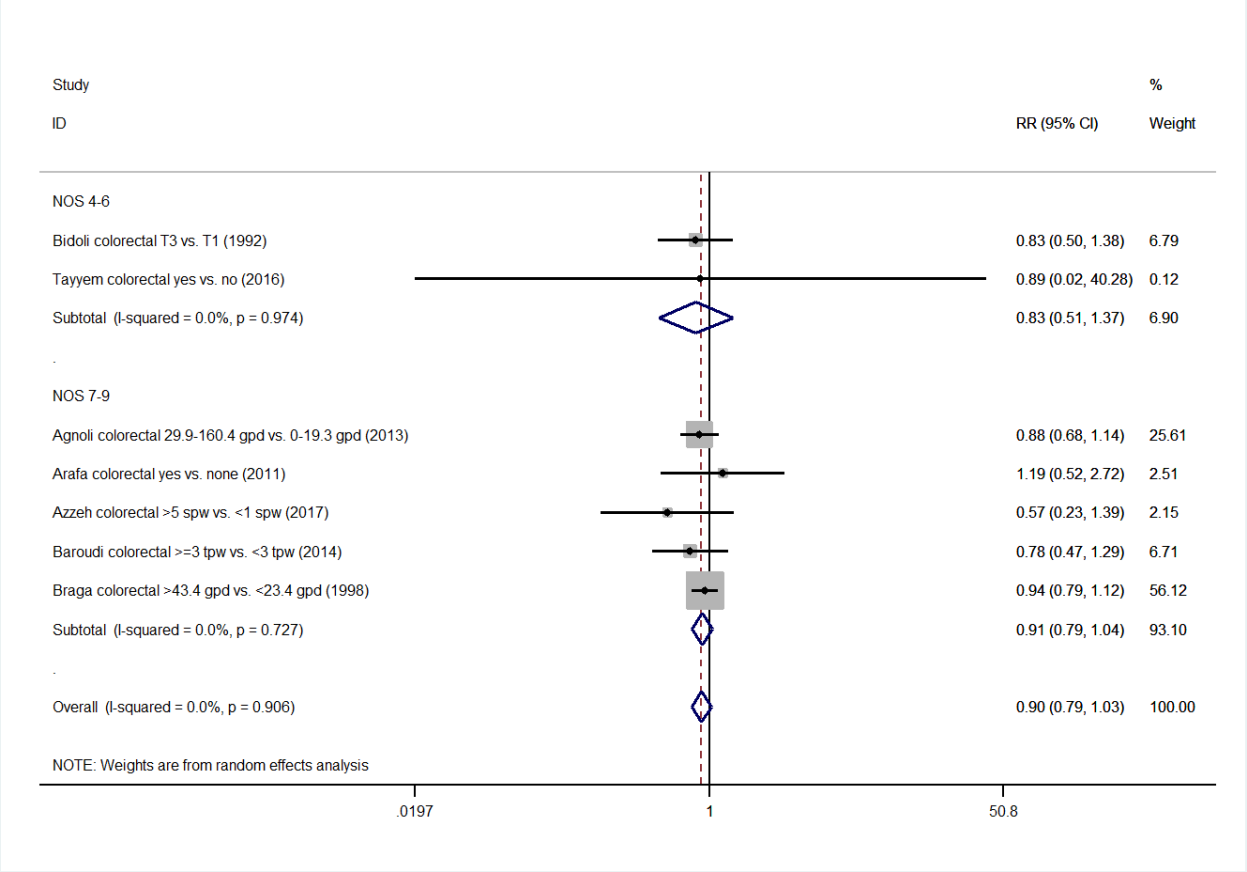
Supplemental Figure 7. Forest plot describing the association between high olive oil consumption and risk for colorectal cancer. Apart from the overall analysis, the subanalyses on study geographic region are presented.



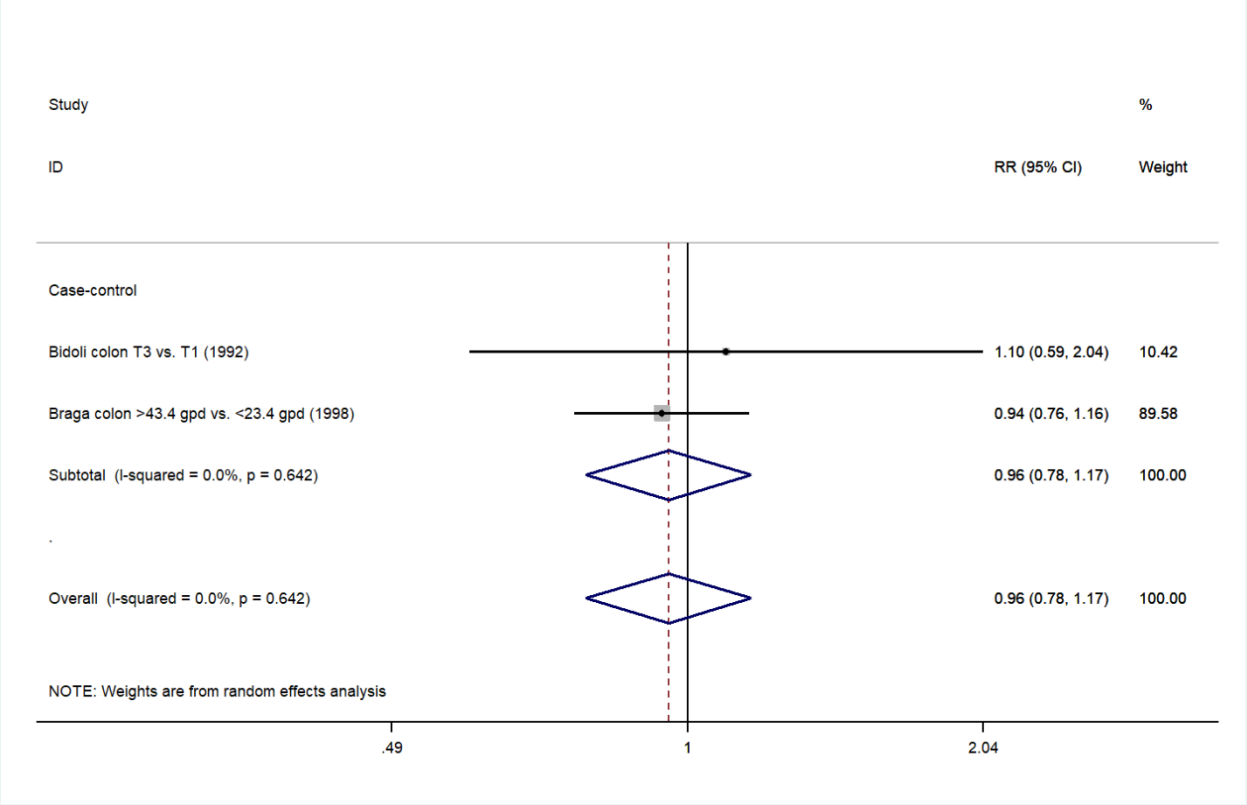
Supplemental Figure 8. Forest plot describing the association between high olive oil consumption and risk for colorectal cancer. Apart from the overall analysis, the subanalyses on degree of adjustment are presented.



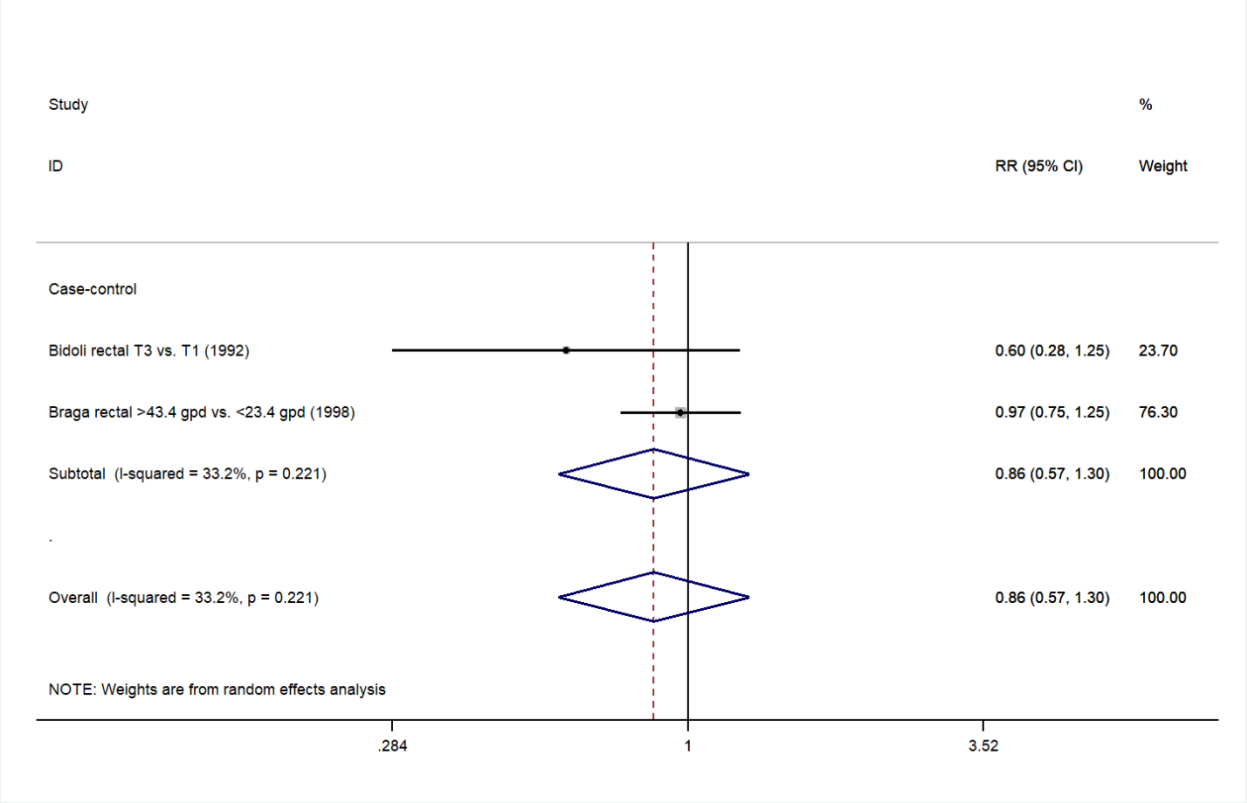
Supplemental Figure 9. Forest plot describing the association between high olive oil consumption and risk for colorectal cancer. Apart from the overall analysis, the subanalyses on overall study quality are presented.



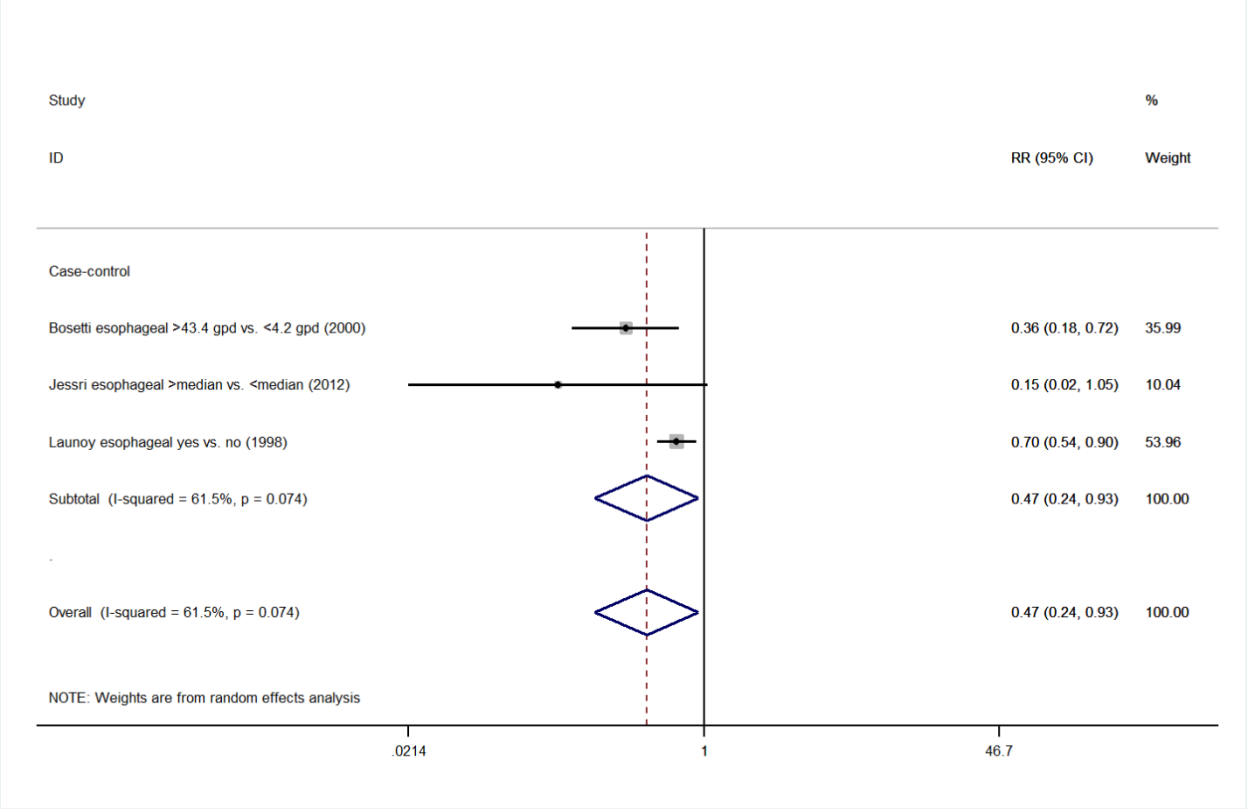
Supplemental Figure 10. Forest plot describing the association between high olive oil consumption and risk for colon cancer. Apart from the overall analysis, the subanalyses on study design are presented.



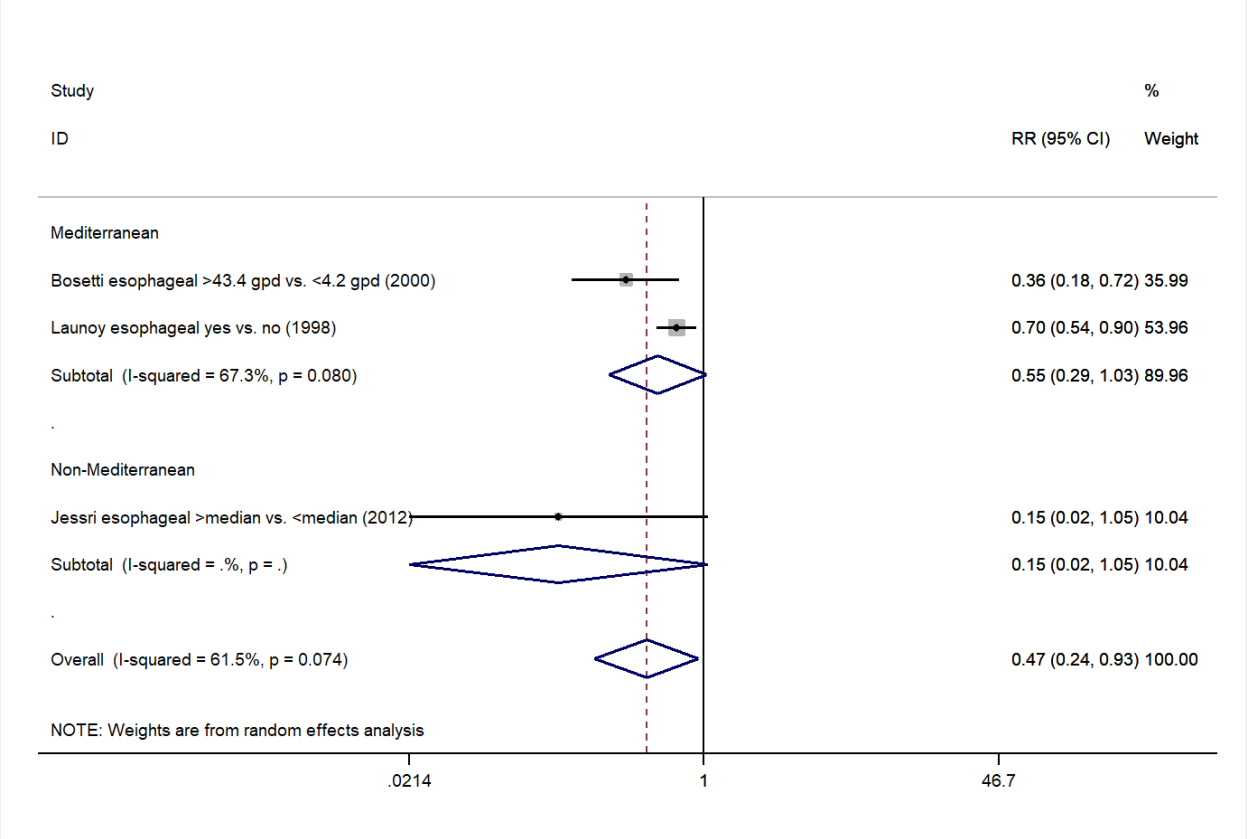
Supplemental Figure 11. Forest plot describing the association between high olive oil consumption and risk for rectal cancer. Apart from the overall analysis, the subanalyses on study design are presented.



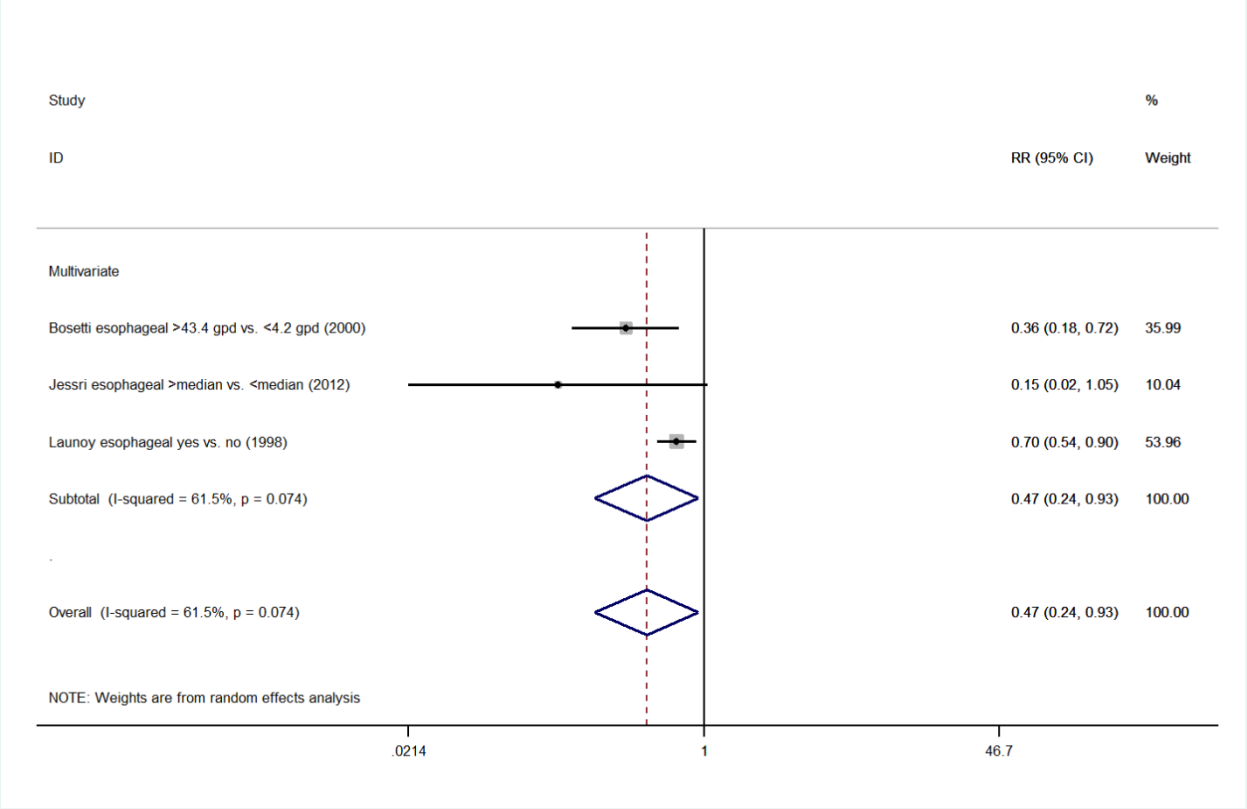
Supplemental Figure 12. Forest plot describing the association between high olive oil consumption and risk for esophageal cancer. Apart from the overall analysis, the subanalyses on study design are presented.



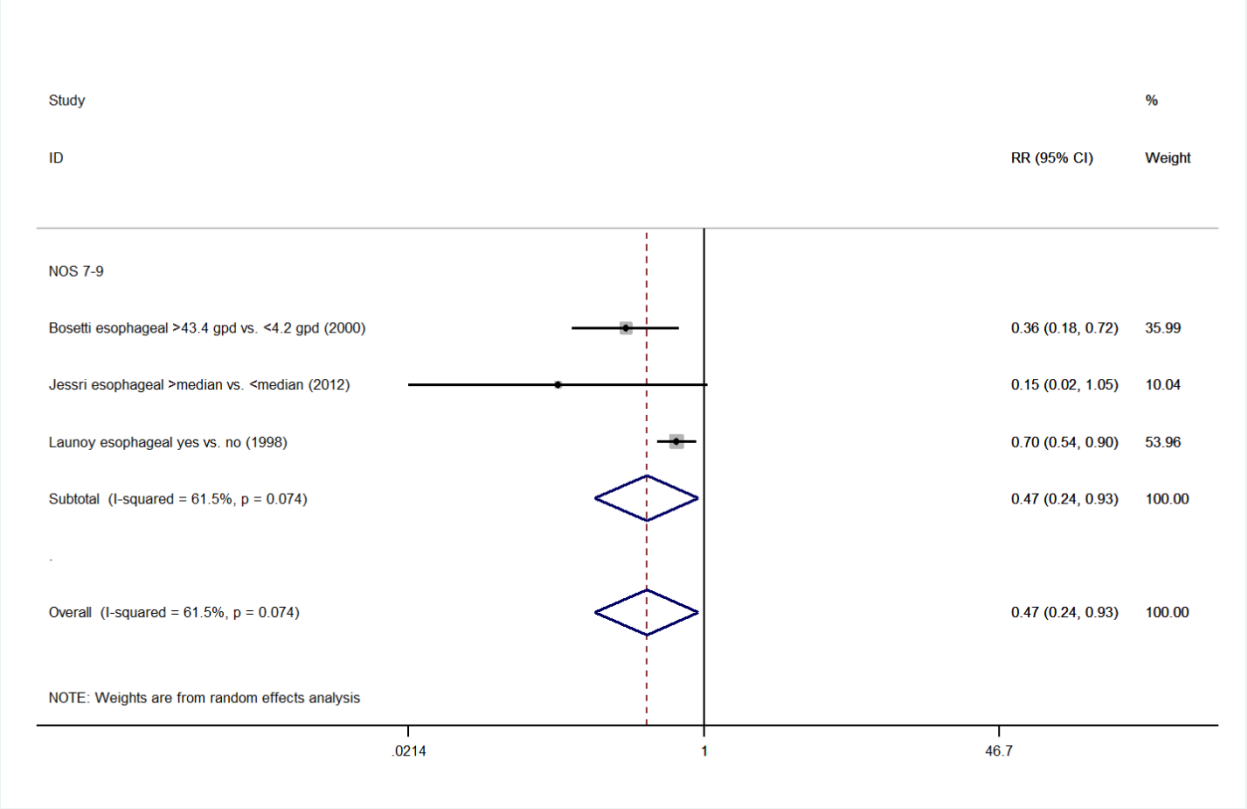
Supplemental Figure 13. Forest plot describing the association between high olive oil consumption and risk for esophageal cancer. Apart from the overall analysis, the subanalyses on study geographic region are presented.



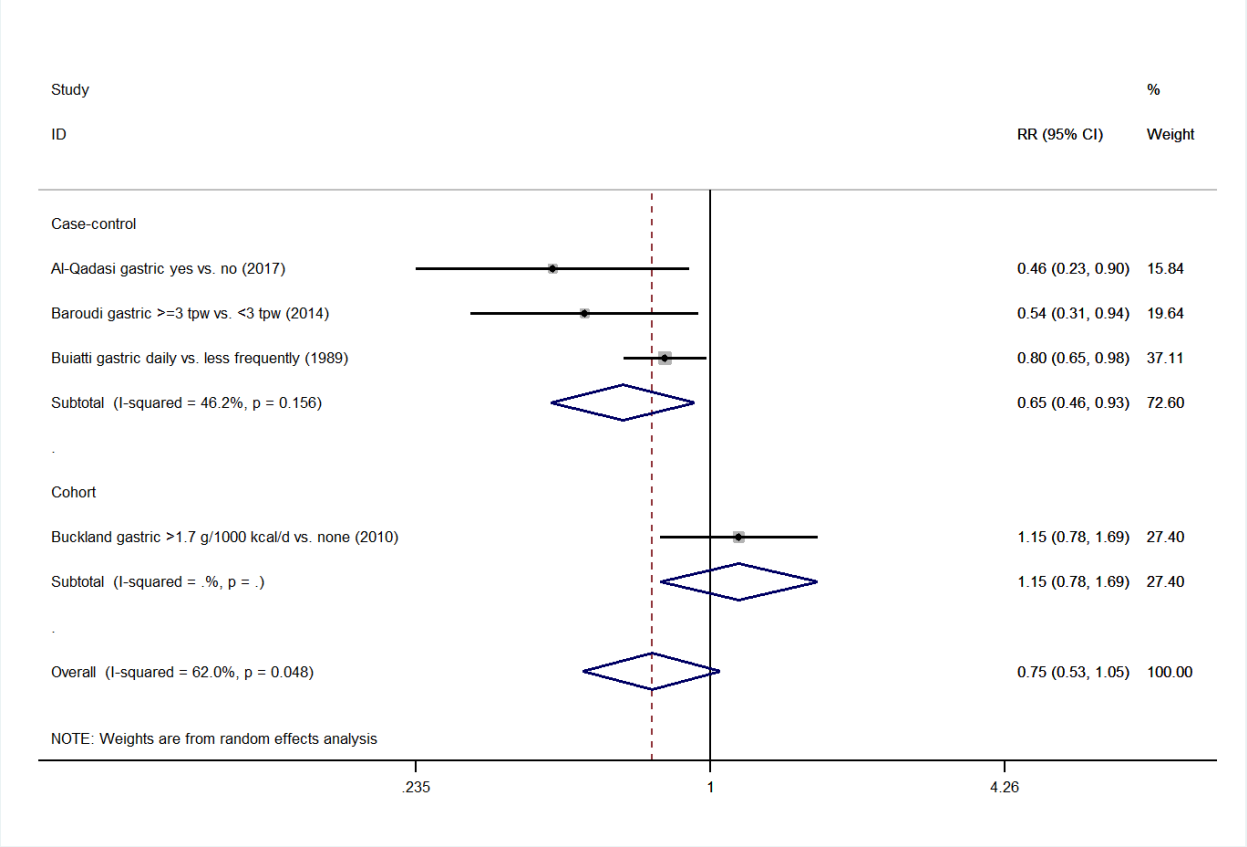
Supplemental Figure 14. Forest plot describing the association between high olive oil consumption and risk for esophageal cancer. Apart from the overall analysis, the subanalyses on degree of adjustment are presented.



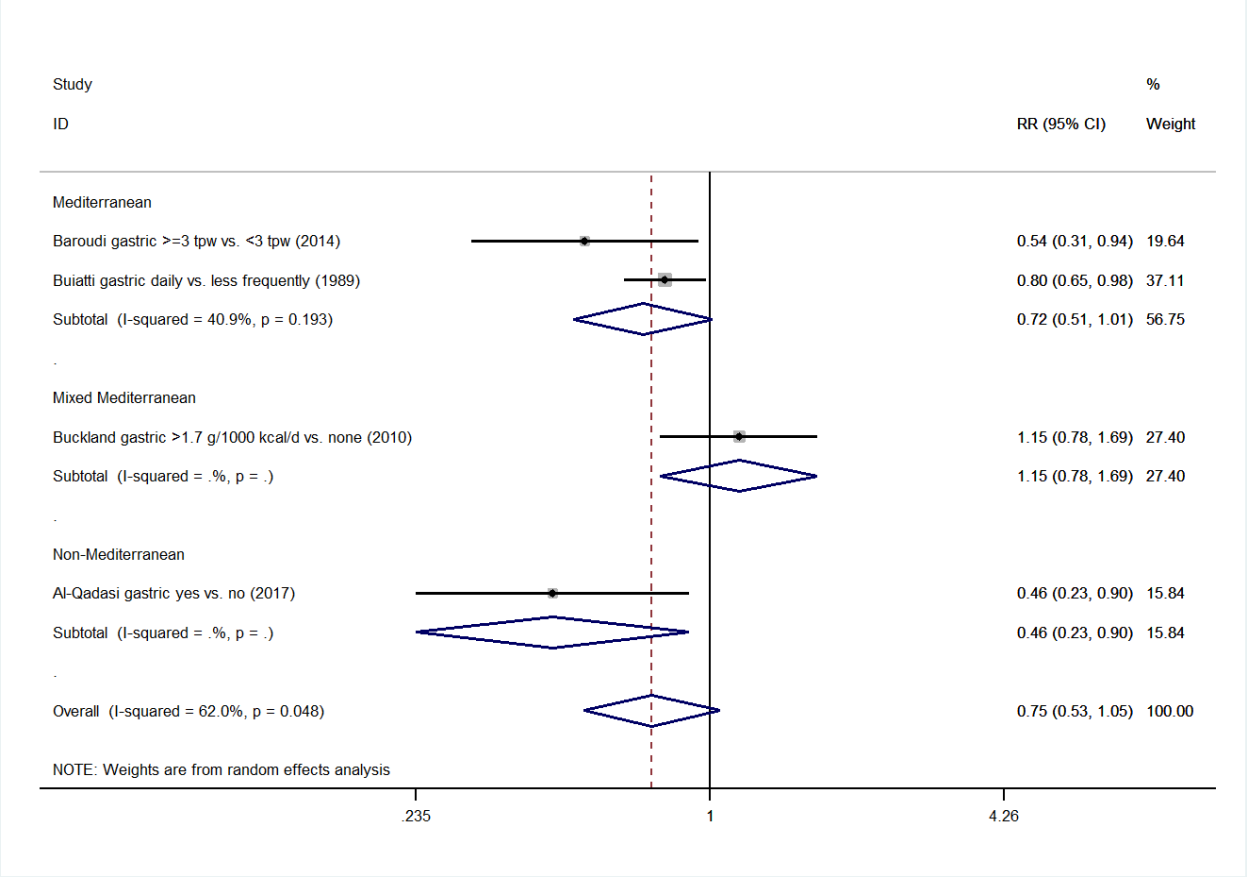
Supplemental Figure 15. Forest plot describing the association between high olive oil consumption and risk for esophageal cancer. Apart from the overall analysis, the subanalyses on overall study quality are presented.



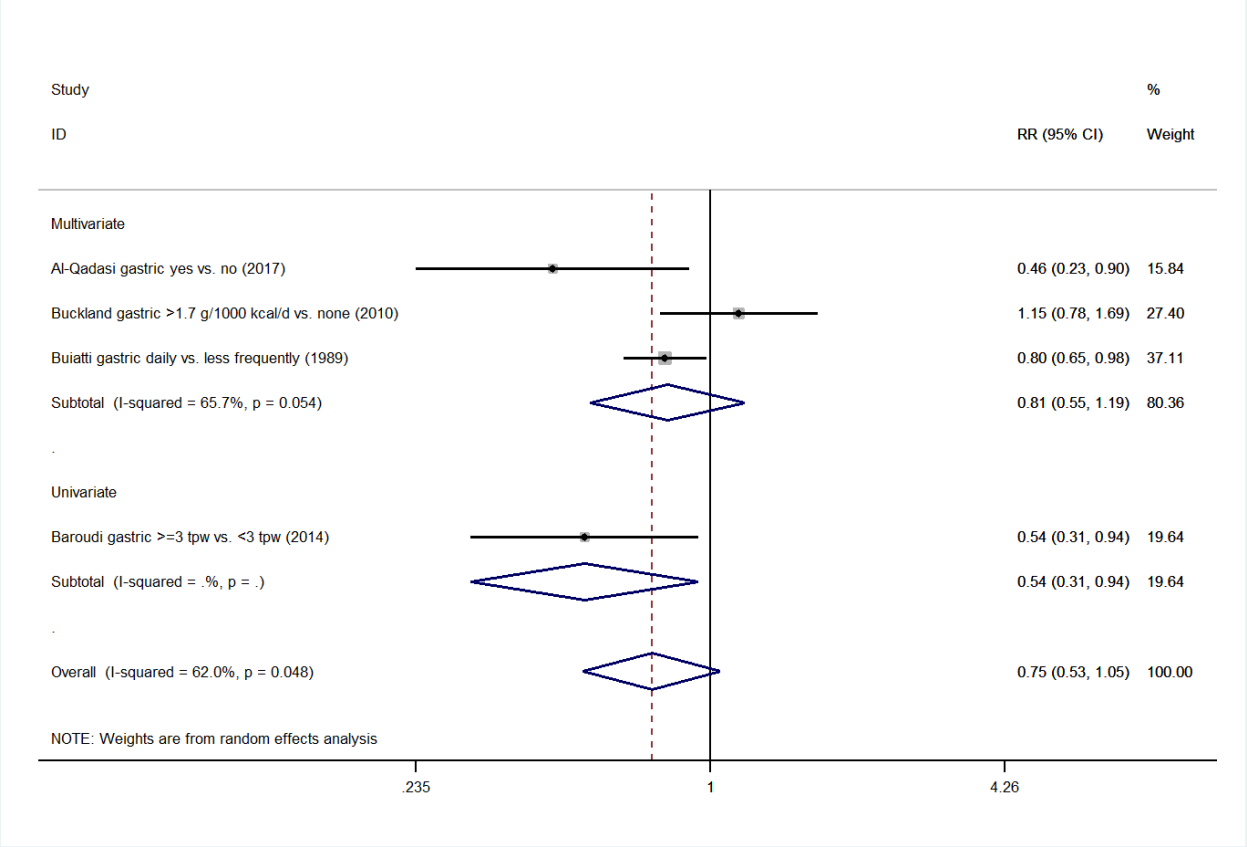
Supplemental Figure 16. Forest plot describing the association between high olive oil consumption and risk for gastric cancer. Apart from the overall analysis, the subanalyses on study design are presented.



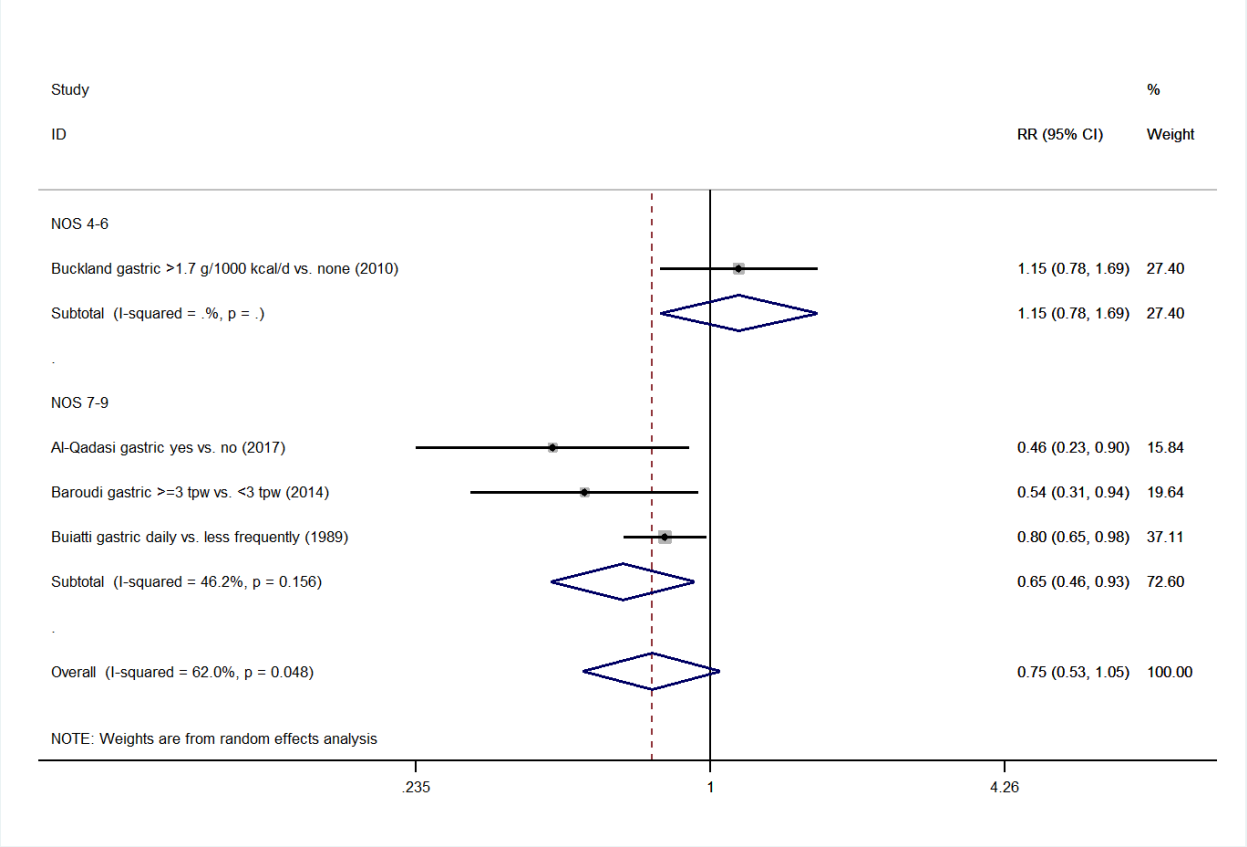
Supplemental Figure 17. Forest plot describing the association between high olive oil consumption and risk for gastric cancer. Apart from the overall analysis, the subanalyses on study geographic region are presented.



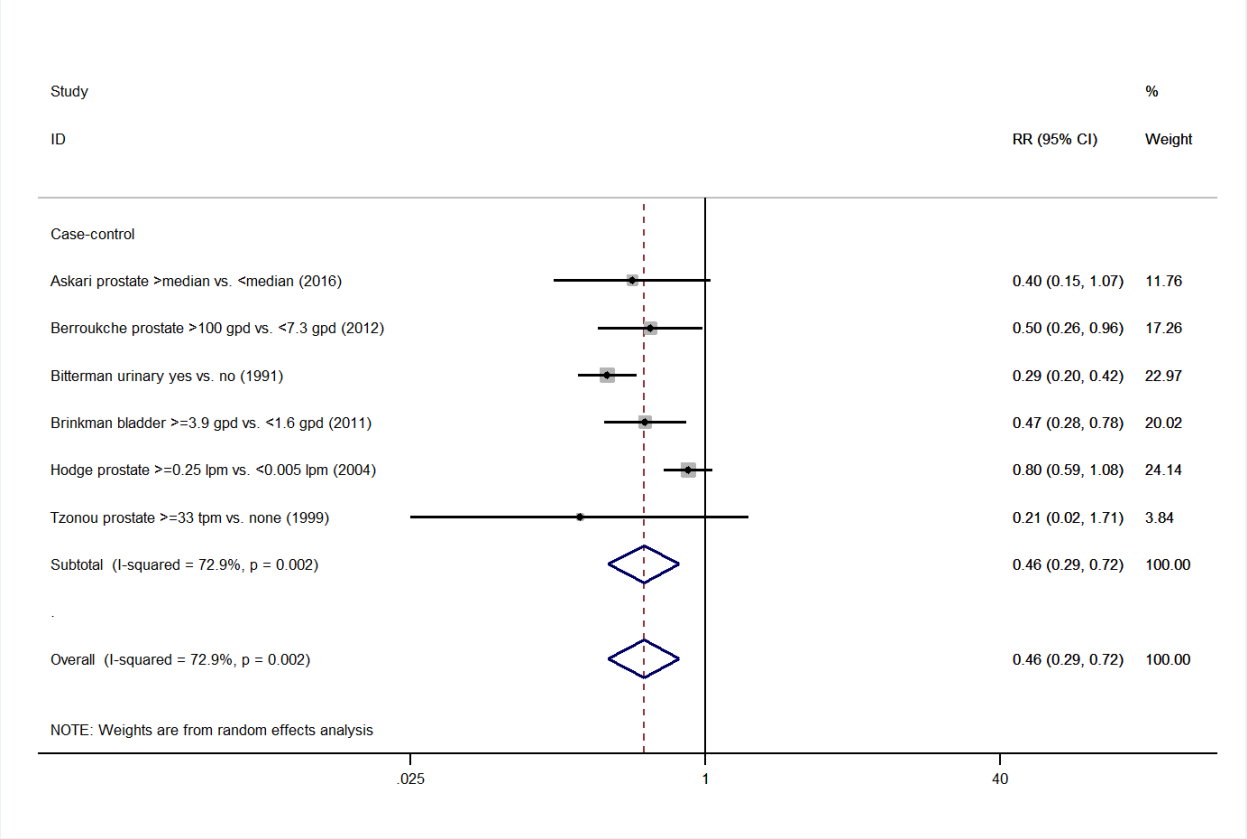
Supplemental Figure 18. Forest plot describing the association between high olive oil consumption and risk for gastric cancer. Apart from the overall analysis, the subanalyses on degree of adjustment are presented.



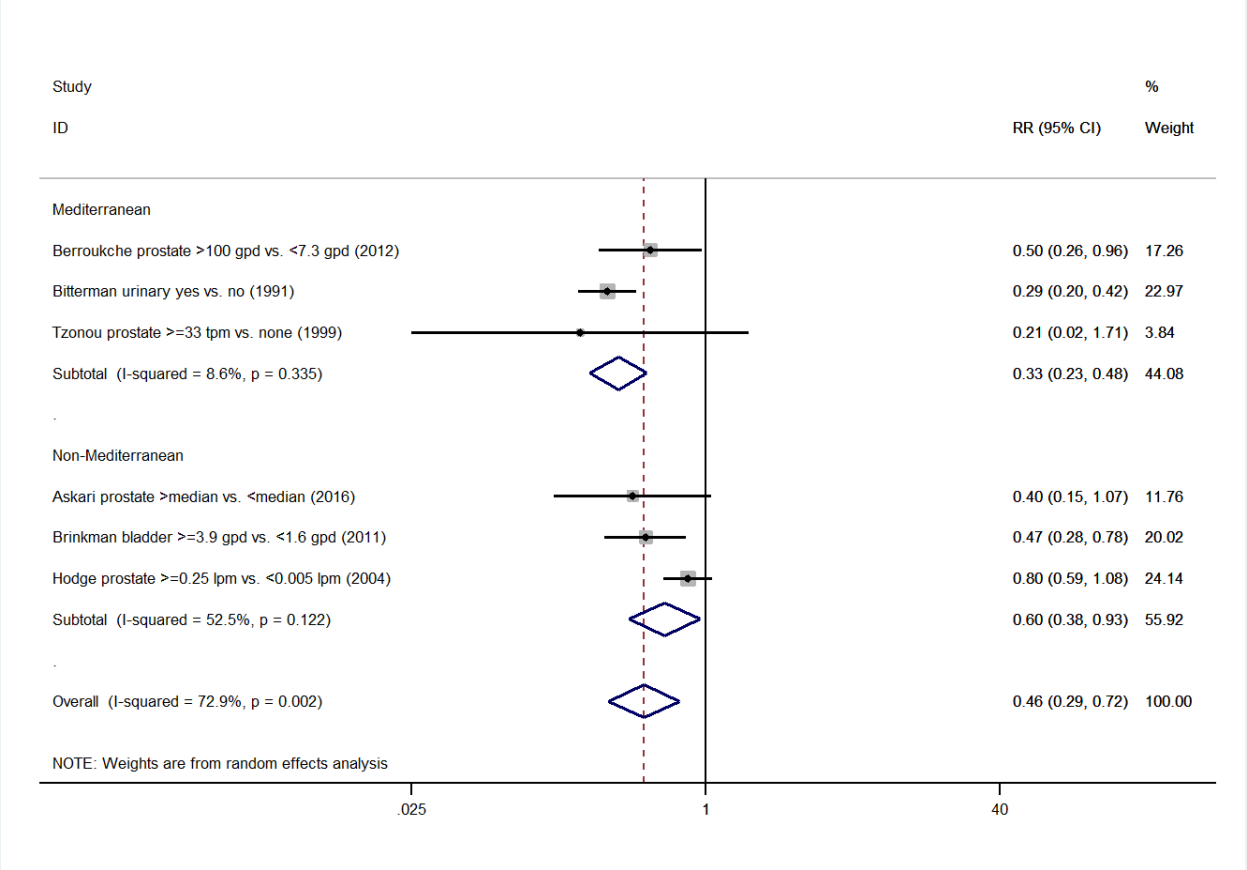
Supplemental Figure 19. Forest plot describing the association between high olive oil consumption and risk for gastric cancer. Apart from the overall analysis, the subanalyses on overall study quality are presented.



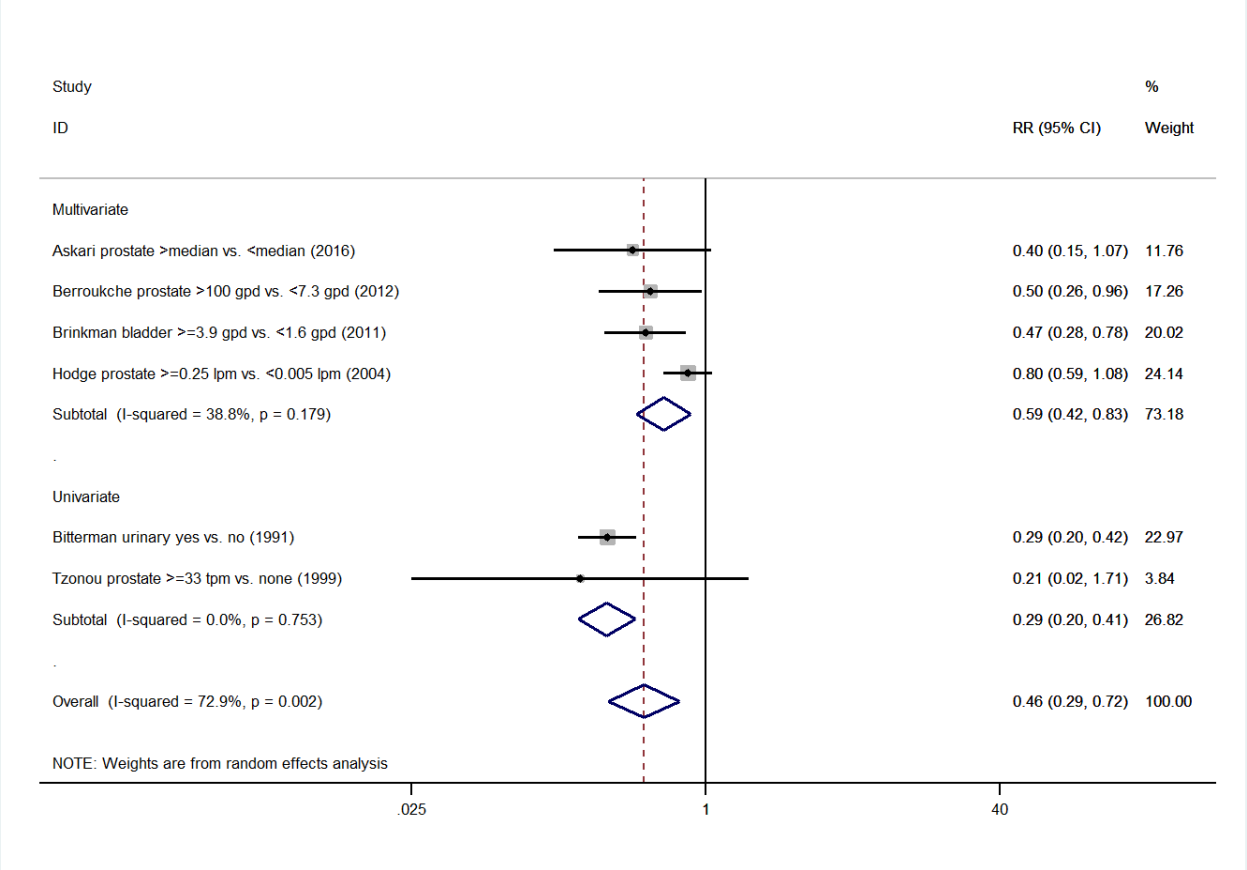
Supplemental Figure 20. Forest plot describing the association between high olive oil consumption and risk for urinary cancer. Apart from the overall analysis, the subanalyses on study design are presented.



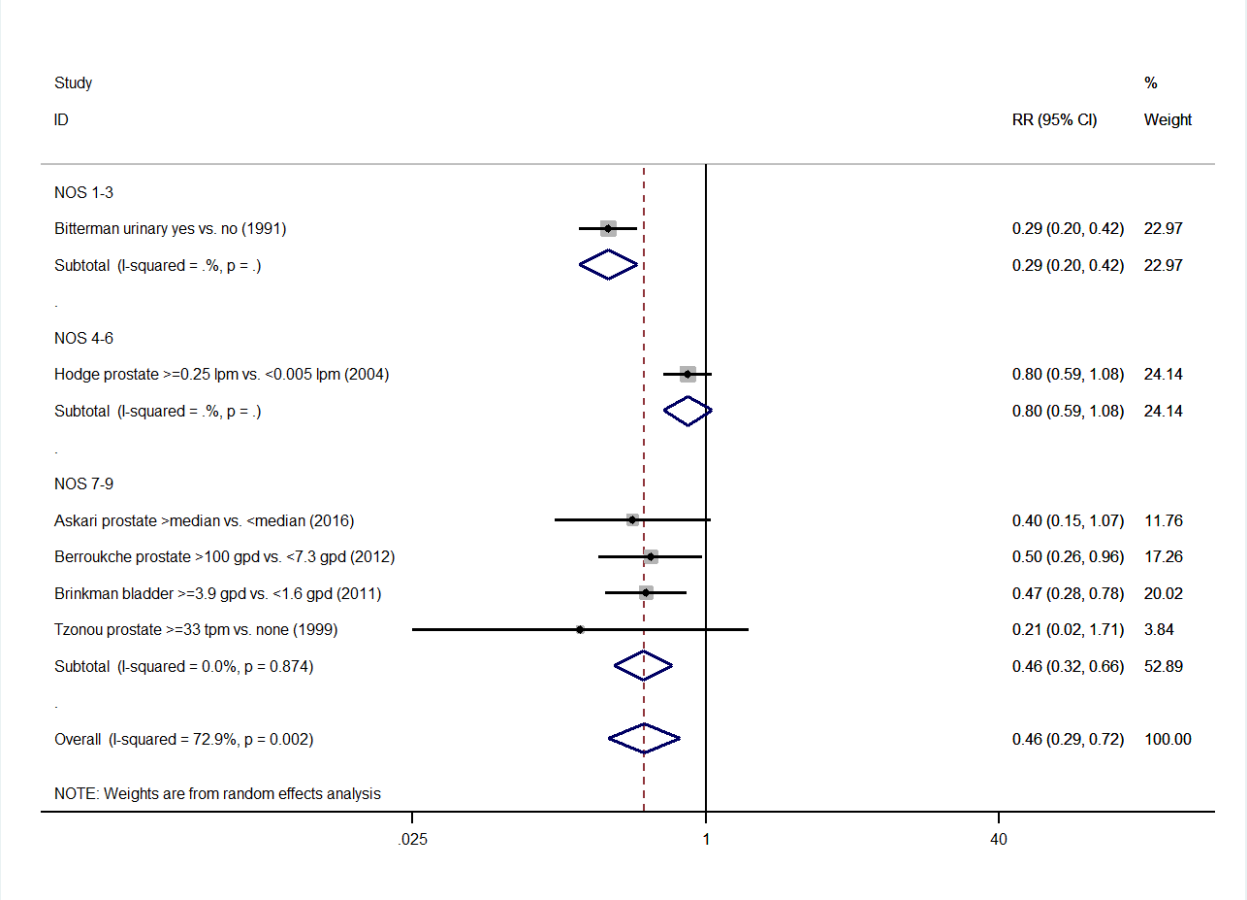
Supplemental Figure 21. Forest plot describing the association between high olive oil consumption and risk for urinary cancer. Apart from the overall analysis, the subanalyses on study geographic region are presented.



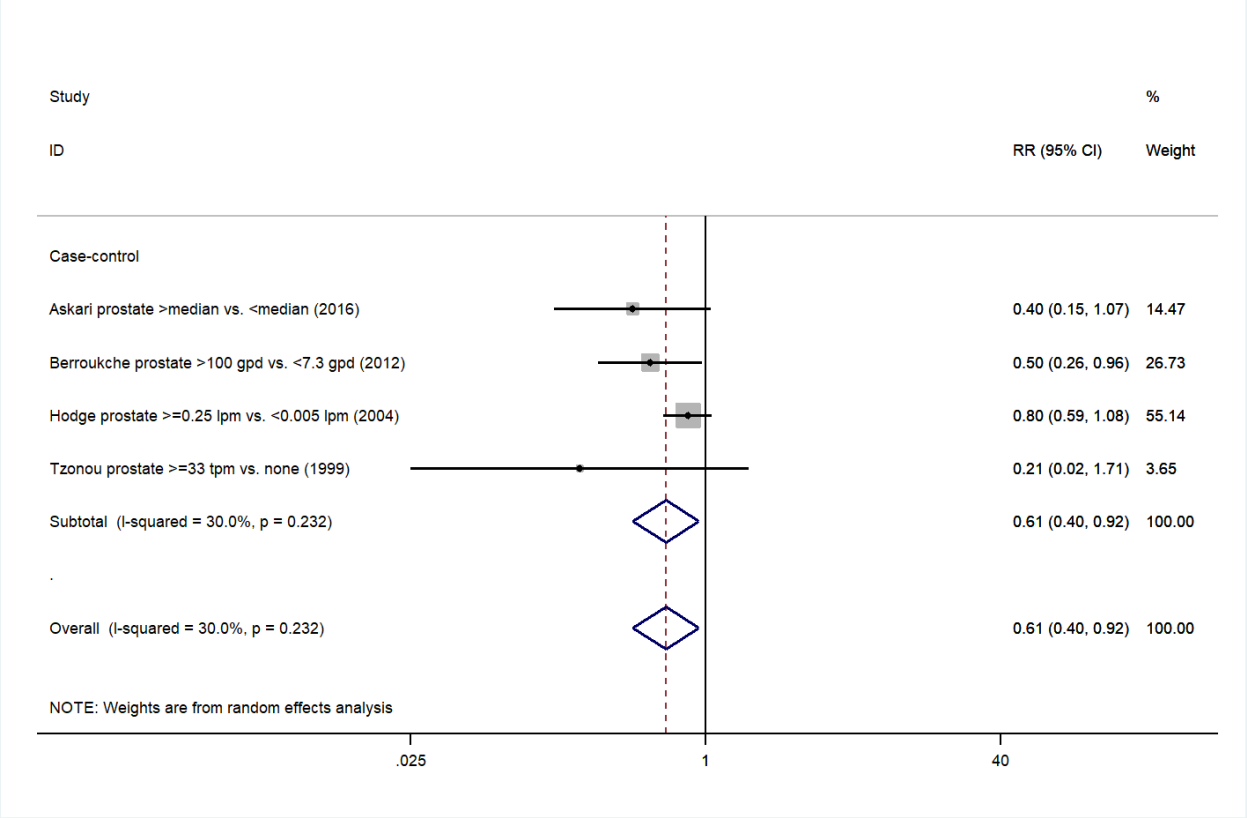
Supplemental Figure 22. Forest plot describing the association between high olive oil consumption and risk for urinary cancer. Apart from the overall analysis, the subanalyses on degree of adjustment are presented.



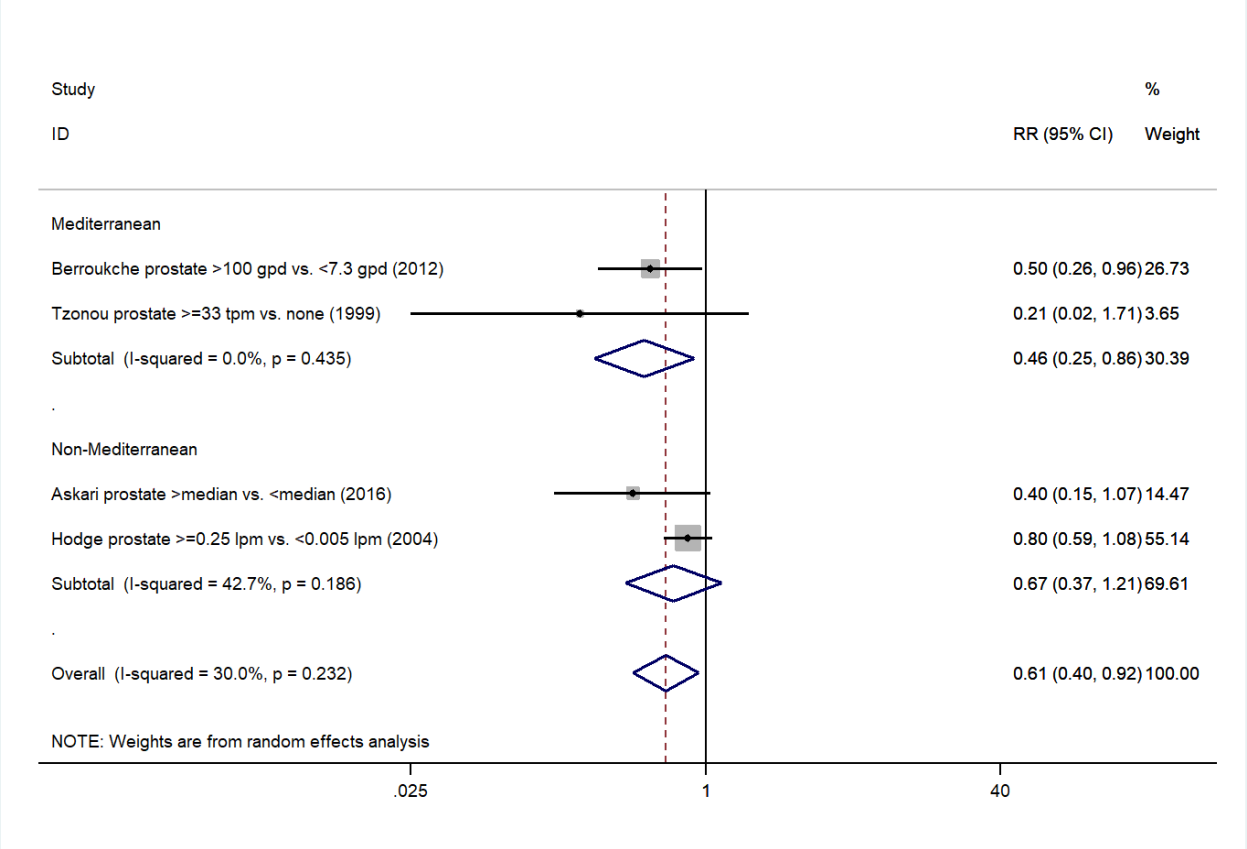
Supplemental Figure 23. Forest plot describing the association between high olive oil consumption and risk for urinary cancer. Apart from the overall analysis, the subanalyses on overall study quality are presented.



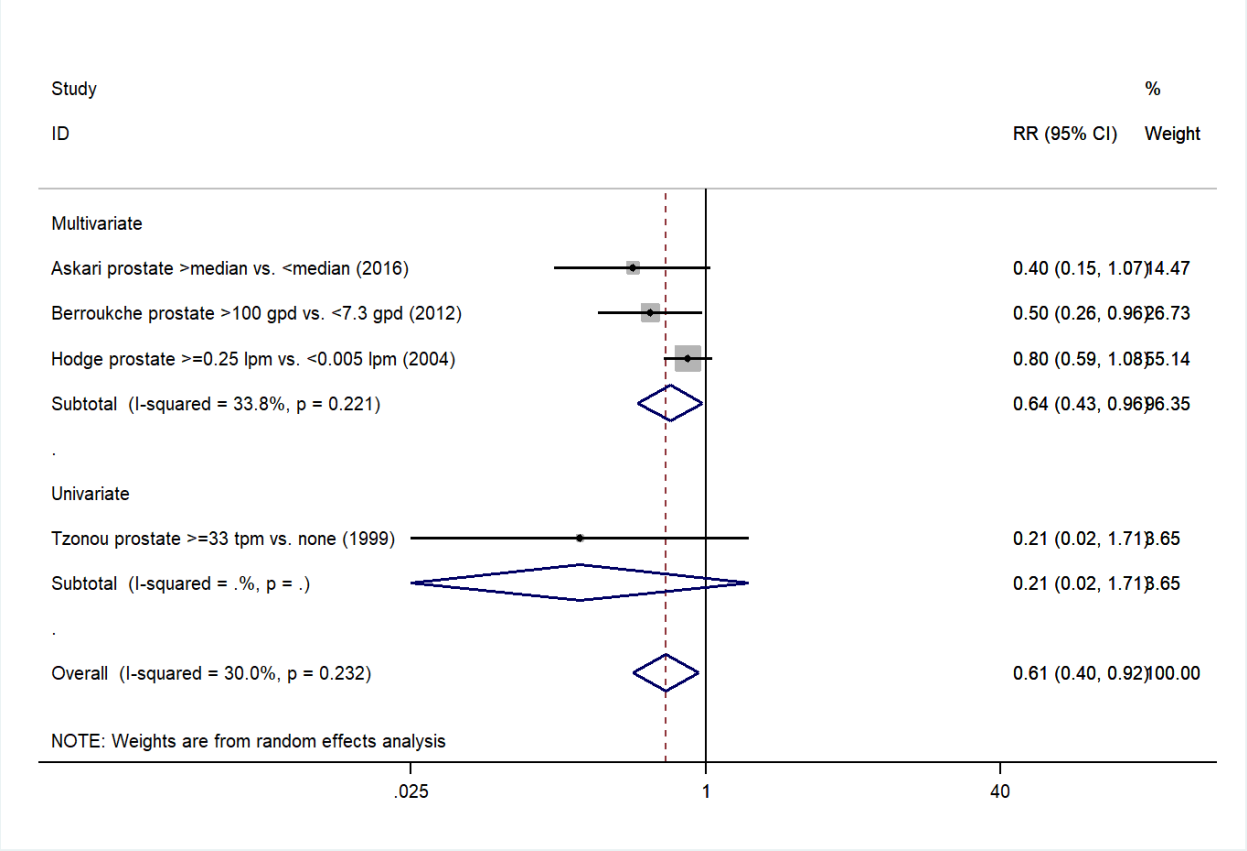
Supplemental Figure 24. Forest plot describing the association between high olive oil consumption and risk for prostate cancer. Apart from the overall analysis, the subanalyses on study design are presented.



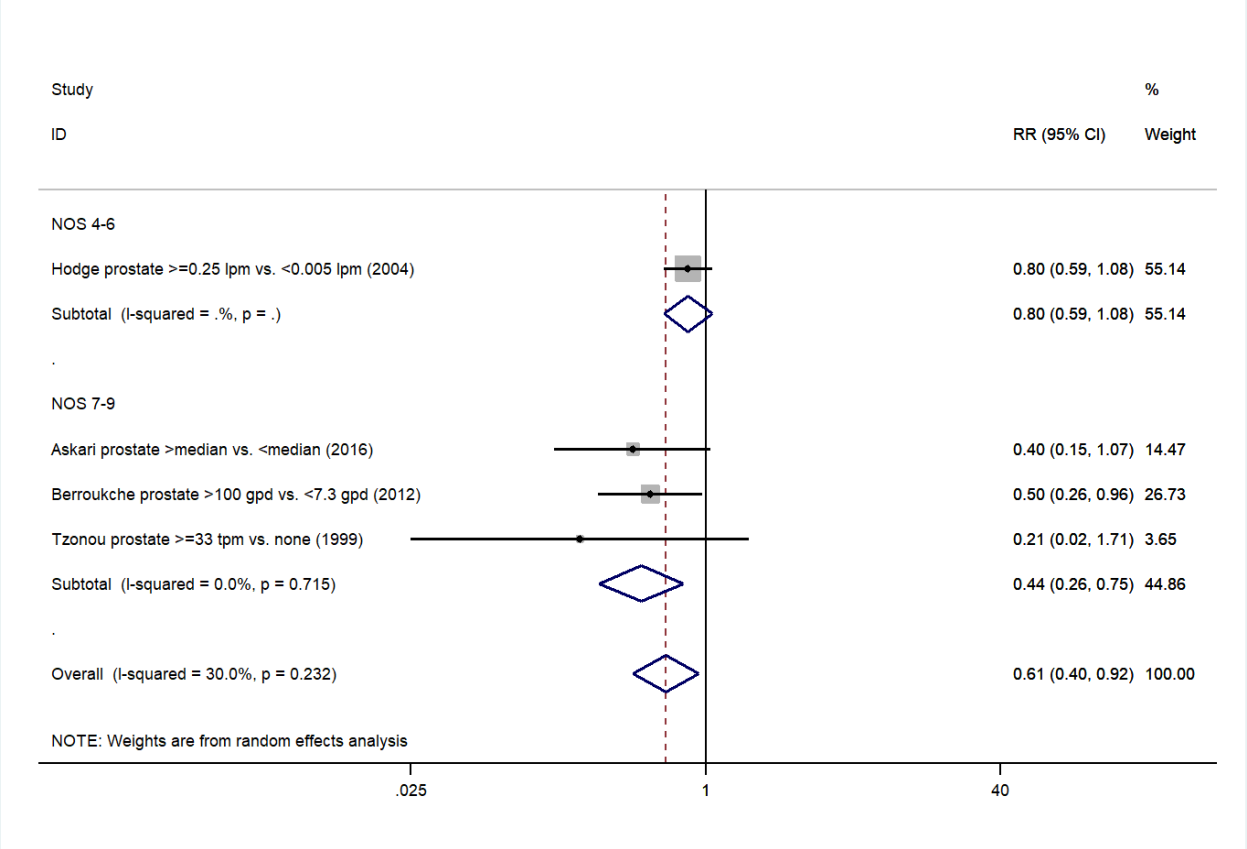
Supplemental Figure 25. Forest plot describing the association between high olive oil consumption and risk for prostate cancer. Apart from the overall analysis, the subanalyses on study geographic region are presented.



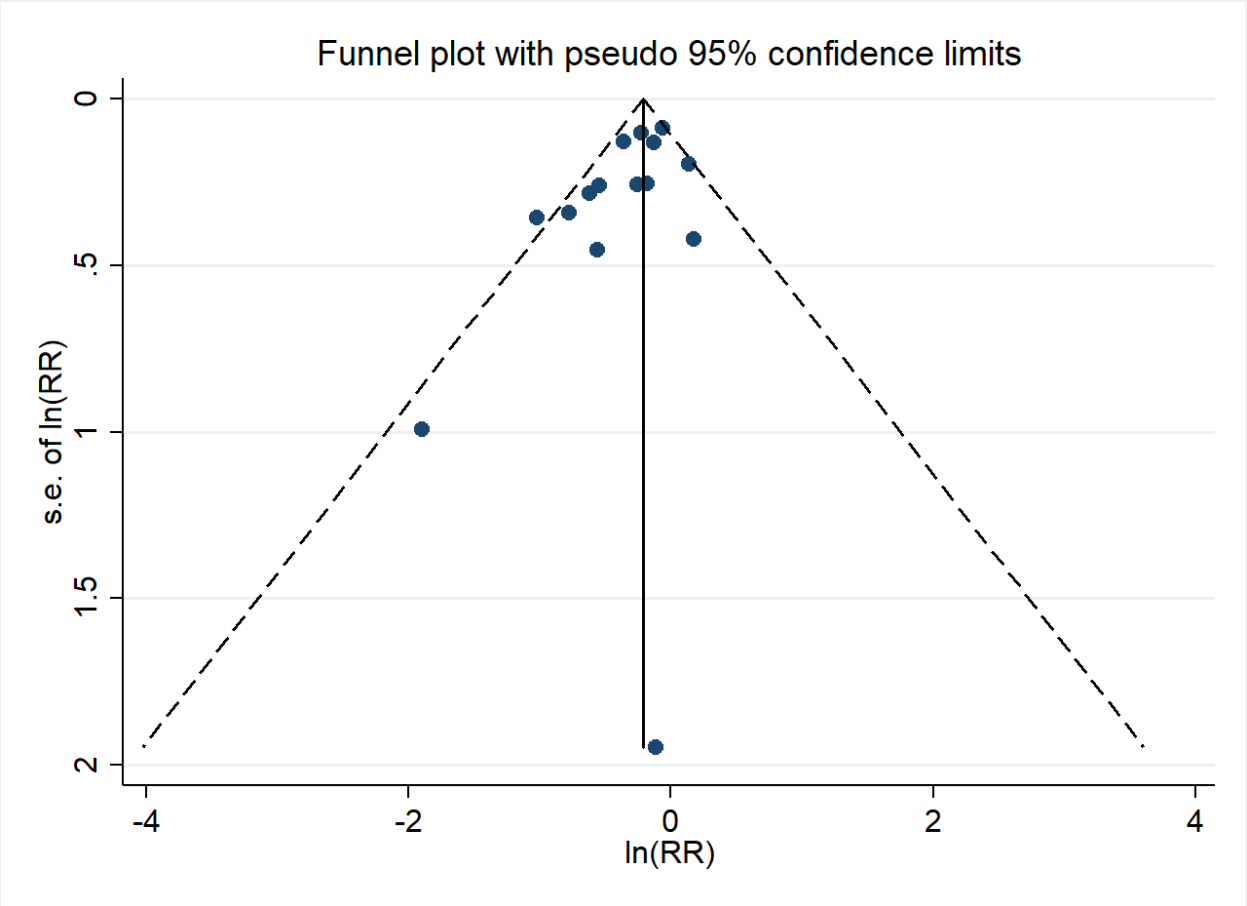
Supplemental Figure 26. Forest plot describing the association between high olive oil consumption and risk for prostate cancer. Apart from the overall analysis, the subanalyses on degree of adjustment are presented.



Supplemental Figure 27. Forest plot describing the association between high olive oil consumption and risk for prostate cancer. Apart from the overall analysis, the subanalyses on overall study quality are presented.



Supplemental Figure 28. Funnel plot of the meta-analysis on gastrointestinal cancer risk showing evidence of publication bias as moderate asymmetry.



Supplemental Figure 29. Plot depicting the modifying effect mediated by gender upon the association between gastrointestinal cancer and high olive oil intake. The circle sizes represent the inverse of each within-study variance.