

Case-Control and Prospective Studies of Dietary Alpha-Linolenic Acid Intake and Prostate Cancer Risk: a Meta-Analysis

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3 4	1	Case-Control and Prospective Studies of Dietary Alpha-Linolenic Acid
5 6	2	Intake and Prostate Cancer Risk: a Meta-Analysis
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Abstract **Background:** ALA is considered a cardioprotective nutrient, however some epidemiological studies have suggested that dietary ALA intake increases the risk of prostate cancer. Objective: To conduct a systematic review and meta-analysis of case-control and prospective studies investigating the association between dietary ALA intake and prostate cancer risk. Data Sources: MEDLINE and EMBASE were searched for relevant prospective and case-control studies. Eligibility Criteria for Selecting Studies: We included all prospective cohort, case-control, nested case-cohort, and nested case-control studies that investigated the effect of dietary ALA intake on the incidence (or diagnosis) of prostate cancer and provided relative risk (RR), hazard ratios (HR), or odds ratios (OR) estimates. **Design:** Data were pooled using the generic inverse variance method with a random-effects model from studies that compared the highest ALA quantile with the lowest ALA quantile. Risk estimates were expressed as relative risk (RR) with 95% confidence intervals (CI). Heterogeneity was assessed by χ^2 and quantified by I^2 . **Results:** Data from 5 prospective and 7 case-control studies were pooled. The overall RR estimate showed ALA intake to be positively, but non-significantly associated with prostate cancer risk (1.08 [0.90 to 1.29], P=0.40, I^2 =85%), but the interpretation was complicated by evidence of heterogeneity not explained by study design. A weak non-significant protective effect of ALA intake on prostate cancer risk in the prospective studies which became significant $(0.91 \ [0.83 \text{ to } 0.99], P=0.02)$ without evidence of heterogeneity $(1^2=8\%, P=0.35)$ on removal of one study during sensitivity analyses. **Conclusions:** This analysis failed to confirm an association between dietary ALA intake and prostate cancer risk. Larger and longer observational and interventional studies are needed to define the role of ALA and prostate cancer.

Key Words: Alpha-linolenic acid, prostate cancer, omega-3 fatty acid, meta-analysis

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62 Introduction

Prostate cancer is the second most common cancer in men worldwide¹. Prostate cancer incidence rates vary widely among countries, populations, and races. Incidence rates vary by more than 25-fold worldwide, with the highest rates documented in the developed countries of North America, Europe, and Oceania, which may be due largely to the wide utilization of prostate- specific antigen (PSA) testing that detects clinically important tumors that might otherwise escape diagnosis². In contrast, males of African descent in the Caribbean region have the highest prostate cancer mortality rates in the world², which is thought to reflect partly a difference in genetic susceptibility ³⁴. The large differences in prostate cancer incidence rates have led to many migration and ecologic studies, which have provided strong evidence for the role of environmental factors, such as diet, in the etiology of prostate cancer ⁵⁻¹⁴. In 1975, Armstrong and Doll first hypothesized that there was an association between dietary fat and death from prostate cancer ¹², and many studies have examined this connection ¹⁵⁻¹⁸, but in recent years more attention has been focused on specific fatty acids. Several studies have examined the association between polyunsaturated fatty acids (PUFAs) and risk of prostate cancer ¹⁹⁻²⁵. There has been particular interest in alpha-linolenic acid (ALA), the parent fatty acid for the ω -3 PUFAs, since increased consumption of ω -3 fatty acids is advised for cardiovascular disease risk reduction $^{26-29}$ despite a possible association with prostate cancer 30 . Dietary ALA occurs mainly in plants and vegetable oils with certain seed oils (flaxseed, perilla, chia seed, and canola), beans (soybeans, navy beans), and nuts (walnuts) singled out as examples of healthy foods due to their high ALA content³¹. However, in the United States, the important sources of ALA are animal-based foods high in saturated fats, such as red meats, beef, pork, and lamb, rather than ALA-rich vegetable sources, such as walnuts.²⁵. The largest proportion of ALA (53.8%) comes from red meat in Uruguay³², but comes from margarine (25%) in the Netherlands ³³. Furthermore, foods such as bread, eggs, and margarine are now

being enriched with ALA to increase their healthfulness. Therefore, it appears timely to

determine whether there are associations between ω -3 fatty acid-rich foods, generally believed to be healthy, and prostate cancer risk.

Methods

 We followed the Cochrane handbook for systematic reviews of interventions version 5.1.0 updated March 2011 for the planning and conduct of this meta-analysis ³⁴. The reporting followed the QUOROM (Quality of Reporting of Meta-analyses) guidelines ³⁵.

Study Selection

We conducted a search of MEDLINE (1948-April 17, 2009) and EMBASE (1974-April 17, 2009) using the following search terms and Boolean operators: prostate AND (cancer OR adenoma OR adenocarcinoma OR neoplasia OR gleason score) AND (alpha-linolenic acid OR *n-3 fatty acids OR omega-3 fatty acids*). The search was restricted to human research studies. No limit was placed on language. Manual searches of references cited by the published original studies and review articles supplemented the database search strategy. This search strategy was last updated on August 28, 2012. We included all prospective cohort, case-control, nested case-cohort, and nested case-control studies that investigated the effect of dietary ALA intake on the incidence (or diagnosis) of prostate cancer and provided relative risk (RR), hazard ratios (HR), or odds ratios (OR) estimates. No randomized controlled trials were identified. No lone abstracts or unpublished studies were identified. In cases where multiple publications existed for the same study, the article with the most recent information was included.

Data Extraction

Two investigators (AJC, JLS) independently extracted relevant data on study characteristics and outcomes using a standardized proforma. These data included information about study design (prospective cohort, case-control, etc.), sample size and participant characteristics (nationality, race, named cohort, country of residence, gender, age, disease status, preexisting medical conditions), follow-up duration, sources of ALA, method of ALA status assessment, endpoints (incidence of prostate cancer, prostate specific antigen (PSA), Gleason score etc.), endpoint assessment (self-reporting, medical records, biopsy, etc.), and number of new incident cases. Bounds of intake categories, quartiles or quintiles, were also recorded. RR, HR, or OR with the greatest degree of control for other environmental and dietary risk factors, and their corresponding 95% CIs for incident prostate cancer risk were extracted as the main endpoint. Disagreements were reconciled by consensus and where necessary by discussion with

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another investigator (DJAJ). Authors were not contacted to request any additional information ortranslation.

121 Statistical Analysis

Data were analyzed using Review Manager (RevMan) 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). We used the reported RR or OR of the highest versus lowest intake category, as the measure of the relation between ALA intake and prostate cancer risk. A pooled analysis of all reports was conducted using the Generic Inverse Variance method using random effects models ³⁶ where the log RRs for cohort studies or log ORs for case-control studies were weighted by the inverse of the variance to obtain a pooled RR estimate. Since nested case-cohort and nested case-control studies are temporally prospective, we analyzed data from these studies with the prospective studies. As in other meta-analyses that have examined prostate cancer ^{30 37 38}, ORs were considered as approximations of RRs. Inter-study heterogeneity was assessed by Cochrane's Q (Chi² P<0.10) and quantified by I². An I² \geq 50% indicated "substantial" heterogeneity and \geq 75% indicated "considerable" heterogeneity. ³⁹. The influence of individual studies was investigated by systematically removing each study and recalculating the pooled effect. An *a priori* subgroup analysis by study design, (prospective versus case-control), was also undertaken to investigate heterogeneity. Meta-regressions were performed to assess the significance of study design on effect modification (STATA 11.2., College Station, USA). Publication bias was investigated by visual inspection of funnel plots, and formally tested using Begg's and Egger's tests.

139 Results

140 Search Results

Figure 1 shows the flow of the literature selection applying the systematic search and selection strategies to identify eligible reports. Two hundred and forty three reports were identified by the search and two reports were manually included after a database search. Of these, 233 were determined to be irrelevant on review of the titles and abstracts. Four additional reports were then manually included. The remaining 16 reports were retrieved and reviewed in full, of which 4 were excluded. Results for The Health Professionals' Follow-up Study were published in three separate publications at different times of follow-up ^{21 23 25}. Only the most

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recent publication of the results, by Giovannucci et al. in 2007, was included in the analyses as representing the cumulative experience of the earlier assessments of this cohort ²¹. A total of 12 reports, 5 prospective and 7 case-control studies, were included in the pooled analyses.

151 Study Characteristics

Table 1 shows the characteristics of the 12 included studies, which were composed of 7 case-control studies ^{32 40-45} and 5 prospective studies ^{19-22 24} that used 3 designs: cohort, nested case-cohort, and nested case-control. Five studies were conducted in North America, 1 in South America, and 6 in Europe. The 12 included studies contained a total of 14,795 cases of prostate cancer and 231,143 controls. All studies obtained dietary data using food frequency questionnaires (FFQ). Individual and average dietary ALA intake in these studies ranged from ≈ 0.05 to 4.16 g/d) and the reported relative risk or odds ratio of the highest versus the lowest intake category ranged from 0.7 to 3.91.

Primary Analysis

The overall analysis of the 12 studies examined prostate cancer, comparing the highest with the lowest ALA intake category. Seven studies reported a protective effect of ALA intake on prostate cancer, 2 of which were significant, and the remaining five studies reported a positive association, of which 3 were significant. Overall, although the relative risk was increased numerically by 8%, this increase in prostate cancer risk was not significant (RR: 1.08; 95%CI: 0.90, 1.29, P=0.40) (Figure 2). However, there was evidence of considerable inter-study heterogeneity ($I^2=85\%$, P<0.00001). Systematic removal of each study during sensitivity analyses did not suggest any single study was an influential outlier.

169 Subgroup Analyses

In an *a priori* subgroup analysis, we found no evidence of effect measure modification according to study design (P for heterogeneity= 0.331). There remained significant unexplained heterogeneity within each type of study design. In case-control studies (n=7), the summary RR was 1.30 (95%CI: 0.81, 2.07, P=0.27), with substantial inter-study heterogeneity (I^2 =90%, P<0.00001) (**Figure 3**). Removal of no single study during sensitivity analyses explained the heterogeneity. In prospective studies alone (n=5), no association between ALA intake and

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176prostate cancer risk was revealed (RR: 0.95; 95%CI: 0.84, 1.09, P=0.48) (Figure 5) but there177existed considerable inter-study heterogeneity ($I^2=69\%$, P=0.01) Sensitivity analyses showed178that removal of the study by Giovannucci et al. ²¹ eliminated heterogeneity with prospective179studies ($I^2=8\%$, P=0.35 and made the protective effect significant (RR=0.91; 95%CI: 0.83,0.99,180P=0.02) (Figure 6). Neither Begg's (P>0.165) nor Egger's (P>0.527) tests revealed evidence of181publication bias, however, one study by Ramon et al. ⁴² had an unusually large effect with a182small standard error.

183 Discussion

184 Summary of Results

The present meta-analysis of 12 observational studies (7 case-control and 5 prospective) comparing the highest with the lowest categories of dietary ALA intake demonstrated heterogeneous effects of ALA on prostate cancer risk. Overall, there was no significant association between ALA intake and risk of prostate cancer. The subgroup analysis of case control studies alone showed a positive non-significant association, but with substantial heterogeneity. However, upon removal of the studies by De Stefani et al.³² and Ramon et al.⁴², which reported large odds ratios greater than 3 but were still within 2 standard deviations of the mean effect, the association became weakly protective with decreased heterogeneity. When examining the prospective studies alone, the association between ALA intake and prostate cancer risk was weakly protective and after removal of the study by Giovannucci et al.²¹ became significantly protective with no heterogeneity.

The results from the prospective studies are similar to those of previously published findings that examined only prospective studies ⁴⁶. Our study additionally investigated the association between dietary ALA intake and prostate cancer risk among case-control studies and reached a similar conclusion although the case control studies suggested an element of increased risk, which was dependent on the inclusion of two studies with very high odds ratios, the reasons for which are difficult to explain.

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203 Variation in the Effect of ALA between Studies

In our study, different findings in the individual studies reviewed may be explained by a number of factors: variation in ALA consumption as a result of the population's dietary patterns,

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206 differing sources of ALA, variation in ALA exposure levels, or use of different FFQs and food207 databases.

In the Netherlands, the chief sources of ALA include margarine (25% of daily intake), meat (11%), bread (10%), and vegetables $(8\%)^{33}$, whereas in the United States, major sources of ALA come from mayonnaise, creamy salad dressings, margarine, butter, beef, pork, lamb, and oil and vinegar-based dressings²⁵. Interestingly, the prospective study from the Netherlands reported a weak protective effect of ALA intake on prostate cancer risk²⁰, but the most recent study from the United States reported a 25% increase in risk²¹. This difference may be due to the nature of the foods that contain ALA since in the United States, the sources of ALA are not the "healthy" sources where ALA is naturally found (e.g. flaxseed, walnuts, and canola oil), but rather profiled an unhealthy diet (e.g. canola oil in the form of mayonnaise and creamy salad dressings), which may be indicative of a less healthy lifestyle and this in itself may contribute to an increased risk of prostate cancer independent of ALA intake levels.

In addition, in the case-control studies from Uruguay ³² and Spain ⁴² that showed the largest increases in prostate cancer risk demonstrated that meat, and not vegetable, was the major source of ALA. When these two studies were removed from the analysis of the case-control studies, the effect of ALA intake on prostate cancer changed from a weakly positive to a weakly protective effect. Compared with the other studies from Europe and the United States, there is a much higher consumption of meat in Spain⁴⁷ and Uruguay, with Uruguay having the highest meat consumption per capita in the world ⁴⁸. An earlier analysis of the Health Professionals Follow-up Study cohort ²⁵ supports this positive association between red meat consumption and prostate cancer risk. Further, the two studies from Spanish-speaking countries also investigated the effect of animal fat on prostate cancer and both found significant positive associations. The Uruguayan study ³² observed an almost 3 times increased risk of prostate cancer at the highest level of ALA derived from animal sources and the Spanish study ⁴² revealed that the highest level of animal fat intake was associated with 2 times the risk of developing prostate cancer. These findings indicate that high meat intake rather than high ALA could explain ALA's apparent adverse effect on prostate cancer. A further explanation for the apparent association of prostate cancer incidence with vegetable sources of ALA may be that in addition those who follow healthy lifestyles with increased plant ALA sources may undergo more frequent prostate specific antigen (PSA) testing and therefore have early prostate cancer detection. In this respect

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it has been found that higher whole grain intake was also associated with increased prostate
cancer risk. However, when frequency of PSA screening was accounted for, the association of
whole grains with prostate cancer incidence disappeared ⁴⁹. These studies indicate the
importance of not only identifying the dietary sources of ALA, but taking into account what the
nature of the foods may indicate in terms of diet and lifestyle since these also may affect prostate
cancer risk.

Another important aspect to consider is the differing exposure levels between the studies. Each study had different cut-offs for each quantile, which makes a true comparison of ALA intake exposure difficult since some studies had higher levels of ALA in their highest intake quantile than others. Further, some studies did not adequately define the absolute upper and/or lower limits of ALA intake ^{21 32 43} and one study did not report numerical exposure levels ⁴¹. Two studies, one from Spain ⁴² and one from the Netherlands ²⁰, with the largest adequately defined upper and lower limits of ALA exposure ranges, paradoxically reported the second highest and the second lowest risk of developing prostate cancer, respectively. Since the studies with the greatest range of exposure do not necessarily show the greatest effects, dietary variation in the levels of exposure does not appear to explain differences among the studies, thereby making differences in dietary sources of ALA of more importance especially in relation to meat consumption in Western countries.

Lastly, in terms of utilizing different FFQs and food databases, each study used a different dietary FFQ. ALA content of processed food can vary, which can be of concern when using food databases to translate food intake into fatty acid intake. For example, the ALA content of 12 margarines available in Australia range from 0.2% to 5.9% ⁵⁰.

260 Overall Non-significant Effect of ALA

The overall effect of ALA on prostate cancer was found to be non-significant and may be attributed to a number of factors including ALA exposure levels that are within health guidelines, confounding from other polyunsaturated fatty acids, and the difference in effect of ALA on mortality versus incidence.

The mean dietary ALA intake levels observed in these studies were all within the dietary reference intake (DRI) range of 1.1 to 1.6 g/d ⁵¹, suggesting that ALA may not increase the risk of cancer more than any other nutrient which provides a stimulus to cell growth and since ALA

is a nutrient in which the Western diet is deficient ⁵², it may be that a deficiency prevents the growth of cancer rather than an excess causing prostate cancer growth.

Another issue to consider is confounding from other polyunsaturated fatty acids such as omega-6 or other omega-3 fatty acids (eicosapentaenoic and docosahexaenoic fatty acids) that might affect ALA metabolism ⁵³ and consequently may introduce bias. The case-control study from the United States ⁴⁵ demonstrated this as there was no significant association between ALA, omega-3, or omega-6 fatty acids and prostate cancer risk individually, but the highest dietary ratio of omega-6/omega-3 fatty acids was significantly associated with increased risk of high grade prostate cancer.

Finally, our analysis involved cancer incidence not mortality and ALA, and most other factors including energy intake, height, body mass index, calcium, and smoking are associated with cancer mortality ²¹. The study by De Stefani et al. ³², which was the only study that defined cases solely as advanced prostate cancer, had the highest risk estimate of prostate cancer, indicating that ALA may be strongly associated with disease severity rather than incidence. In support of this point, the prospective study by Giovannucci et al.²¹ found that higher ALA intake was more strongly associated with increased risk of fatal prostate cancer than with incident. However, three other prospective studies did not find any difference between the effects of ALA on incident or advanced prostate cancer cases ^{19 20 22}. From these mixed findings, it is unclear whether ALA is associated with severity of prostate cancer, but determining whether ALA impacts prostate cancer incidence or progression is an important distinction that should be investigated in the future. Furthermore, the picture of ALA's effect on prostate cancer is complicated by the positive association of incident prostate cancer with either serum or adipose tissue ALA levels ^{24 54-58} despite the in vitro evidence which suggests that ALA may suppress prostate cancer cell growth ^{59 60}. However, there appears to be some correlation between ALA intake and serum ALA levels. In terms of intake, Gann et al. ⁵⁴ found that plasma ALA levels were significantly positively correlated with meat and dairy product intake, and similar to the prospective analysis from the Health Professionals Follow-Up Study ²⁵, they found that red meat was positively associated with advanced prostate cancer, whereas diary foods were not. This corroboration not only suggests a correlation between ALA intake and serum ALA levels, but enforces the positive association between ALA from red meat and prostate cancer as seen in the studies from Uruguay ³² and Spain ⁴², rather than from plant foods.

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300 Limitations and Possible Sources of Heterogeneity

In considering the limitations of the meta-analysis, it should be noted currently available for inclusion come from epidemiological studies since the randomized controlled trials due to ethical concerns. Interpretation of the ana by the evidence of considerable heterogeneity among the studies, therefore a contributing factors should be considered. First, study design should be taken association between ALA intake and prostate cancer risk was stronger overal studies than in the prospective. However, since case-control studies collect di information after disease development there is the possibility of recall bias, w studies collect intake information before disease diagnosis. Secondly, follow-have an effect on heterogeneity, especially since the study by Giovannucci et longest follow-up duration (16 years). Comparing previous prospective studie same cohort ^{23 25} with this most recent study ²¹, demonstrates a shift over time from a non-significant to a significant positive association between ALA inta cancer. So, the heterogeneity induced by this study may indicate that follow-positively related to the strength of the association between ALA and prostate investigating this suggestion, the effect of follow-up duration on relative risk prospective studies was found to be positively, but not significantly correlate

318 Conclusion

In conclusion, these findings provide no clear evidence of an associati ALA intake and prostate cancer risk since studies that show an association be and prostate cancer are observational and causation is difficult to establish. T research from epidemiological, clinical, and in vitro studies are required to el ALA has a promotional or inhibitory effect on prostate cancer risk and development present, no significant association has been found and where any support of a seen, red meat sources have been strongly implicated. The source of ALA ap importance, particularly identifying whether it is from animal or vegetable so be a marker for higher meat and fat intake in some countries both of which ha with increased prostate cancer risk. Attention should also be paid to the effect of ALA on

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3 4	329	prostate cancer progression to address the issues of specific vulnerability identified in the studies
5 6	330	of ^{21 32} . However, the relation of dietary intake of ALA to prostate cancer risk is likely to
7	331	continue to be difficult to resolve through randomized controlled trials due to the significant
8 9	332	public health implications of reducing/eliminating a dietary fatty acid which is essential and has
10 11	333	suggested heart health benefits. Of probably greater importance is determination of the sources
12 13	334	of the fatty acid since ALA is associated in the North American diet with meat membranes and
14	335	creamy salad dressings, which themselves may be markers of a suboptimal dietary pattern and
15 16	336	lifestyle
17 18	337	
19 20	338	Article Summary
21 22	339	Article Focus
23 24	340	• ALA is considered a cardioprotective nutrient, however some epidemiological studies
25 26	341	have suggested that dietary ALA intake increases the risk of prostate cancer
27	342	• A systematic review and meta-analysis of case-control and prospective studies was
28 29	343	conducted to investigate the association between dietary ALA intake and prostate cancer
30 31	344	risk
32 33	345	Key messages
34 35	346	• The present meta-analysis of 12 observational studies (7 case-control and 5 prospective)
36	347	comparing the highest with the lowest categories of dietary ALA intake demonstrated
37 38	348	overall no significant association between ALA intake and risk of prostate cancer
39 40	349	• The subgroup analysis of case control studies alone showed a positive non-significant
41 42	350	association, but with substantial heterogeneity. However, upon removal of the studies,
43 44	351	which reported large odds ratios, the association became weakly protective with
45	352	decreased heterogeneity
46 47	353	• The subgroup analysis of case control studies alone showed a positive non-significant
48 49	354	association, but with substantial heterogeneity, which suggests an element of increased
50 51	355	risk dependent on the inclusion of two studies with very high odds ratios, the reasons for
52 53	356	which are difficult to explain
54	357	Strengths and Limitations:
55 56	358	• This meta-analysis includes both prospective and case control studies to determine the
57 58 59 60	359	effect of ALA on prostate cancer

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Possible confounders and sources of heterogeneity were discussed and explored in relation to the results

Interpretation of analyses was complicated by considerable heterogeneity among the studies, which may be due to lack of randomized controlled trials, study design, and follow-up duration

"What this Paper Adds"

Protected by copyright, including for uses related ALA is considered a cardioprotective nutrient, however some epidemiological studies have suggested that dietary ALA intake increases the risk of prostate cancer. Although Caravol et al. conducted a meta-analysis on the effect of dietary ALA on prostate cancer in 2010, only prospective studies were analyzed and case-control studies were not included. Overall, we found no significant association between ALA intake and risk of prostate cancer. The results from the prospective studies were similar to those of previously published findings. However, the subgroup analysis of case control studies alone showed a positive non-significant association, but with substantial heterogeneity. The case control studies suggested an element of increased risk, which was dependent on the inclusion of two data mining, Al studies with very high odds ratios, the reasons for which are difficult to explain. Additional research from epidemiological, clinical, and in vitro studies are required to elucidate whether ALA has a promotional or inhibitory effect on prostate cancer risk and development.

Authorship

All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Details of Contributors: AJC was involved in the conception and design, analysis and

interpretation of data, drafting the article and revising it critically for important intellectual

content, and final approval of the version to be published. JLS was involved in the conception

and design, some analysis, and revising the article critically for important intellectual content. RS

was involved in revising the article critically for important intellectual content. GE was involved

in the conception and design and in revising the article critically for important intellectual

377 content. DJAJ was in the conception and design, revising the article critically for important

intellectual content, and final approval of the version to be published.

There is no additional data available.

Data Sharing

Competing Interest Declaration

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) AJC, JLS, RS, GE, and DJAJ have not had financial support from any company for the submitted work; (2) AJC, JLS, RS, GE, and DJAJ have no relationships with any companies that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) AJC, JLS, RS, GE, and DJAJ have no non-financial interests that may be relevant to the submitted work."

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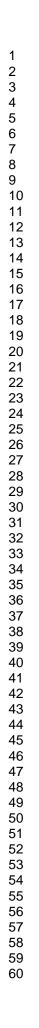
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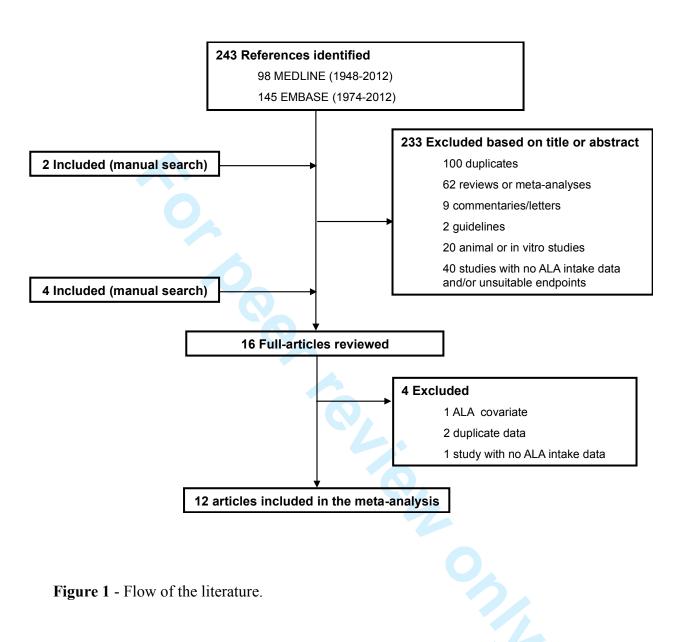
Study	Country of Origin	Study Design	Sample size	Age (years)	Incident Cases	Follow-up (years)	Exposure level (g/d)	Relative Risk or Odds Ratio	95%CI
Andersson et al. 1996 [38]	Sweden	Case-control	526 cases/536 controls	<80	-	-	0.817 - 1.352	0.93	0.65-1.32
Vleyer et al. 1997 [39]	Canada	Case-control	215 cases/593 controls	<u>∠</u> 45	-	-	-	0.98	0.54-1.78
Schuurman et al. 1999 [18]*	Netherlands	Nested case-cohort	58279 (1525 subcohort)	55-69	642	6.3	0.7 - 2.1	0.76	0.66-1.04
De Stefani et al. 2000 [29]	Uruguay	Case-control	217 cases/431 controls	40-89	-	-	⊴0.8 - ≥1.5	3.91	1.50-10.1
Ramon et al. 2000 [40]	Spain	Case-control	217 cases/434 controls	<60-80	-	-	0.72 - 2.1	3.1	2.2-4.7
Vannisto et al. 2003 [22]*	Finland	Nested case-control	198 cases/198 controls	50-69	246	5-8	1.0 - 2.3	1.16	0.64-2.13
Bidoli et al. 2005 [41]	Italy	Case-control	1294 cases/1451 controls	45-74	-	-	mean 1.6	0.7	0.6-0.9
Koralek et al. 2006 [20]*	United States	Prospective cohort	29,592	55-74	1898	5.1	1.09 - 1.75	0.94	0.81-1.09
Hedelin et al. 2007 [42]	Sweden	Case-control	1499 cases/1130 controls	mean 67.3	-	-	0.05 - 0.60	1.35	0.99-1.84
Giovannucci et al. 2007 [19]*	United States	Prospective cohort	47,750	40-75	3544	16	<0.79 - ≥1.32	1.12	1.01-1.2
Park et al. 2007 [17]*	United States	Prospective cohort	82,483	≥ 45	4404	8	1.1 - 2.14†	0.92	0.84-1.02
Williams et al. 2011 [43]	United States	Case-control	79 cases/187 controls	≥18	-	-	<u>≤</u> 1.0 - 4.156†	0.82	0.41-1.6
* Prospective studies.									
† Based on a 2000 kcal diet.									

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		Risk Ratio	Risk Ratio
Study or Subgroup	Weight	IV, Random, 95% CI Year	IV, Random, 95% CI
Andersson 1996 [38]	8.4%	0.93 [0.65, 1.33] 1996	
Meyer 1997 [39]	5.2%	0.98 [0.54, 1.78] 1997	
Schuurman 1999 [18]	10.5%	0.76 [0.61, 0.95] 1999	
De Stefani 2000 [29]	2.7%	3.91 [1.51, 10.15] 2000	
Ramon 2000 [40]	8.0%	3.10 [2.12, 4.53] 2000	
Mannisto 2003 [22]	5.1%	1.16 [0.64, 2.12] 2003	
Bidoli 2005 [41]	10.9%	0.70 [0.57, 0.86] 2005	
Koralek 2006 [20]	11.6%	0.94 [0.81, 1.09] 2006	-
Giovannucci 2007 [19]	12.1%	1.12 [1.01, 1.25] 2007	-
Hedelin 2007 [42]	9.1%	1.35 [0.99, 1.84] 2007	
Park 2007 [17]	12.2%	0.92 [0.83, 1.01] 2007	-
Williams 2011 [43]	4.3%	0.82 [0.41, 1.64] 2011	
Total (95% CI)	100.0%	1.08 [0.90, 1.29]	•
Heterogeneity: Tau ² = 0.	06; Chi² =		
Test for overall effect: Z	= 0.84 (P =	= 0.40)	0.1 0.2 0.5 1 2 5 10 Favours ALA Favours Control

Figure 2 – Pooled effect of dietary ALA intake on prostate cancer risk in case-control, nested case-cohort, and cohort studies. Relative Risk (RR) with 95% CI, study weights, and pooled effect estimates were generated using the general inverse variance method with random effects models (RevMan 5.1, Cochrane Library software, Oxford, UK). Inter-study heterogeneity was tested by Cochrane's Q (Chi²) at a significance level of P<0.10 and quantified by I², where I² \geq 50 % is considered to be evidence of substantial heterogeneity and \geq 75%, considerable heterogeneity ³⁴.

	Risk Ratio	Risk Ratio
Weight	IV, Random, 95% CI Year	IV, Random, 95% CI
15.7%	0.93 [0.65, 1.33] 1996	
13.5%	0.98 [0.54, 1.78] 1997	
15.5%	3.10 [2.12, 4.53] 2000	_ _
10.0%	3.91 [1.51, 10.15] 2000	
16.7%	0.70 [0.57, 0.86] 2005	
16.1%	1.35 [0.99, 1.84] 2007	
12.5%	0.82 [0.41, 1.64] 2011	
100.0%	1.30 [0.81, 2.07]	
).33; Chi² =	+ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$	
z = 1.10 (P	Favours ALA Favours Control	
	15.7% 13.5% 15.5% 10.0% 16.7% 16.1% 12.5% 100.0% 0.33; Chi ² =	WeightIV, Random, 95% Cl Year15.7%0.93 [0.65, 1.33]199613.5%0.98 [0.54, 1.78]199715.5%3.10 [2.12, 4.53]200010.0%3.91 [1.51, 10.15]200016.7%0.70 [0.57, 0.86]200516.1%1.35 [0.99, 1.84]200712.5%0.82 [0.41, 1.64]2011

Figure 3 – Pooled effect of dietary ALA intake on prostate cancer risk in case-control studies. Relative Risk (RR) with 95% CI, study weights, and pooled effect estimates were generated

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using the general inverse variance method with random effects models (RevMan 5.1, Cochrane Library software, Oxford, UK). Inter-study heterogeneity was tested by Cochrane's Q (Chi²) at a significance level of P<0.10 and quantified by I^2 , where $I^2 \ge 50$ % is considered to be evidence of substantial heterogeneity and \geq 75%, considerable heterogeneity³⁴. **Risk Ratio Risk Ratio** Weight IV, Random, 95% CI Year IV, Random, 95% CI 22.2% 0.93 [0.65, 1.33] 1996 14.0% 0.98 [0.54, 1.78] 1997 0.0% 3.10 [2.12, 4.53] 2000 0.0% 3.91 [1.51, 10.15] 2000 28.2% 2005 0.70 [0.57, 0.86] 24.0% 1.35 [0.99, 1.84] 2007 11.6% 0.82 [0.41, 1.64] 2011 100.0% 0.93 [0.69, 1.25] Heterogeneity: Tau² = 0.07; Chi² = 12.46, df = 4 (P = 0.01); l² = 68% 0.1 0.2 0.5 5 10 2 Test for overall effect: Z = 0.47 (P = 0.64) Favours ALA Favours Control Figure 4 – Pooled effect of dietary ALA intake on prostate cancer risk in case-control studies after the removal of the studies by Ramon et al.⁴² and De Stefani et al.³² following a sensitivity analysis. Relative Risk (RR) with 95% CI, study weights, and pooled effect estimates were

generated using the general inverse variance method with random effects models (RevMan 5.1, Cochrane Library software, Oxford, UK). Inter-study heterogeneity was tested by Cochrane's Q (Chi²) at a significance level of P<0.10 and quantified by I², where I² \ge 50 % is considered to be evidence of substantial heterogeneity and \geq 75%, considerable heterogeneity ³⁴.

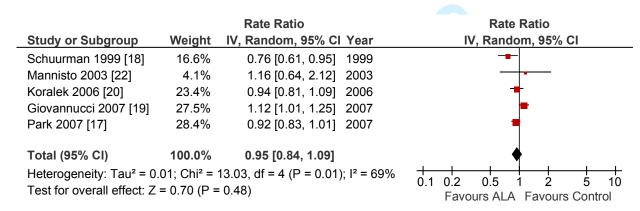


Figure 5 – Pooled effect of dietary ALA intake on prostate cancer risk in prospective studies. Relative Risk (RR) with 95% CI, study weights, and pooled effect estimates were generated using the general inverse variance method with random effects models (RevMan 5.1, Cochrane

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Study or Subgroup

Andersson 1996 [38]

De Stefani 2000 [29]

Meyer 1997 [39]

Ramon 2000 [40]

Bidoli 2005 [41]

Total (95% CI)

Hedelin 2007 [42]

Williams 2011 [43]

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Library software, Oxford, UK). Inter-study heterogeneity was tested by Cochrane's Q (Chi²) at a significance level of P<0.10 and quantified by I², where I² \geq 50 % is considered to be evidence of substantial heterogeneity and \geq 75%, considerable heterogeneity ³⁴.

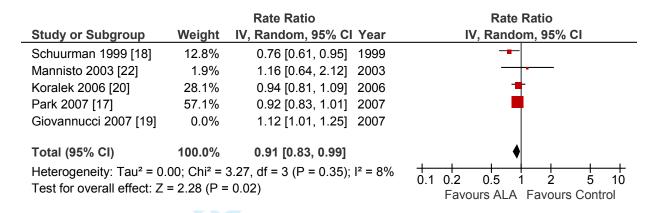


Figure 6 – Pooled effect of dietary ALA intake on prostate cancer risk in prospective studies after the systematic removal of the study by Giovannucci et al. ²¹ following a sensitivity analysis. Relative Risk (RR) with 95% CI, study weights, and pooled effect estimates were generated using the general inverse variance method with random effects models (RevMan 5.1, Cochrane Library software, Oxford, UK). Inter-study heterogeneity was tested by Cochrane's Q (Chi²) at a significance level of P<0.10 and quantified by I², where I² \geq 50 % is considered to be evidence of substantial heterogeneity and \geq 75%, considerable heterogeneity ³⁴.

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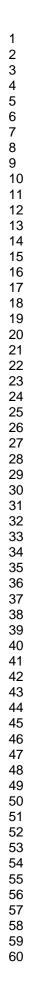
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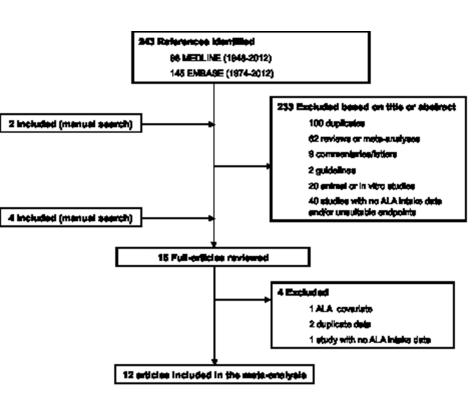
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Study	Country of Origin	Study Design	Bampio alco	Age (pears)	Cames	Pallan-ap (pears)	Expense level (g/d)	Relative Netcor Odde Raillo	MTK CI
Andersson al al. 1998 (25)	Svedan	Case-control	528 cases/638 carbola	<\$0		•	0.617 - 1.552	0.98	0.65-1.32
Mayer at al. 1997 [39]	Canada	Case-control	215 ceses/893 controls	346	•	•		0.98	0.84-1.76
Schuumen at al. 1999 [18]*	Natharkanda	Nasted case cohort	58278 (1525 missolant)	55-64	642	8.3	67-21	0.76	0.00-1.04
De Stelani et al. 2000 [29]	Unguay	Case-control	217 cases/431 cantrols	40-38	-	-	sti.8 - 21.5	2.91	1.60-10.1
Remon et el. 2000 (40)	Spein	Case-control	217 ceses/434 controls	<80-80		•	0.72-2.1	3.1	2.24.7
Marmisto at al. 2006 [22]*	Finland	Neutral case-control	190 cases/198 cantrols	50-68	248	5-8	1.0 - 2.5	1.18	0.64-2.15
Bidol at al. 2005 [41]	liniy	Case-control	1284 pases/1451 particle	45-74	-	-	maan 1.6	0.7	0.60.8
Koralek el al. 2008 [20]*	United States	Prospective exhert	29,692	65-74	1598	L1	1.09 - 1.70	0.94	0.81-1.09
Heddelin at al. 2007 (42)	Sweden	Case-control	1489 comm/1130 controls	mean 67.2	-	-	0.05 - 0.60	1.35	0.80-1.84
Observanced of al. 2007 [19]*	Unlind States	Prospective other:	47,750	40-75	3544	18	<0.79-21.52	1.12	1.01-1.25
Perk et el. 2007 [17]*	United States	Prospective echort	62,483	346	4404	8	1.1 - 2.14	0.92	0.54-1.02
Williams at al. 2011 [45]	Unlied States	Case-control	79 cases/187 cardrain	218	-	-	£1.0 - 4.168†	0.82	0.41-1.65
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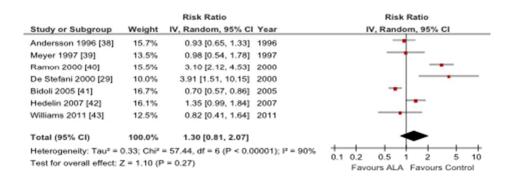
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Andersson 1996 [38] 8.4% 0.93 [Meyer 1997 [39] 5.2% 0.98 [Schuurman 1999 [18] 10.5% 0.76 [De Stefani 2000 [29] 2.7% 3.91 [1 Ramon 2000 [40] 8.0% 3.10 [om, 95% CI Year IV, Random, 95% CI
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Meyer 1997 [39] 5.2% 0.98 [Schuurman 1999 [18] 10.5% 0.76 [De Stefani 2000 [29] 2.7% 3.91 [1 Ramon 2000 [40] 8.0% 3.10 [
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De Stefani 2000 [29] 2.7% 3.91 [1 Ramon 2000 [40] 8.0% 3.10 [0.54, 1.78] 1997
Ramon 2000 [40] 8.0% 3.10 [0.61, 0.95] 1999
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Mannisto 2003 [22] 5.1% 1.16 [0.64, 2.12] 2003
	0.57, 0.86] 2005
	0.81, 1.09] 2006
	1.01, 1.25] 2007
	0.99, 1.84] 2007
	0.83, 1.01] 2007
Williams 2011 [43] 4.3% 0.82 [0.41, 1.64] 2011
Fotal (95% CI) 100.0% 1.08 [0.90, 1.29]
Heterogeneity: Tau ² = 0.06; Chi ² = 71.45, df =	
Test for overall effect: Z = 0.84 (P = 0.40)	0.1 0.2 0.5 1 2 5 10
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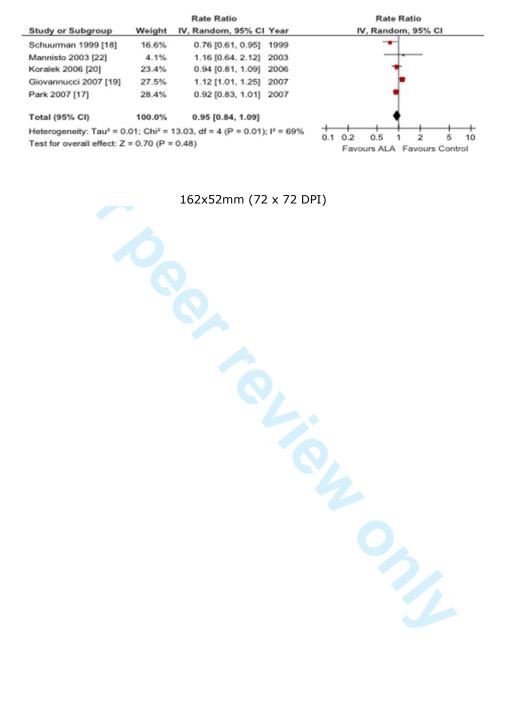
		Risk Ratio	Risk Ratio
Study or Subgroup	Weight	IV, Random, 95% CI Year	IV, Random, 95% CI
Andersson 1996 [38]	22.2%	0.93 [0.65, 1.33] 1996	-
Meyer 1997 [39]	14.0%	0.98 [0.54, 1.78] 1997	
Ramon 2000 [40]	0.0%	3.10 [2.12, 4.53] 2000	
De Stefani 2000 [29]	0.0%	3.91 [1.51, 10.15] 2000	1.1
Bidoli 2005 [41]	28.2%	0.70 [0.57, 0.86] 2005	
Hedelin 2007 [42]	24.0%	1.35 [0.99, 1.84] 2007	
Williams 2011 [43]	11.6%	0.82 [0.41, 1.64] 2011	
Total (95% CI)	100.0%	0.93 [0.69, 1.25]	+
Heterogeneity: Tau ² =	0.07; Chi ² :	= 12.46, df = 4 (P = 0.01); I ² = 68%	
Test for overall effect:	Z = 0.47 (P	= 0.64)	0.1 0.2 0.5 1 2 5 10 Favours ALA Favours Control

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		Rate Ratio	Rate Ratio
Study or Subgroup	Weight	IV, Random, 95% CI Year	IV, Random, 95% CI
Schuurman 1999 [18]	12.8%	0.76 [0.61, 0.95] 1999	
Mannisto 2003 [22]	1.9%	1.16 [0.64, 2.12] 2003	
Koralek 2006 [20]	28.1%	0.94 [0.81, 1.09] 2006	+
Park 2007 [17]	57.1%	0.92 [0.83, 1.01] 2007	-
Giovannucci 2007 [19]	0.0%	1.12 [1.01, 1.25] 2007	
Total (95% CI)	100.0%	0.91 [0.83, 0.99]	•
Heterogeneity: Tau ² = 0.	00; Chi ² = 3	3.27, df = 3 (P = 0.35); I ^z = 8%	
Test for overall effect: Z	= 2.28 (P =	0.02)	0.1 0.2 0.5 1 2 5 10 Favours ALA Favours Control

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Case-Control and Prospective Studies of Dietary Alpha-Linolenic Acid Intake and Prostate Cancer Risk: a Meta-Analysis

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Primary Subject Heading :	Nutrition and metabolism	
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Keywords:	NUTRITION & DIETETICS, Prostate disease < UROLOGY, PREVENTIVE MEDICINE	
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2 3	1	Case-Control and Prospective Studies of Dietary Alpha-Linolenic Acid Intake
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6 7	2	and Prostate Cancer Risk: a Meta-Analysis
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10	4	Amanda J Carleton, MSc ^{1,2,3} ; John L Sievenpiper ^{1,2,4} , MD, PhD; Russell de Souza, ScD ^{1,2,5} ;
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45 46	24	Tel: 416-867-7475, Fax: 416-978-5310, E-mail: <u>amanda.carleton@utoronto.ca</u>
47	25	
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50 51	27	Text word count: 5184;
52 53	28	Abstract word count: 274;
54	29	Tables: 1; Figures: 7;
55 56	30	References: 74
57 58		
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2 3 4	31	ABSTRACT
$\begin{array}{c} 5 \\ 6 \\ 7 \\ 8 \\ 9 \\ 10 \\ 11 \\ 12 \\ 13 \\ 14 \\ 15 \\ 16 \\ 17 \\ 18 \\ 19 \\ 20 \\ 21 \\ 22 \\ 23 \\ 24 \\ 25 \\ 26 \\ 27 \\ 28 \\ 29 \\ 30 \\ 1 \\ 32 \\ 34 \\ 35 \end{array}$	32	Background: ALA is considered a cardioprotective nutrient, however some epidemiological
	33	studies have suggested that dietary ALA intake increases the risk of prostate cancer.
	34	Objective: To conduct a systematic review and meta-analysis of case-control and prospective
	35	studies investigating the association between dietary ALA intake and prostate cancer risk.
	36	Data Sources: MEDLINE and EMBASE were searched for relevant prospective and case-
	37	control studies.
	38	Eligibility Criteria for Selecting Studies: We included all prospective cohort, case-control,
	39	nested case-cohort, and nested case-control studies that investigated the effect of dietary ALA
	40	intake on the incidence (or diagnosis) of prostate cancer and provided relative risk (RR), hazard
	41	ratios (HR), or odds ratios (OR) estimates.
	42	Design: Data were pooled using the generic inverse variance method with a random-effects
	43	model from studies that compared the highest ALA quantile with the lowest ALA quantile. Risk
	44	estimates were expressed as relative risk (RR) with 95% confidence intervals (CI). Heterogeneity
	45	was assessed by χ^2 and quantified by I ² .
	46	Results: Data from 5 prospective and 7 case-control studies were pooled. The overall RR
	47	estimate showed ALA intake to be positively, but non-significantly associated with prostate
	48	cancer risk (1.08 [0.90 to 1.29], P=0.40, I^2 =85%), but the interpretation was complicated by
36	49	evidence of heterogeneity not explained by study design. A weak non-significant protective
37 38	50	effect of ALA intake on prostate cancer risk in the prospective studies became significant (0.91
39 40	51	[0.83 to 0.99], P=0.02) without evidence of heterogeneity ($I^2=8\%$, P=0.35) on removal of one
41 42	52	study during sensitivity analyses.
43 44	53	Conclusions: This analysis failed to confirm an association between dietary ALA intake and
45	54	prostate cancer risk. Larger and longer observational and interventional studies are needed to
46 47	55	define the role of ALA and prostate cancer.
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	60	Key Words: Alpha-linolenic acid, prostate cancer, omega-3 fatty acid, meta-analysis
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INTRODUCTION

Prostate cancer is the second most common cancer in men worldwide¹. Prostate cancer incidence rates vary widely among countries, populations, and races. Incidence rates vary by more than 25-fold worldwide, with the highest rates documented in the developed countries of North America, Europe, and Oceania, which may be due largely to the wide utilization of prostate- specific antigen (PSA) testing that detects clinically important tumors that might otherwise escape diagnosis². In contrast, males of African descent in the Caribbean region have the highest prostate cancer mortality rates in the world 2 , which is thought to reflect partly a difference in genetic susceptibility ³⁴. The large differences in prostate cancer incidence rates have led to many migration and ecologic studies, which have provided strong evidence for the role of environmental factors, such as diet, in the etiology of prostate cancer ⁵⁻¹⁴. In 1975. Armstrong and Doll first hypothesized that there was an association between dietary fat and death from prostate cancer¹², and many studies have examined this connection¹⁵⁻¹⁸, but in recent years more attention has been focused on specific fatty acids. Several studies have examined the association between polyunsaturated fatty acids (PUFAs) and risk of prostate cancer ¹⁹⁻²⁵. There has been particular interest in alpha-linolenic acid (ALA), the parent fatty acid for the ω -3 PUFAs, since increased consumption of ω -3 fatty acids is advised for cardiovascular disease risk reduction $^{26-29}$ despite a possible association with prostate cancer 30 . Dietary ALA occurs mainly in plants and vegetable oils with certain seed oils (flaxseed, perilla, chia seed, and canola), beans (soybeans, navy beans), and nuts (walnuts) singled out as examples of healthy foods due to their high ALA content³¹. However, in the United States, the important sources of ALA are animal-based foods high in saturated fats, such as red meats, beef, pork, and lamb, rather than ALA-rich vegetable sources, such as walnuts.²⁵. The largest proportion of ALA (53.8%) comes from red meat in Uruguay³², but comes from margarine (25%) in the Netherlands ³³. Furthermore, foods such as bread, eggs, and margarine are now being enriched with ALA to increase their healthfulness.

There are currently divergent health views on ALA. Numerous epidemiological ³⁴⁻³⁹ and clinical studies ⁴⁰⁻⁴² have shown that ALA is associated with a reduction in coronary heart disease (CHD) incidence and heart disease mortality. However, since ALA has also been associated with an increased risk of prostate cancer, ^{25 30 32 43-47} the seriousness of this potential

association requires that any favourable effects of ALA on CHD be weighed against its possible adverse effects on prostate cancer. Numerous prospective cohort ^{19-22 24} and case-control studies ^{32 45 48-52} have investigated the association between ALA and prostate cancer risk. While previous meta-analyses ^{30 53 54} have been conducted to determine whether a relationship exists, there has been no meta-analysis since 2010, examining the specific effect of dietary ALA on prostate cancer risk and none since 2009, that included in both prospective cohort and case-control studies. Therefore, it appears timely to determine whether there are associations between dietary ALA from ω -3 fatty acid-rich foods, generally believed to be healthy, and prostate cancer risk.

100 METHODS

 We followed the Cochrane handbook for systematic reviews of interventions version
 5.1.0 updated March 2011 for the planning and conduct of this meta-analysis ⁵⁵. The reporting
 followed the QUOROM (Quality of Reporting of Meta-analyses) guidelines ⁵⁶.

104 Study Selection

We conducted a search of MEDLINE (1948-April 17, 2009) and EMBASE (1974-April 17, 2009) using the following search terms and Boolean operators: prostate AND (cancer OR adenoma OR adenocarcinoma OR neoplasia OR gleason score) AND (alpha-linolenic acid OR *n-3 fatty acids OR omega-3 fatty acids*). The search was restricted to human research studies. No limit was placed on language. Manual searches of references cited by the published original studies and review articles supplemented the database search strategy. This search strategy was last updated on August 28, 2012. We included all prospective cohort, case-control, nested case-cohort, and nested case-control studies that investigated the effect of dietary ALA intake on the incidence (or diagnosis) of prostate cancer and provided relative risk (RR), hazard ratios (HR), or odds ratios (OR) estimates. No randomized controlled trials were identified. No lone abstracts or unpublished studies were identified. In cases where multiple publications existed for the same study, the article with the most recent information was included.

Data Extraction

Two investigators (AJC, JLS) independently extracted relevant data on study
 characteristics and outcomes using a standardized proforma. These data included information
 about study design (prospective cohort, case-control, etc.), sample size and participant

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characteristics (nationality, race, named cohort, country of residence, gender, age, disease status, preexisting medical conditions), follow-up duration, sources of ALA, method of ALA status assessment, endpoints (incidence of prostate cancer, prostate specific antigen (PSA), Gleason score etc.), endpoint assessment (self-reporting, medical records, biopsy, etc.), and number of new incident cases. Bounds of intake categories, quartiles or quintiles, were also recorded. RR, HR, or OR with the greatest degree of control for other environmental and dietary risk factors, and their corresponding 95% CIs for incident prostate cancer risk were extracted as the main endpoint. Disagreements were reconciled by consensus and where necessary by discussion with another investigator (DJAJ). Authors were not contacted to request any additional information or translation.

Statistical Analysis

Data were analyzed using Review Manager (RevMan) 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). We used the reported RR or OR of the highest versus lowest intake category, as the measure of the relation between ALA intake and prostate cancer risk. A pooled analysis of all reports was conducted using the Generic Inverse Variance method using random effects models ⁵⁷ where the log RRs for cohort studies or log ORs for case-control studies were weighted by the inverse of the variance to obtain a pooled RR estimate. Since nested case-cohort and nested case-control studies are temporally prospective, we analyzed data from these studies with the prospective studies. As in other meta-analyses that have examined prostate cancer ^{30 54 58}, ORs were considered as approximations of RRs. Since the initial risk of prostate cancer is low, it is unlikely that there will be a substantial discrepancy in approximating ORs to RRs. ⁵⁹ Inter-study heterogeneity was assessed by Cochrane's Q (Chi² P < 0.10) and guantified by I². An I² > 50% indicated "substantial" heterogeneity and >75% indicated "considerable" heterogeneity. ⁶⁰ Sources of heterogeneity were explored by sensitivity analyses whereby the influence of individual studies was investigated by systematic removal of each study followed by recalculation of the pooled effect estimate and heterogeneity, as well as removal of outlier studies with risk estimates larger than 2 standard deviations from the mean risk estimate and recalculation of the pooled effect estimate and heterogeneity. We also performed *a priori* subgroup analyses to assess effect modification by study design (prospective versus case-control). Post-hoc analyses included dichotomous subgroup analyses to assess effect

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modification by study design (STATA 11.2., College Station, USA) and continuous analyses to

assess the effect of the duration of follow-up on relative risk among prospective studies.

Publication bias that was formally tested using Begg's and Egger's tests.

RESULTS

Search Results

Figure 1 shows the flow of the literature selection applying the systematic search and selection strategies to identify eligible reports. Two hundred and forty three reports were identified by the search and two reports were manually included after a database search. Of these, 233 were determined to be irrelevant on review of the titles and abstracts. Four additional reports were then manually included. The remaining 16 reports were retrieved and reviewed in full, of which 4 were excluded. Results for The Health Professionals' Follow-up Study were published in three separate publications at different times of follow-up ^{21 23 25}. Only the most recent publication of the results, by Giovannucci et al. in 2007, was included in the analyses as representing the cumulative experience of the earlier assessments of this cohort ²¹. A total of 12 reports, 5 prospective and 7 case-control studies, were included in the pooled analyses.

Study Characteristics

Table 1 shows the characteristics of the 12 included studies, which were composed of 7 case-control studies ^{32 45 48-52} and 5 prospective studies ^{19-22 24} that used 3 designs: cohort, nested case-cohort, and nested case-control. Five studies were conducted in North America, 1 in South America, and 6 in Europe. The 12 included studies contained a total of 14,795 cases of prostate cancer and 231,143 controls. All studies obtained dietary data using food frequency questionnaires (FFQ). Individual and average dietary ALA intake in these studies ranged from ≈ 0.05 to 4.16 g/d) and the reported relative risk or odds ratio of the highest versus the lowest intake category ranged from 0.7 to 3.91.

Primary Analysis

The overall analysis of the 12 studies examined prostate cancer, comparing the highest with the lowest ALA intake category. Seven studies reported a protective effect of ALA intake on prostate cancer, one of which was significant, and the remaining five studies reported a

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positive association, of which 3 were significant. Overall, although the relative risk was
increased numerically by 8%, this increase in prostate cancer risk was not significant (RR: 1.08;
95%CI: 0.90, 1.29, P=0.40) (Figure 2). However, there was evidence of considerable inter-study
heterogeneity (I²=85%, P<0.00001). Systematic removal of each study during sensitivity
analyses did not suggest any single study was an influential outlier.

184 Subgroup Analyses

185 Case-Control Studies

In an *a priori* meta-regression, we found no evidence of effect measure modification according to study design (P for heterogeneity = 0.331). There remained significant unexplained heterogeneity within each type of study design. In case-control studies (n=7), the summary RR was 1.30 (95%CI: 0.81, 2.07, P=0.27), with considerable inter-study heterogeneity ($I^2=90\%$, P<0.00001) (Figure 3). Systematic removal of each individual study during sensitivity analyses did not explain the heterogeneity. Removal of the 2 case-control studies by Ramon et al.⁴⁵, De Stefani et al.³² that reported risk estimates larger than 2 standard deviations from the pooled RR estimate reduced the inter-study heterogeneity ($I^2=68\%$, P=0.01) but did not eliminate it (Figure 4). The overall association became weakly protective but was not significant (RR=0.93; 95%CI: 0.69,1.25, P=0.64) (Figure 4). Removal of the 3 case-control studies by Ramon et al.⁴⁵. De Stefani et al.³², and Bidoli et al.⁵⁰ that had risk estimates outside the 95% CI of the pooled RR estimate, eliminated heterogeneity in the case-control studies ($I^2=11\%$, P=0.34), but the overall non-significant association between ALA intake and prostate cancer risk remained (RR=1.08; 95%CI: 0.86,1.36, P=0.49) (Figure 5).

201 Prospective Studies

In prospective studies alone (n=5), no association between ALA intake and prostate cancer risk was revealed (RR: 0.95; 95%CI: 0.84, 1.09, P=0.48) (**Figure 6**) but there existed substantial inter-study heterogeneity (I^2 =69%, P=0.01). Sensitivity analyses showed that removal of the study by Giovannucci et al. ²¹ eliminated heterogeneity with prospective studies (I^2 =8%, P=0.35) and made the protective effect significant (RR=0.91; 95%CI: 0.83,0.99, P=0.02) (**Figure 7**). Duration of follow-up in prospective studies was found to be positively but not significantly associated with the magnitude of relative risk (r=0.47).

Publication Bias Neither Begg's (P>0.165) nor Egger's (P>0.527) tests revealed evidence of publication bias, however, one study by Ramon et al. ⁴⁵ had an unusually large effect with a small standard error. DISCUSSION **Summary of Results** The present meta-analysis of 12 observational studies (7 case-control and 5 prospective) comparing the highest with the lowest categories of dietary ALA intake demonstrated non-significant heterogeneous effects of ALA on prostate cancer risk. Overall, there was no significant association between ALA intake and risk of prostate cancer. The subgroup analysis of case control studies alone showed a positive non-significant association, but with substantial heterogeneity. However, upon removal of the studies by De Stefani et al.³² and Ramon et al.⁴⁵, which reported large odds ratios greater than 3 but were still within 2 standard deviations of the mean effect, the association became weakly protective with decreased heterogeneity. When examining the prospective studies alone, the association between ALA intake and prostate cancer risk was weakly protective and after removal of the study by Giovannucci et al.²¹ became significantly protective with no heterogeneity. The results from the prospective studies are similar to those of previously published findings that examined only prospective studies ⁵³. Our study additionally investigated the association between dietary ALA intake and prostate cancer risk among case-control studies and reached a similar conclusion although the case control studies suggested an element of increased risk, which was dependent on the inclusion of two studies with very high odds ratios, the reasons for which are difficult to explain. Heterogeneity and the Effect of ALA between Studies In our study, different findings reviewed and inter-study heterogeneity may be explained by a number of factors: variation in ALA consumption and sources of ALA as a result of the population's dietary patterns, variation in ALA exposure levels, use of different FFQs and food

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databases, variation in adjustment factors, and difference in follow-up times among prospective 6 studies. Variation in ALA Consumption and Sources, and Population Dietary Patterns. In the Netherlands, the chief sources of ALA include margarine (25% of daily intake), meat (11%), bread (10%), and vegetables $(8\%)^{33}$, whereas in the United States, major sources of ALA come from mayonnaise, creamy salad dressings, margarine, butter, beef, pork, lamb, and oil and vinegar-based dressings²⁵. Interestingly, the prospective study from the Netherlands reported a weak protective effect of ALA intake on prostate cancer risk²⁰, but the most recent study from the United States reported a 25% increase in risk ²¹. This difference may be due to the nature of the foods that contain ALA since in the United States, the sources of ALA are not the "healthy" sources where ALA is naturally found (e.g. flaxseed, walnuts, and canola oil), but rather profiled an unhealthy diet (e.g. canola oil in the form of mayonnaise and creamy salad dressings), which may be indicative of a less healthy lifestyle and this in itself may contribute to an increased risk of prostate cancer independent of ALA intake levels ^{61 62}. In addition, in the case-control studies from Uruguay ³² and Spain ⁴⁵ that showed the largest increases in prostate cancer risk demonstrated that meat, and not vegetable, was the major source of ALA. When these two studies were removed from the analysis of the case-control studies, the effect of ALA intake on prostate cancer changed from a weakly positive to a weakly protective effect. Compared with the other studies from Europe and the United States, there is a much higher consumption of meat in Spain⁶³ and Uruguay, with Uruguay having the highest meat consumption per capita in the world ⁶⁴. An earlier analysis of the Health Professionals Follow-up Study cohort ²⁵ supports this positive association between red meat consumption and prostate cancer risk. Furthermore, the two studies from Spanish-speaking countries also investigated the effect of animal fat on prostate cancer and both found significant positive associations. The Uruguayan study ³² observed that at the highest level of ALA intake derived from animal sources resulted in almost 3 times the risk of developing prostate cancer and the Spanish study ⁴⁵ revealed that the highest level of animal fat intake was associated with 2 times the risk. These findings indicate that high meat intake rather than high ALA may explain ALA's apparent adverse effect on prostate cancer. In further support of this idea, the study by Bidoli et al.⁵⁰ demonstrated a significant protective association between ALA and prostate cancer risk in

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> an Italian population where ALA is mainly derived from olive oil ⁶⁵ and the diet is rich in raw vegetables ⁵⁰ rather than meat, profiling an overall more "healthy" diet.

An explanation for the apparent association of prostate cancer incidence with vegetable sources of ALA may be that in addition those who follow healthy lifestyles with increased plant ALA sources may undergo more frequent prostate specific antigen (PSA) testing and therefore have early prostate cancer detection. In this respect it has been found that higher whole grain intake was also associated with increased prostate cancer risk. However, when frequency of PSA screening was accounted for, the association of whole grains with prostate cancer incidence disappeared ⁶⁶. These studies indicate the importance of not only identifying the dietary sources of ALA, but taking into account what the nature of the foods may indicate in terms of diet and lifestyle since these also may affect prostate cancer risk.

Variation in ALA Exposure Levels.

Another important aspect to consider is the differing exposure levels between the studies. Each study had different cut-offs for each quantile, which makes a true comparison of ALA intake exposure difficult since some studies had higher levels of ALA in their highest intake quantile than others. Further, some studies did not adequately define the absolute upper and/or lower limits of ALA intake ^{21 32 50} and one study did not report numerical exposure levels ⁴⁹. Two studies, one from Spain⁴⁵ and one from the Netherlands²⁰, with the largest adequately defined upper and lower limits of ALA exposure ranges, paradoxically reported the second highest and the second lowest risk of developing prostate cancer, respectively. Since the studies with the greatest range of exposure do not necessarily show the greatest effects, dietary variation in the levels of exposure does not appear to explain differences among the studies, thereby making differences in dietary sources of ALA of more importance especially in relation to meat consumption in Western countries.

Variation in FFQs and Food Databases.

In terms of utilizing different FFQs and food databases, each study used a different dietary FFQ. ALA content of processed food can vary, which can be of concern when using food databases to translate food intake into fatty acid intake. For example, the ALA content of 12 margarines available in Australia range from 0.2% to 5.9%⁶⁷.

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300 Variation in Adjustment Factors.

Although all the studies reported adjusted RRs or ORs, the adjustment factors were not consistent among the studies. Some of the adjustment factors in these studies included age, smoking history, physical activity level, BMI, family history of prostate cancer, history of diabetes mellitus, race, education, socioeconomic status, area of residence and intakes of total calories, fat, processed meat, fish, lycopene, and vitamin E supplements. Currently, the most well-established risk factors for prostate cancer are age, family history of the disease, and race/ethnicity ⁶⁸ and consequently are the most important adjustment factors. Only 4 ^{20-22 52} of the 12 included studies adjusted for all of these 3 factors. The studies conducted by Park et al.¹⁹ and Mannisto et al.²⁴ did not adjust for age, which is by far the strongest predictor of prostate cancer incidence and death ⁶⁸. A family history of prostate cancer has been shown to increase the risk of diagnosis and death and this factor was not adjusted for in studies by Hedelin et al.⁵¹, Andersson et al.⁴⁸, and Mannisto et al.²⁴ Race is a prostate cancer risk factor and prognostic factor, with African-American or Black men being at increased risk, and this was not adjusted for in the studies by Bidoli et al. ⁵⁰, De Stefani et al. ³², Ramon et al. ⁴⁵, and Meyer et al. ⁴⁹ Differences in adjustment among the included studies, particularly with respect to the important factors of age, family history of prostate cancer, and race could result in differences in risk estimates, thereby contributing to inter-study heterogeneity.

⁵ 318

319 Variation in Follow-up Duration.

Follow-up time may also have an effect on heterogeneity, especially since the study by Giovannucci et al.²¹ had the longest follow-up duration (16 years). Comparing previous prospective studies following the same cohort ^{23 25} with this most recent study ²¹, demonstrates a shift over time (total of 12 years) from a non-significant to a significant positive association between ALA intake and prostate cancer. So, the heterogeneity induced by this study may indicate that follow-up duration is positively related to the strength of the association between ALA and prostate cancer risk. After investigating this suggestion, the effect of follow-up duration on relative risk among the prospective studies was found to be positively, but not significantly correlated (r=0.47).

330 Reasons for the Lack of Effect of ALA

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The overall effect of ALA on prostate cancer was found to be non-significant but may
result from a number of factors including ALA exposure levels that are within health guidelines,
confounding from other polyunsaturated fatty acids, and the difference in effect of ALA on
mortality versus incidence.

The mean dietary ALA intake levels observed in these studies were all within the dietary reference intake (DRI) range of 1.1 to 1.6 g/d ⁶⁹, suggesting that ALA may not increase the risk of cancer more than any other nutrient promoting cell growth. Rather, since ALA is a nutrient deficient in the Western diet ⁷⁰, it may be that a deficiency inhibits all cell growth, including tumour growth, instead of adequate or excess levels causing prostate cancer growth.

Another issue to consider is confounding from other polyunsaturated fatty acids such as omega-6 or other omega-3 fatty acids (eicosapentaenoic and docosahexaenoic fatty acids) that might affect ALA metabolism ⁷¹ and consequently may introduce bias. The case-control study from the United States ⁵² demonstrated this as there was no significant association between ALA, omega-3, or omega-6 fatty acids and prostate cancer risk individually, but the highest dietary ratio of omega-6/omega-3 fatty acids was significantly associated with increased risk of high grade prostate cancer.

Finally, our analysis involved cancer incidence rather than mortality and ALA, among other factors such as energy intake, height, body mass index, calcium, and smoking, are also associated with cancer mortality²¹. The study by De Stefani et al.³², which was the only study that defined cases solely as advanced prostate cancer, had the highest risk estimate of prostate cancer, indicating that ALA may be strongly associated with disease severity rather than incidence. In support of this point, the prospective study by Giovannucci et al.²¹ found that higher ALA intake was more strongly associated with increased risk of fatal prostate cancer than with incident. However, three other prospective studies did not find any difference between the effects of ALA on incident or advanced prostate cancer cases ^{19 20 22}. From these mixed findings, it is unclear whether ALA is associated with severity of prostate cancer, but determining whether ALA impacts prostate cancer incidence or progression is an important distinction that should be investigated in the future. Furthermore, the picture of ALA's effect on prostate cancer is complicated by the positive association of incident prostate cancer with either serum or adipose tissue ALA levels ^{24 43 44 46 47 72} despite the in vitro evidence which suggests that ALA may suppress prostate cancer cell growth ^{73 74}. However, there appears to be some correlation between

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ALA intake and serum ALA levels. In terms of intake, Gann et al. ⁴³ found that plasma ALA levels were significantly positively correlated with meat and dairy product intake, and similar to the prospective analysis from the Health Professionals Follow-Up Study ²⁵, they found that red meat was positively associated with advanced prostate cancer, whereas diary foods were not. This corroboration not only suggests a correlation between ALA intake and serum ALA levels, but enforces the positive association between ALA from red meat and prostate cancer as seen in the studies from Uruguay ³² and Spain ⁴⁵, rather than from plant foods.

370 Limitations

The first limitation of the meta-analysis is that all data currently available for inclusion come from epidemiological studies since there are no data from randomized controlled trials due to ethical concerns. Second, interpretation of the analyses was complicated by the evidence of considerable heterogeneity among the studies, which as discussed above may have resulted from differences in ALA sources and population dietary patterns, ALA exposure levels, FFOs and food databases, adjustment factors, and duration of follow-up. There are also inherent limitations in the studies included based on study design. The association between ALA intake and prostate cancer risk was stronger overall in the case-control studies than in the prospective studies. However, there is the possibility of recall bias in case-control studies, as dietary intake information is collected after disease development.

382 CONCLUSION

In conclusion, these findings provide no clear evidence of an association between dietary ALA intake and prostate cancer risk. Further, since these observational studies can only show association between ALA intake and prostate cancer, possible causation would be difficult to establish. Therefore, additional research from epidemiological, clinical, and in vitro studies are required to elucidate whether ALA has a promotional, inhibitory, or no effect on prostate cancer risk and development. For the present, no significant association has been found and where any support of a positive effect was seen, red meat sources have been strongly implicated. The source of ALA appears to be of importance, particularly identifying whether it is from animal or vegetable sources, as ALA may be a marker for higher meat and fat intake in some countries both of which have been associated with increased prostate cancer risk. Attention should also be

3 4	393	paid to the effect of ALA on prostate cancer progression to address the issues of specific
5	394	vulnerability identified in the studies of ^{21 32} . However, resolving the relation of dietary ALA to
6 7	395	prostate cancer risk through randomized controlled trials will likely continue to be difficult due
8 9	396	to the significant public health implications of reducing/eliminating a dietary fatty acid which is
10 11	397	essential and has suggested heart health benefits. Of probably greater importance is
12 13	398	determination of the sources of the fatty acid since ALA is associated in the North American diet
14	399	with meat membranes and creamy salad dressings, which themselves may be markers of a
15 16	400	suboptimal dietary pattern and lifestyle
17 18	401	
19 20	402	ARTICLE SUMMARY
21	403	Article Focus
22 23	404	• ALA is considered a cardioprotective nutrient, however some epidemiological studies
24 25	405	have suggested that dietary ALA intake increases the risk of prostate cancer
26 27	406	• A systematic review and meta-analysis of case-control and prospective studies was
28 29	407	conducted to investigate the association between dietary ALA intake and prostate cancer
30	408	risk
31 32	409	Key messages
33 34	410	• The present meta-analysis of 12 observational studies (7 case-control and 5 prospective)
35 36	411	comparing the highest with the lowest categories of dietary ALA intake demonstrated
37	412	overall no significant association between ALA intake and risk of prostate cancer
38 39	413	• The subgroup analysis of case control studies alone showed a positive non-significant
40 41	414	association, but with substantial heterogeneity. However, upon removal of the studies,
42 43	415	which reported large odds ratios, the association became weakly protective but remained
44 45	416	non-significant, with decreased heterogeneity
46	417	• The subgroup analysis of case control studies alone showed a positive non-significant
47 48	418	association, but with substantial heterogeneity, which suggests an element of increased
49 50	419	risk dependent on the inclusion of two studies with very high odds ratios, the reasons for
51 52	420	which are difficult to explain
53 54	421	Strengths and Limitations:
55	422	• This meta-analysis includes both prospective and case control studies to determine the
56 57	423	effect of ALA on prostate cancer
58 59		
60		

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• Possible confounders and sources of heterogeneity were discussed and explored in relation to the results

• Interpretation of analyses was complicated by considerable heterogeneity among the studies, which may be due to lack of randomized controlled trials, variation in ALA sources and dietary patterns, variation in ALA exposure levels, differences in FFQs and food databases, variation in adjustment factors, follow-up duration, and study design

"What this Paper Adds"

ALA is considered a cardioprotective nutrient, however some epidemiological studies have suggested that dietary ALA intake increases the risk of prostate cancer. Although Carayol et al. conducted a meta-analysis on the effect of dietary ALA on prostate cancer in 2010, only prospective studies were analyzed and case-control studies were not included. Overall, we found no significant association between ALA intake and risk of prostate cancer. The results from the prospective studies were similar to those of previously published findings. However, the subgroup analysis of case control studies alone showed a positive non-significant association, but with substantial heterogeneity. The case control studies suggested an element of increased risk, which was dependent on the inclusion of two studies with very high odds ratios, the reasons for which are difficult to explain. Additional research from epidemiological, clinical, and in vitro studies are required to elucidate whether ALA has a promotional, null, or inhibitory effect on prostate cancer risk and development.

432 AUTHORSHIP

All authors, external and internal, had full access to all of the data (including statistical reports
and tables) in the study and can take responsibility for the integrity of the data and the accuracy
of the data analysis.
Details of Contributors: AJC was involved in the conception and design, analysis and

437 interpretation of data, drafting the article and revising it critically for important intellectual

438 content, and final approval of the version to be published. JLS was involved in the conception

439 and design, some analysis, and revising the article critically for important intellectual content. RS

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was involved in revising the article critically for important intellectual content. GE was involved

in the conception and design and in revising the article critically for important intellectual

content. DJAJ was in the conception and design, revising the article critically for important

intellectual content, and final approval of the version to be published.

DATA SHARING

There is no additional data available.

COMPETING INTEREST DECLARATION

All authors have completed the Unified Competing Interest form at www.icmje.org/coi disclosure.pdf (available on request from the corresponding author) and declare that (1) AJC, JLS, RS, and GE have not had financial support from any company for the submitted work; (2) AJC, JLS, RS, and GE have no relationships with any companies that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) AJC, JLS, RS, and GE have no non-financial interests that may be relevant to the submitted work. DJAJ has served on the Scientific Advisory Board of Sanitarium Company, Agri-Culture and Agri-Food Canada (AAFC), Canadian Agriculture Policy Institute (CAPI), California Strawberry Commission, Loblaw Supermarket, Herbal Life International, Nutritional Fundamental for Health, Pacific Health Laboratories, Metagenics, Bayer Consumer Care, Orafti, Dean Foods, Kellogg's, Quaker Oats, Procter & Gamble, Coca-Cola, NuVal Griffin Hospital, Abbott, Pulse Canada. Saskatchewan Pulse Growers, and Canola Council of Canada; received honoraria for scientific advice from Sanitarium Company, Orafti, the Almond Board of California, the American Peanut Council, International Tree Nut Council Nutrition Research and Education Foundation and the Peanut Institute, Herbal Life International, Pacific Health Laboratories, Nutritional Fundamental for Health, Barilla, Metagenics, Bayer Consumer Care, Unilever Canada and Netherlands, Solae, Oldways, Kellogg's, Quaker Oats, Procter & Gamble, Coca-Cola, NuVal Griffin Hospital, Abbott, Canola Council of Canada, Dean Foods, California Strawberry Commission, Haine Celestial, Pepsi, and Alpro Foundation; has been on the speakers panel for the Almond Board of California; received research grants from Saskatchewan Pulse Growers, the Agricultural Bioproducts Innovation Program (ABIP) through the Pulse Research Network (PURENet), Advanced Food Materials Network (AFMNet), Loblaw, Unilever, Barilla,

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Almond Board of California, Coca-Cola, Solae, Haine Celestial, Sanitarium Company, Orafti, International Tree Nut Council Nutrition Research and Education Foundation and the Peanut Institute, the Canola and Flax Councils of Canada, Calorie Control Council, Canadian Institutes of Health Research, Canada Foundation for Innovation, and the Ontario Research Fund; and received travel support to meetings from the Solae, Sanitarium Company, Orafti, AFMNet, Coca-Cola, The Canola and Flax Councils of Canada, Oldways Preservation Trust, Kellogg's, Quaker Oats, Griffin Hospital, Abbott Laboratories, Dean Foods, the California Strawberry Commission, American Peanut Council, Herbal Life International, Nutritional Fundamental for Health, Metagenics, Bayer Consumer Care, AAFC, CAPI, Pepsi, Almond Board of California, Unilever, Alpro Foundation, International Tree Nut Council, Barilla, Pulse Canada, and the Saskatchewan Pulse Growers. DJAJ's wife is a director of Glycemic Index Laboratories, Toronto, Ontario, Canada.

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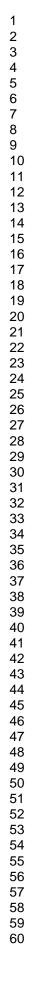
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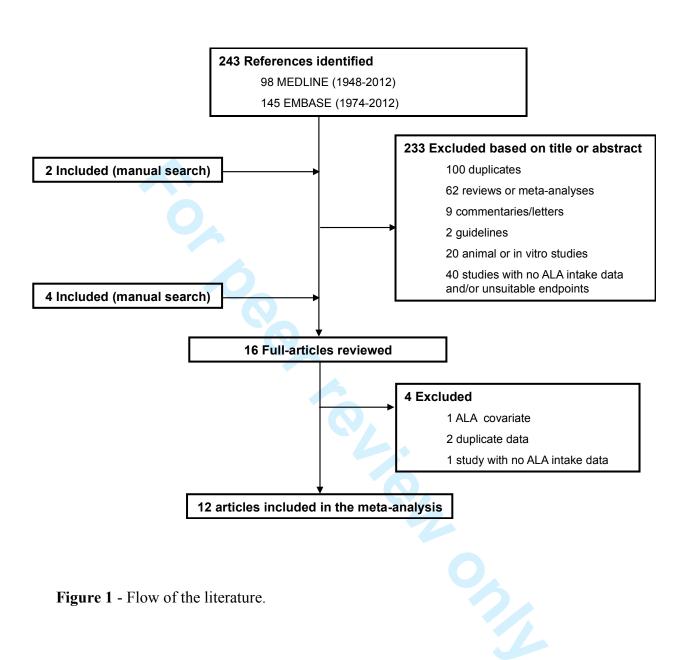
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Study	Country of Origin	Study Design	Sample size	Age (years)	Incident Cases	Follow-up (years)	Exposure level (g/d)	Relative Risk or Odds Ratio	95% CI
Andersson et al. 1996 [38]	Sweden	Case-control	526 cases/536 controls	<80	-	-	0.817 - 1.352	0.93	0.65-1.32
Meyer et al. 1997 [39]	Canada	Case-control	215 cases/593 controls	<u>≥</u> 45	-	-	-	0.98	0.54-1.78
Schuurman et al. 1999 [18]*	Netherlands	Nested case-cohort	58279 (1525 subcohort)	55-69	642	6.3	0.7 - 2.1	0.76	0.66-1.04
De Stefani et al. 2000 [29]	Uruguay	Case-control	217 cases/431 controls	40-89	-	-	⊴0.8 - ≥1.5	3.91	1.50-10.1
Ramon et al. 2000 [40]	Spain	Case-control	217 cases/434 controls	<60-80	-	-	0.72 - 2.1	3.1	2.2-4.7
Mannisto et al. 2003 [22]*	Finland	Nested case-control	198 cases/198 controls	50-69	246	5-8	1.0 - 2.3	1.16	0.64-2.13
Bidoli et al. 2005 [41]	Italy	Case-control	1294 cases/1451 controls	45-74	-	-	mean 1.6	0.7	0.6-0.9
Koralek et al. 2006 [20]*	United States	Prospective cohort	29,592	55-74	1898	5.1	1.09 - 1.75	0.94	0.81-1.09
Hedelin et al. 2007 [42]	Sweden	Case-control	1499 cases/1130 controls	mean 67.3	-	-	0.05 - 0.60	1.35	0.99-1.84
Giovannucci et al. 2007 [19]*	United States	Prospective cohort	47,750	40-75	3544	16	<0.79 - ≥1.32	1.12	1.01-1.25
Park et al. 2007 [17]*	United States	Prospective cohort	82,483	<u>≥</u> 45	4404	8	1.1 - 2.14 †	0.92	0.84-1.02
Williams et al. 2011 [43]	United States	Case-control	79 cases/187 controls	≥18	-	-	≤1.0 - 4.156†	0.82	0.41-1.65
* Prospective studies.									
† Based on a 2000 kcal diet.									

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Test for overall effect: Z = 1.10 (P = 0.27)

Study or Subgroup	Waight	Risk Ratio	Vear	Risk Ratio
Study or Subgroup Andersson 1996 [48]	8.4%	IV, Random, 95% CI 0.93 [0.65, 1.33]	Year	IV, Random, 95% CI
Meyer 1997 [49]	5.2%			
Schuurman 1999 [20]	10.5%			
De Stefani 2000 [32]	2.7%			
Ramon 2000 [45]	8.0%			
Mannisto 2003 [24]	5.1%			
Bidoli 2005 [50]	10.9%	0.70 [0.57, 0.86]	2005	
Koralek 2006 [22]	11.6%	0.94 [0.81, 1.09]	2006	-
Hedelin 2007 [51]	9.1%	1.35 [0.99, 1.84]	2007	
Park 2007 [19]	12.2%	0.92 [0.83, 1.01]	2007	-
Giovannucci 2007 [21]	12.1%			-
Williams 2011 [52]	4.3%	0.82 [0.41, 1.64]	2011	
Total (95% CI)	100.0%	1.08 [0.90, 1.29]		•
Heterogeneity: Tau ² = 0 Test for overall effect: Z	.06; Chi ² =	= 71.45, df = 11 (P <		0.1 0.2 0.5 1 2 5 10 Favours ALA Favours Control
Figure 2 – Pooled eff	fect of di	ietary ALA intake	on prostate cance	r risk in case-control, nested
case-control, nested c	ase-coho	ort, and cohort stud	dies. Relative Risl	x (RR) with 95% CI, study
weights, and pooled e	effect est	imates were gener	ated using the ger	neral inverse variance method
with random effects r	nodels (I	RevMan 5.1, Coch	rane Library softw	ware, Oxford, UK). Inter-study
heterogeneity was tes	ted by C	cochrane's Q (Chi ²) at a significance	level of P<0.10 and quantified
by I^2 , where $I^2 \ge 50$ %	6 is cons	idered to be evider	nce of substantial	heterogeneity and \geq 75%,
considerable heteroge	eneity ⁵⁵			
		Risk Ratio		Risk Ratio
Study or Subgroup		, ,	Year	IV, Random, 95% CI
Andersson 1996 [48]	15.7%	0.93 [0.65, 1.33]	1996	
Meyer 1997 [49]	13.5%	0.98 [0.54, 1.78]		
Ramon 2000 [45]	15.5%	3.10 [2.12, 4.53]		— -
De Stefani 2000 [32]	10.0%	3.91 [1.51, 10.15]		· · · · · · · · · · · · · · · · · · ·
Bidoli 2005 [50]	16.7%	0.70 [0.57, 0.86]		
Hedelin 2007 [51]	16.1%	1.35 [0.99, 1.84]		_
Williams 2011 [52]	12.5%	0.82 [0.41, 1.64]	2011	
Total (95% CI)	100.0%	1.30 [0.81, 2.07]		
Heterogeneity: $Tau^2 = 0$			$0.00001) \cdot I^2 = 90\%$	
Test for success of the start 7			0.00001), 1 = 50%	0.10.2 0.5 1 2 5 10

Favours ALA Favours Control

Figure 3 – Pooled effect of dietary ALA intake on prostate cancer risk in case-control studies. Relative Risk (RR) with 95% CI, study weights, and pooled effect estimates were generated using the general inverse variance method with random effects models (RevMan 5.1, Cochrane Library software, Oxford, UK). Inter-study heterogeneity was tested by Cochrane's Q (Chi²) at a

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significance level of P<0.10 and quantified by I^2 , where $I^2 \ge 50$ % is considered to be evidence of substantial heterogeneity and ≥ 75 %, considerable heterogeneity ⁵⁵.

Study or Subgroup	Weight	Risk Ratio IV, Random, 95% CI	Year	Risk Ratio IV, Random, 95% CI
Andersson 1996 [48]	22.2%	0.93 [0.65, 1.33]		
Meyer 1997 [49]	14.0%	0.98 [0.54, 1.78]		
De Stefani 2000 [32]	0.0%	3.91 [1.51, 10.15]		
Ramon 2000 [45]	0.0%	3.10 [2.12, 4.53]		
Bidoli 2005 [50]	28.2%	0.70 [0.57, 0.86]	2005	
Hedelin 2007 [51]	24.0%	1.35 [0.99, 1.84]	2007	
Williams 2011 [52]	11.6%	0.82 [0.41, 1.64]	2011	
Total (95% CI)	100.0%	0.93 [0.69, 1.25]		•
Heterogeneity: Tau ² =	0.07; Chi ²	= 12.46, $df = 4 (P =$	0.01 ; $I^2 = 68\%$	
Test for overall effect: 2	Z = 0.47 (P = 0.64)		Favours ALA Favours Control

Figure 4 – Pooled effect of dietary ALA intake on prostate cancer risk in case-control studies after the removal of the studies by De Stefani et al. ³² and Ramon et al. ⁴⁵ and following a sensitivity analysis. Relative Risk (RR) with 95% CI, study weights, and pooled effect estimates were generated using the general inverse variance method with random effects models (RevMan 5.1, Cochrane Library software, Oxford, UK). Inter-study heterogeneity was tested by Cochrane's Q (Chi²) at a significance level of P<0.10 and quantified by I², where I² \geq 50 % is considered to be evidence of substantial heterogeneity and \geq 75%, considerable heterogeneity ⁵⁵.

		Risk Ratio		Risk Ratio
Study or Subgroup	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Andersson 1996 [48]	34.1%	0.93 [0.65, 1.33]	1996	
Meyer 1997 [49]	13.4%	0.98 [0.54, 1.78]	1997	
De Stefani 2000 [32]	0.0%	3.91 [1.51, 10.15]	2000	
Ramon 2000 [45]	0.0%	3.10 [2.12, 4.53]	2000	
Bidoli 2005 [50]	0.0%	0.70 [0.57, 0.86]	2005	
Hedelin 2007 [51]	42.5%	1.35 [0.99, 1.84]	2007	-∎
Williams 2011 [52]	10.0%	0.82 [0.41, 1.64]	2011	
Total (95% CI)	100.0%	1.08 [0.86, 1.36]		•
Heterogeneity: $Tau^2 = 0$	0.01; Chi ²		$(.34); I^2 = 11\%$	
Test for overall effect: Z				0.10.2 0.5 1 2 5 10
				Favours ALA Favours Control

Figure 5 – Pooled effect of dietary ALA intake on prostate cancer risk in case-control studies after the removal of the studies by De Stefani et al. ³², Ramon et al. ⁴⁵, and Bidoli et al. ⁵⁰ and following a sensitivity analysis. Relative Risk (RR) with 95% CI, study weights, and pooled effect estimates were generated using the general inverse variance method with random effects

models (RevMan 5.1, Cochrane Library software, Oxford, UK). Inter-study heterogeneity was tested by Cochrane's Q (Chi²) at a significance level of P<0.10 and quantified by I², where I² \geq 50 % is considered to be evidence of substantial heterogeneity and \geq 75%, considerable heterogeneity ⁵⁵.

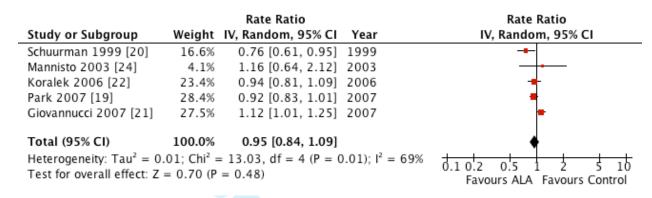


Figure 6 – Pooled effect of dietary ALA intake on prostate cancer risk in prospective studies. Relative Risk (RR) with 95% CI, study weights, and pooled effect estimates were generated using the general inverse variance method with random effects models (RevMan 5.1, Cochrane Library software, Oxford, UK). Inter-study heterogeneity was tested by Cochrane's Q (Chi²) at a significance level of P<0.10 and quantified by I², where I² \geq 50 % is considered to be evidence of substantial heterogeneity and \geq 75%, considerable heterogeneity ⁵⁵.

		Rate Ratio		Rate Ratio
Study or Subgroup	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Schuurman 1999 [20]	12.8%	0.76 [0.61, 0.95]	1999	
Mannisto 2003 [24]	1.9%	1.16 [0.64, 2.12]	2003	_
Koralek 2006 [22]	28.1%	0.94 [0.81, 1.09]	2006	+
Park 2007 [19]	57.1%	0.92 [0.83, 1.01]	2007	•
Giovannucci 2007 [21]	0.0%	1.12 [1.01, 1.25]	2007	
Total (95% CI)	100.0%	0.91 [0.83, 0.99]		•
Heterogeneity: Tau ² = (0.00; Chi ² =	= 3.27, df = 3 (P = 0.1)	35); $I^2 = 8\%$	
Test for overall effect: 2	r = 2.28 (P	= 0.02		0.10.2 0.5 1 2 5 10
rest ist steral effect.		0.02/		Favours ALA Favours Control

Figure 7 – Pooled effect of dietary ALA intake on prostate cancer risk in prospective studies after the systematic removal of the study by Giovannucci et al. ²¹ following a sensitivity analysis. Relative Risk (RR) with 95% CI, study weights, and pooled effect estimates were generated using the general inverse variance method with random effects models (RevMan 5.1, Cochrane Library software, Oxford, UK). Inter-study heterogeneity was tested by Cochrane's Q (Chi²) at a

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significance level of P<0.10 and quantified by I^2 , where $I^2 \ge 50$ % is considered to be evidence of substantial heterogeneity and ≥ 75 %, considerable heterogeneity ⁵⁵.

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	Case-Control and Prospective Studies of Dietary Alpha-Linolenic Acid Intake	Pormatted. Font. Times New Rom
	and Prostate Cancer Risk: a Meta-Analysis	
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	Amanda J Carleton, MSc ^{1,2,3} ; John L Sievenpiper ^{1,2,4} , MD, PhD; Russell de Souza,	Formatted: Font: Times New Rom
	SD⁴ScD^{1,2,5}; Gail McKeown-Eyssen, PhD^{2,6}; David JA Jenkins, MD, <u>PhD, DSe⁴PhD^{1,2,3}</u>.	
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31	Abstract	Formatted: Font: Times New Roman, 12 pt, Bold
32	ABSTRACT	Protected by copyright, including for uses related
33	Background: ALA is considered a cardioprotective nutrient, however some epidemiological	cted
34	studies have suggested that dietary ALA intake increases the risk of prostate cancer.	by
35	Objective: To conduct a systematic review and meta-analysis of case-control and prospective	Copy
36	studies investigating the association between dietary ALA intake and prostate cancer risk.	/rigt
37	Data Sources: MEDLINE and EMBASE were searched for relevant prospective and case-	t, ir
38	control studies.	nclu
39	Eligibility Criteria for Selecting Studies: We included all prospective cohort, case-control,	ding
40	nested case-cohort, and nested case-control studies that investigated the effect of dietary ALA	l for
41	intake on the incidence (or diagnosis) of prostate cancer and provided relative risk (RR), hazard	use
42	ratios (HR), or odds ratios (OR) estimates.	is rec
43	Design: Data were pooled using the generic inverse variance method with a random-effects	late
44	model from studies that compared the highest ALA quantile with the lowest ALA quantile. Risk	to e
45	estimates were expressed as relative risk (RR) with 95% confidence intervals (CI). Heterogeneity	text
46	was assessed by χ^2 and quantified by I ² .	t and
47	Results: Data from 5 prospective and 7 case-control studies were pooled. The overall RR	text and data mining, Al training, and similar technologies
48	estimate showed ALA intake to be positively, but non-significantly associated with prostate	ta n
49	cancer risk (1.08 [0.90 to 1.29], P=0.40, $I^2=85\frac{6}{2}$, but the interpretation was complicated by	
50	evidence of heterogeneity not explained by study design. A weak non-significant protective	
51	effect of ALA intake on prostate cancer risk in the prospective studies which became significant	l tra
52	$(0.91 \ [0.83 \text{ to } 0.99], P=0.02)$ without evidence of heterogeneity (I ² =8%, P=0.35) on removal of	linin
53	one study during sensitivity analyses.	(<u>Ŭ</u> , a
54	Conclusions: This analysis failed to confirm an association between dietary ALA intake and	nd «
55	prostate cancer risk. Larger and longer observational and interventional studies are needed to	simi
56	define the role of ALA and prostate cancer.	lar to
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8 9 10	61	Key Words: Alpha-linolenic acid, prostate cancer, omega-3 fatty acid, meta-analysis	 shed as
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10	63	Introduction <u>INTRODUCTION</u>	Bold
11 12	64	Prostate cancer is the second most common cancer in men worldwide ¹ . Prostate cancer	rote
12	65	incidence rates vary widely among countries, populations, and races. Incidence rates vary by	octeo
14	66	more than 25-fold worldwide, with the highest rates documented in the developed countries of	d by
15 16	67	North America, Europe, and Oceania, which may be due largely to the wide utilization of	
17	68	prostate- specific antigen (PSA) testing that detects clinically important tumors that might	yrig
18 19	69	otherwise escape diagnosis ² . In contrast, males of African descent in the Caribbean region have	lht, i
20	70	the highest prostate cancer mortality rates in the world ² , which is thought to reflect partly a	inclu
21 22	71	difference in genetic susceptibility ^{3 4} . The large differences in prostate cancer incidence rates	in a state of the
22	72	have led to many migration and ecologic studies, which have provided strong evidence for the	g fo
24	73	role of environmental factors, such as diet, in the etiology of prostate cancer ⁵⁻¹⁴ . In 1975,	
25 26	74	Armstrong and Doll first hypothesized that there was an association between dietary fat and	nsei src
27	75	death from prostate cancer ¹² , and many studies have examined this connection ¹⁵⁻¹⁸ , but in recent	slate
28 29	76	years more attention has been focused on specific fatty acids. Several studies have examined the	id men tc
30	77	association between polyunsaturated fatty acids (PUFAs) and risk of prostate cancer ¹⁹⁻²⁵ . There) tex
31 32	78	has been particular interest in alpha-linolenic acid (ALA), the parent fatty acid for the ω -3	tan
33	79	PUFAs, since increased consumption of ω -3 fatty acids is advised for cardiovascular disease risk	d da
34 35	80	reduction ²⁶⁻²⁹ despite a possible association with prostate cancer ³⁰ .	Formatted: Not Highlight
36	81	Dietary ALA occurs mainly in plants and vegetable oils with certain seed oils (flaxseed,	ninir Ninir
37	82	perilla, chia seed, and canola), beans (soybeans, navy beans), and nuts (walnuts) singled out as	jā,
38 39	83	examples of healthy foods due to their high ALA content ³¹ . However, in the United States, the	Al tra
40	84	important sources of ALA are animal-based foods high in saturated fats, such as red meats, beef,	ainir
	85	pork, and lamb, rather than ALA-rich vegetable sources, such as walnuts. ²⁵ . The largest	Ű, a
43	86	proportion of ALA (53.8%) comes from red meat in Uruguay ³² , but comes from margarine	ind s
44 45	87	(25%) in the Netherlands ³³ . Furthermore, foods such as bread, eggs, and margarine are now	sim <u>i</u>
	88	being enriched with ALA to increase their healthfulness. Therefore, it appears timely to	lar t
47	89	determine whether there are associations between ω -3 fatty acid-rich foods, generally believed to	echr
	90	be healthy, and prostate cancer risk.	
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41 42 43 44 45 46 47 48 49	85 86 87 88 89	pork, and lamb, rather than ALA-rich vegetable sources, such as walnuts. ²⁵ . The largest proportion of ALA (53.8%) comes from red meat in Uruguay ³² , but comes from margarine (25%) in the Netherlands ³³ . Furthermore, foods such as bread, eggs, and margarine are now being enriched with ALA to increase their healthfulness. Therefore, it appears timely to determine whether there are associations between ω 3 fatty acid rich foods, generally believed to	Enseignement Superieur (ABES) . Formatted: Not Highlight

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Methods

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We followed the Cochrane handbook for systematic reviews of interventions version 5.1.0 updated March 2011 for the planning and conduct of this meta-analysis ³⁴. The reporting followed the OUOROM (Ouality of Reporting of Meta analyses) guidelines 35.

There are currently divergent health views on ALA. Numerous epidemiological ³⁴⁻³⁹ and clinical studies 40.42 have shown that ALA is associated with a reduction in coronary heart disease (CHD) incidence and heart disease mortality. However, since ALA has also been associated with an increased risk of prostate cancer, ^{25 30 32 43-47} the seriousness of this potential association requires that any favourable effects of ALA on CHD be weighed against its possible adverse effects on prostate cancer. Numerous prospective cohort ^{19-22 24} and case-control studies ^{32 45 48-52} have investigated the association between ALA and prostate cancer risk. While previous meta-analyses ^{30 53 54} have been conducted to determine whether a relationship exists, there has been no meta-analysis since 2010, examining the specific effect of dietary ALA on prostate cancer risk and none since 2009, that included in both prospective cohort and case-control studies. Therefore, it appears timely to determine whether there are associations between dietary ALA from ω -3 fatty acid-rich foods, generally believed to be healthy, and prostate cancer risk.

METHODS

We followed the Cochrane handbook for systematic reviews of interventions version 5.1.0 updated March 2011 for the planning and conduct of this meta-analysis ⁵⁵. The reporting followed the QUOROM (Quality of Reporting of Meta-analyses) guidelines ⁵⁶.

Study Selection

We conducted a search of MEDLINE (1948-April 17, 2009) and EMBASE (1974-April 17, 2009) using the following search terms and Boolean operators: prostate AND (cancer OR adenoma OR adenocarcinoma OR neoplasia OR gleason score) AND (alpha-linolenic acid OR *n-3 fatty acids OR omega-3 fatty acids*). The search was restricted to human research studies. No limit was placed on language. Manual searches of references cited by the published original studies and review articles supplemented the database search strategy. This search strategy was last updated on August 28, 2012. We included all prospective cohort, case-control, nested casecohort, and nested case-control studies that investigated the effect of dietary ALA intake on the

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incidence (or diagnosis) of prostate cancer and provided relative risk (RR), hazard ratios (HR), or odds ratios (OR) estimates. No randomized controlled trials were identified. No lone abstracts or unpublished studies were identified. In cases where multiple publications existed for the same study, the article with the most recent information was included.

Data Extraction

Two investigators (AJC, JLS) independently extracted relevant data on study characteristics and outcomes using a standardized proforma. These data included information about study design (prospective cohort, case-control, etc.), sample size and participant characteristics (nationality, race, named cohort, country of residence, gender, age, disease status, preexisting medical conditions), follow-up duration, sources of ALA, method of ALA status assessment, endpoints (incidence of prostate cancer, prostate specific antigen (PSA), Gleason score etc.), endpoint assessment (self-reporting, medical records, biopsy, etc.), and number of new incident cases. Bounds of intake categories, quartiles or quintiles, were also recorded. RR, HR, or OR with the greatest degree of control for other environmental and dietary risk factors, and their corresponding 95% CIs for incident prostate cancer risk were extracted as the main endpoint. Disagreements were reconciled by consensus and where necessary by discussion with another investigator (DJAJ). Authors were not contacted to request any additional information or translation.

Statistical Analysis

Data were analyzed using Review Manager (RevMan) 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). We used the reported RR or OR of the highest versus lowest intake category, as the measure of the relation between ALA intake and prostate cancer risk. A pooled analysis of all reports was conducted using the Generic Inverse Variance method using random effects models ³⁶⁵⁷ where the log RRs for cohort studies or log ORs for case-control studies were weighted by the inverse of the variance to obtain a pooled RR estimate. Since nested case-cohort and nested case-control studies are temporally prospective, we analyzed data from these studies with the prospective studies. As in other meta-analyses that have examined prostate cancer ^{30 37<u>54</u> 38<u>58</u>, ORs were considered as approximations of RRs. Since} the initial risk of prostate cancer is low, it is unlikely that there will be a substantial discrepancy

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in approximating ORs to RRs. ⁵⁹ Inter-study heterogeneity was assessed by Cochrane's Q (Chi ²			
P<0.10) and quantified by I^2 —. An $I^2 \ge 50\%$ indicated "substantial" heterogeneity and $\ge 75\%$			
indicated "considerable" heterogeneity. ³⁹ . The ⁶⁰ Sources of heterogeneity were explored by			
sensitivity analyses whereby the influence of individual studies was investigated by			
systematically removingsystematic removal of each study and recalculatingfollowed by			
recalculation of the pooled effect. An a estimate and heterogeneity, as well as removal of outlier			
studies with risk estimates larger than 2 standard deviations from the mean risk estimate and			
recalculation of the pooled effect estimate and heterogeneity. We also performed a priori			
subgroup analysis analyses to assess effect modification by study design, (prospective versus			
case-control), was also undertaken to investigate heterogeneity. Meta-regressions were			
performed to assess the significance of). Post-hoc analyses included dichotomous subgroup			
analyses to assess effect modification by study design on effect modification (STATA 11.2.,			
College Station, USA)-) and continuous analyses to assess the effect of the duration of follow-up			
on relative risk among prospective studies, Publication bias was investigated by visual inspection			
of funnel plots, and that was formally tested using Begg's and Egger's tests.			

Results

RESULTS

Search Results

Figure 1 shows the flow of the literature selection applying the systematic search and selection strategies to identify eligible reports. Two hundred and forty three reports were identified by the search and two reports were manually included after a database search. Of these, 233 were determined to be irrelevant on review of the titles and abstracts. Four additional reports were then manually included. The remaining 16 reports were retrieved and reviewed in full, of which 4 were excluded. Results for The Health Professionals' Follow-up Study were published in three separate publications at different times of follow-up ^{21 23 25}. Only the most recent publication of the results, by Giovannucci et al. in 2007, was included in the analyses as representing the cumulative experience of the earlier assessments of this cohort ²¹. A total of 12 reports, 5 prospective and 7 case-control studies, were included in the pooled analyses.

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177	Study Characteristics	Bold
178	Table 1 shows the characteristics of the 12 included studies, which were composed of 7	Prc 10
179	case-control studies ^{32 40 4545 48-52} and 5 prospective studies ^{19-22 24} that used 3 designs: cohort,	otect
180	nested case-cohort, and nested case-control. Five studies were conducted in North America, 1 in	ed t
181	South America, and 6 in Europe. The 12 included studies contained a total of 14,795 cases of	by njop
182	prostate cancer and 231,143 controls. All studies obtained dietary data using food frequency	оруг
183	questionnaires (FFQ). Individual and average dietary ALA intake in these studies ranged from	ight 1
184	≈ 0.05 to 4.16 g/d) and the reported relative risk or odds ratio of the highest versus the lowest	;; inc
185	intake category ranged from 0.7 to 3.91.	Sludi
186	Primary Analysis	as 10.1136/bmjopen-2012-002280 on 14 Protected by copyright, includingt, includingt, for Formatted: Font: Times New Roman, 19 for Bold
187	The overall analysis of the 12 studies examined prostate cancer, comparing the highest	5 2
188	with the lowest ALA intake category. Seven studies reported a protective effect of ALA intake	Aay 2013. Dow Enseignemen ses related to
189	on prostate cancer, 2 <u>one</u> of which werewas significant, and the remaining five studies reported a	ateo
190	positive association, of which 3 were significant. Overall, although the relative risk was	d to
191	increased numerically by 8%, this increase in prostate cancer risk was not significant (RR: 1.08;	text Sup
192	95%CI: 0.90, 1.29, P=0.40) (Figure 2). However, there was evidence of considerable inter-study	Downloaded d to text and
193	heterogeneity (I ² =85%, P<0.00001). Systematic removal of each study during sensitivity	ur (A ur (A data
194	analyses did not suggest any single study was an influential outlier.	a mi mi
195	Subgroup Analyses	Formatted: Font: Times New Roman, 1109 Bold AI training, and simi
196	In an a priori subgroup analysis, we found no evidence of effect measure modification	mjopen.bmj.com/ on June 13, 2025 a Al training, and similar technologies
197	according to study design (P for heterogeneity= 0.331). There remained significant unexplained	ain an b
198	heterogeneity within each type of study design. In case control studies (n=7), the summary RR	(Ģ. <mark>∃</mark> . a o
199	was 1.30 (95%CI: 0.81, 2.07, P=0.27), with substantial inter-study heterogeneity (1 ² =90%,	nd s
200	P<0.00001) (Figure 3). Removal of no single study during sensitivity analyses explained the	sim on
201	heterogeneity. In prospective studies alone (n=5), no association between ALA intake and	June lar teo
202	prostate cancer risk was revealed (RR: 0.95; 95%CI: 0.84, 1.09, P=0.48) (Figure 5) but there	ichn 3,
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204	that removal of the study by Giovannucci et al. ²¹ eliminated heterogeneity with prospective	yies at
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P=0.02) (Figure 6). Neither Begg's (P>0.165) nor Egger's (P>0.527) tests revealed evidence of publication bias, however, one study by Ramon et al.⁴² had an unusually large effect with a small standard error.

Discussion

Case-Control Studies

In an *a priori* meta-regression, we found no evidence of effect measure modification according to study design (P for heterogeneity= 0.331). There remained significant unexplained heterogeneity within each type of study design. In case-control studies (n=7), the summary RR was 1.30 (95%CI: 0.81, 2.07, P=0.27), with considerable inter-study heterogeneity (I^2 =90%, P<0.00001) (**Figure 3**). Systematic removal of each individual study during sensitivity analyses did not explain the heterogeneity. Removal of the 2 case-control studies by Ramon et al.⁴⁵, De Stefani et al.³² that reported risk estimates larger than 2 standard deviations from the pooled RR estimate reduced the inter-study heterogeneity (I^2 =68%, P=0.01) but did not eliminate it (**Figure** 4). The overall association became weakly protective but was not significant (RR=0.93; 95%CI: 0.69,1.25, P=0.64) (**Figure 4**). Removal of the 3 case-control studies by Ramon et al.⁴⁵, De Stefani et al.³², and Bidoli et al.⁵⁰ that had risk estimates outside the 95% CI of the pooled RR estimate, eliminated heterogeneity in the case-control studies (I^2 =11%, P=0.34), but the overall non-significant association between ALA intake and prostate cancer risk remained (RR=1.08; 95%CI: 0.86,1.36, P=0.49) (**Figure 5**).

Prospective Studies

In prospective studies alone (n=5), no association between ALA intake and prostate cancer risk was revealed (RR: 0.95; 95%CI: 0.84, 1.09, P=0.48) (**Figure 6**) but there existed substantial inter-study heterogeneity (I^2 =69%, P=0.01). Sensitivity analyses showed that removal of the study by Giovannucci et al. ²¹ eliminated heterogeneity with prospective studies (I^2 =8%, P=0.35) and made the protective effect significant (RR=0.91; 95%CI: 0.83,0.99, P=0.02) (**Figure 7**). Duration of follow-up in prospective studies was found to be positively but not significantly associated with the magnitude of relative risk (r=0.47).

Publication Bias

13	10
Neither Begg's (P>0.165) nor Egger's (P>0.527) tests revealed evi	dence of publication
bias, however, one study by Ramon et al. ⁴⁵ had an unusually large effect	with a small standard
error.	

DISCUSSION

Summary of Results

The present meta-analysis of 12 observational studies (7 case-control and 5 prospective) comparing the highest with the lowest categories of dietary ALA intake demonstrated nonsignificant heterogeneous effects of ALA on prostate cancer risk. Overall, there was no significant association between ALA intake and risk of prostate cancer. The subgroup analysis of case control studies alone showed a positive non-significant association, but with substantial heterogeneity. However, upon removal of the studies by De Stefani et al.³² and Ramon et al. $\frac{4245}{2}$, which reported large odds ratios greater than 3 but were still within 2 standard deviations of the mean effect, the association became weakly protective with decreased heterogeneity. When examining the prospective studies alone, the association between ALA intake and prostate cancer risk was weakly protective and after removal of the study by Giovannucci et al.²¹ became significantly protective with no heterogeneity.

The results from the prospective studies are similar to those of previously published findings that examined only prospective studies $\frac{46}{7}$. Our study additionally investigated the association between dietary ALA intake and prostate cancer risk among case-control studies and reached a similar conclusion although the case control studies suggested an element of increased risk, which was dependent on the inclusion of two studies with very high odds ratios, the reasons for which are difficult to explain.

Variation in Heterogeneity and the Effect of ALA between Studies

In our study, different findings in the individual studies reviewed and inter-study heterogeneity may be explained by a number of factors: variation in ALA consumption and sources of ALA as a result of the population's dietary patterns, differing sources of ALA, variation in ALA exposure levels, or use of different FFQs and food databases, variation in adjustment factors, and difference in follow-up times among prospective studies.

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Variation in ALA Consumption and Sources, and Population Dietary Patterns. In the Netherlands, the chief sources of ALA include margarine (25% of daily intake), meat (11%), bread (10%), and vegetables (8%)³³, whereas in the United States, major sources of ALA come from mayonnaise, creamy salad dressings, margarine, butter, beef, pork, lamb, and oil and vinegar-based dressings²⁵. Interestingly, the prospective study from the Netherlands reported a weak protective effect of ALA intake on prostate cancer risk ²⁰, but the most recent study from the United States reported a 25% increase in risk ²¹. This difference may be due to the nature of the foods that contain ALA since in the United States, the sources of ALA are not the "healthy" sources where ALA is naturally found (e.g. flaxseed, walnuts, and canola oil), but rather profiled an unhealthy diet (e.g. canola oil in the form of mayonnaise and creamy salad dressings), which may be indicative of a less healthy lifestyle and this in itself may contribute to an increased risk of prostate cancer independent of ALA intake levels.⁶¹⁶². In addition, in the case-control studies from Uruguay³² and Spain⁴²⁴⁵ that showed the largest increases in prostate cancer risk demonstrated that meat, and not vegetable, was the major source of ALA. When these two studies were removed from the analysis of the case-control studies, the effect of ALA intake on prostate cancer changed from a weakly positive to a weakly protective effect. Compared with the other studies from Europe and the United States, there is a much higher consumption of meat in Spain ⁴⁷⁶³ and Uruguay, with Uruguay having the highest meat consumption per capita in the world $\frac{48.64}{7}$. An earlier analysis of the Health Professionals Follow-up Study cohort ²⁵ supports this positive association between red meat consumption and prostate cancer risk. FurtherFurthermore, the two studies from Spanish-speaking countries also investigated the effect of animal fat on prostate cancer and both found significant positive associations. The Uruguayan study ³² observed an almost 3 times increased risk of prostate cancer at the highest level of ALA derived from animal sources and the Spanish study 42 revealed that the highest level of animal fat intake was associated with 2 times the risk of developing prostate cancer. These findings indicate that high meat intake rather than high ALA could explain ALA's apparent adverse effect on prostate cancer. A further that at the highest level of ALA intake derived from animal sources resulted in almost 3 times the risk of developing prostate cancer and the Spanish study ⁴⁵ revealed that the highest level of animal fat intake was

associated with 2 times the risk. These findings indicate that high meat intake rather than high ALA may explain ALA's apparent adverse effect on prostate cancer. In further support of this

idea, the study by Bidoli et al.⁵⁰ demonstrated a significant protective association between ALA and prostate cancer risk in an Italian population where ALA is mainly derived from olive oil ⁶⁵ and the diet is rich in raw vegetables ⁵⁰ rather than meat, profiling an overall more "healthy" diet.

An explanation for the apparent association of prostate cancer incidence with vegetable sources of ALA may be that in addition those who follow healthy lifestyles with increased plant ALA sources may undergo more frequent prostate specific antigen (PSA) testing and therefore have early prostate cancer detection. In this respect it has been found that higher whole grain intake was also associated with increased prostate cancer risk. However, when frequency of PSA screening was accounted for, the association of whole grains with prostate cancer incidence disappeared ⁴⁹, ⁶⁶. These studies indicate the importance of not only identifying the dietary sources of ALA, but taking into account what the nature of the foods may indicate in terms of diet and lifestyle since these also may affect prostate cancer risk.

Variation in ALA Exposure Levels.

Another important aspect to consider is the differing exposure levels between the studies. Each study had different cut-offs for each quantile, which makes a true comparison of ALA intake exposure difficult since some studies had higher levels of ALA in their highest intake quantile than others. Further, some studies did not adequately define the absolute upper and/or lower limits of ALA intake ^{21 32 4350} and one study did not report numerical exposure levels.⁴¹. Two studies, one from Spain ⁴² and one study did not report numerical exposure levels.⁴⁹. Two studies, one from Spain ⁴⁵ and one from the Netherlands ²⁰, with the largest adequately defined upper and lower limits of ALA exposure ranges, paradoxically reported the second highest and the second lowest risk of developing prostate cancer, respectively. Since the studies with the greatest range of exposure do not necessarily show the greatest effects, dietary variation in the levels of exposure does not appear to explain differences among the studies, thereby making differences in dietary sources of ALA of more importance especially in relation to meat consumption in Western countries.

Lastly, in

Variation in FFQs and Food Databases.

<u>In</u> terms of utilizing different FFQs and food databases, each study used a different dietary FFQ. ALA content of processed food can vary, which can be of concern when using food

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databases to translate food intake into fatty acid intake. For example, the ALA content of 12	
margarines available in Australia range from 0.2% to $5.9\%_{A}^{\frac{5967}{2}}$.	Field Code Changed
Variation in Adjustment Factors.	Ticla coac changea
Although all the studies reported adjusted RRs or ORs, the adjustment factors were not	
consistent among the studies. Some of the adjustment factors in these studies included age,	
smoking history, physical activity level, BMI, family history of prostate cancer, history of	
diabetes mellitus, race, education, socioeconomic status, area of residence and intakes of total	
calories, fat, processed meat, fish, lycopene, and vitamin E supplements. Currently, the most	
well-established risk factors for prostate cancer are age, family history of the disease, and	
race/ethnicity ⁶⁸ and consequently are the most important adjustment factors. Only 4 ^{20-22 52} of the	
12 included studies adjusted for all of these 3 factors. The studies conducted by Park et al. ¹⁹ and	
Mannisto et al. ²⁴ did not adjust for age, which is by far the strongest predictor of prostate cancer	
incidence and death ⁶⁸ . A family history of prostate cancer has been shown to increase the risk of	
diagnosis and death and this factor was not adjusted for in studies by Hedelin et al. ⁵¹ , Andersson	
et al. 48, and Mannisto et al. 24 Race is a prostate cancer risk factor and prognostic factor, with	
African-American or Black men being at increased risk, and this was not adjusted for in the	
studies by Bidoli et al. ⁵⁰ , De Stefani et al. ³² , Ramon et al. ⁴⁵ , and Meyer et al. ⁴⁹ Differences in	
adjustment among the included studies, particularly with respect to the important factors of age,	
family history of prostate cancer, and race could result in differences in risk estimates, thereby	
contributing to inter-study heterogeneity.	
Variation in Follow-up Duration.	
Follow-up time may also have an effect on heterogeneity, especially since the study by	
Giovannucci et al. ²¹ had the longest follow-up duration (16 years). Comparing previous	
prospective studies following the same cohort ^{23 25} with this most recent study ²¹ , demonstrates a	
shift over time (total of 12 years) from a non-significant to a significant positive association	
between ALA intake and prostate cancer. So, the heterogeneity induced by this study may	
indicate that follow-up duration is positively related to the strength of the association between	
ALA and prostate cancer risk. After investigating this suggestion, the effect of follow-up	
duration on relative risk among the prospective studies was found to be positively, but not	
significantly correlated (r=0.47).	

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59	Overall Non-significant	
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1	Reasons for the Lack of Effect of ALA	Formatted: Font: Not Italic
2	The overall effect of ALA on prostate cancer was found to be non-significant and but may	
	be attributed toresult from a number of factors including ALA exposure levels that are within	
	health guidelines, confounding from other polyunsaturated fatty acids, and the difference in	
,	effect of ALA on mortality versus incidence.	
)	The mean dietary ALA intake levels observed in these studies were all within the dietary	
,	reference intake (DRI) range of 1.1 to 1.6 g/d 5469 , suggesting that ALA may not increase the risk	
	of cancer more than any other nutrient which provides a stimulus topromoting cell growth-and.	
)	<u>Rather</u> , since ALA is a nutrient <u>deficient</u> in which the Western diet is deficient $\frac{5270}{10}$, it may be that	
)	a deficiency prevents theinhibits all cell growth, including tumour growth, instead of cancer	
	rather than anadequate or excess levels causing prostate cancer growth.	
	Another issue to consider is confounding from other polyunsaturated fatty acids such as	
	omega-6 or other omega-3 fatty acids (eicosapentaenoic and docosahexaenoic fatty acids) that	
	might affect ALA metabolism ⁵³⁷¹ and consequently may introduce bias. The case-control study	
	from the United States ⁴⁵⁵² demonstrated this as there was no significant association between	
	ALA, omega-3, or omega-6 fatty acids and prostate cancer risk individually, but the highest	
	dietary ratio of omega-6/omega-3 fatty acids was significantly associated with increased risk of	
	high grade prostate cancer.	
	Finally, our analysis involved cancer incidence notrather than mortality and ALA, and	
	mostamong other factors includingsuch as energy intake, height, body mass index, calcium, and	
	smoking, are <u>also</u> associated with cancer mortality 21 . The study by De Stefani et al. 32 , which	
	was the only study that defined cases solely as advanced prostate cancer, had the highest risk	
	estimate of prostate cancer, indicating that ALA may be strongly associated with disease severity	
	rather than incidence. In support of this point, the prospective study by Giovannucci et al. ²¹	
	found that higher ALA intake was more strongly associated with increased risk of fatal prostate	
	cancer than with incident. However, three other prospective studies did not find any difference	
	between the effects of ALA on incident or advanced prostate cancer cases ^{19 20 22} . From these	
	mixed findings, it is unclear whether ALA is associated with severity of prostate cancer, but	
)	determining whether ALA impacts prostate cancer incidence or progression is an important	

Limitations-and Possible Sources of Heterogeneity

In considering the limitations The first limitation of the meta-analysis, it should be noted is that all data currently available for inclusion come from epidemiological studies since there are no data from randomized controlled trials due to ethical concerns. InterpretationSecond, interpretation of the analyses iswas complicated by the evidence of considerable heterogeneity among the studies, therefore a number of potential contributing which as discussed above may have resulted from differences in ALA sources and population dietary patterns, ALA exposure levels, FFQs and food databases, adjustment factors should be considered. First, and duration of follow-up. There are also inherent limitations in the studies included based on study design should be taken into account. The association between ALA intake and prostate cancer risk was stronger overall in the case-control studies than in the prospective. However, since case control studies collect dietary intake information after disease development there is the possibility of recall bias, whereas prospective studies collect intake information before disease diagnosis. Secondly, follow up time could studies. However, there is the possibility of recall bias in casecontrol studies, as dietary intake information is collected after disease development. also have an effect on heterogeneity, especially since the study by Giovannucci et al.²¹ had the longest follow-up duration (16 years). Comparing previous prospective studies following the same cohort.^{23,25} with this most recent study.²¹, demonstrates a shift over time (total of 12 years) from

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a non-significant to a significant positive association between ALA intake and prostate cancer. So, the heterogeneity induced by this study may indicate that follow up duration is positively related to the strength of the association between ALA and prostate cancer risk. After investigating this suggestion, the effect of follow up duration on relative risk among the prospective studies was found to be positively, but not significantly correlated (r=0.47).

Conclusion

CONCLUSION

In conclusion, these findings provide no clear evidence of an association between dietary ALA intake and prostate cancer risk. Further, since these observational studies that can only show an-association between ALA intake and prostate cancer-are observational and, possible causation iswould be difficult to establish. Therefore, additional research from epidemiological, clinical, and in vitro studies are required to elucidate whether ALA has a promotional-or-, inhibitory, or no effect on prostate cancer risk and development. For the present, no significant association has been found and where any support of a positive effect was seen, red meat sources have been strongly implicated. The source of ALA appears to be of importance, particularly identifying whether it is from animal or vegetable sources, as ALA may be a marker for higher meat and fat intake in some countries both of which have been associated with increased prostate cancer risk. Attention should also be paid to the effect of ALA on prostate cancer progression to address the issues of specific vulnerability identified in the studies of $^{21 32}$. However, resolving the relation of dietary intake of ALA to prostate cancer risk is likely to continue to be difficult to resolve through randomized controlled trials will likely continue to be difficult due to the significant public health implications of reducing/eliminating a dietary fatty acid which is essential and has suggested heart health benefits. Of probably greater importance is determination of the sources of the fatty acid since ALA is associated in the North American diet with meat membranes and creamy salad dressings, which themselves may be markers of a suboptimal dietary pattern and lifestyle _____

Article Summary ARTICLE SUMMARY

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9	451	Article Focus
10 11	452	ALA is considered a cardioprotective nutrient, however some epidemiological studies
12	453	have suggested that dietary ALA intake increases the risk of prostate cancer
13	454	• A systematic review and meta-analysis of case-control and prospective studies was
14 15	455	conducted to investigate the association between dietary ALA intake and prostate cancer
16	456	risk
17 18	457	Key messages
19	458	• The present meta-analysis of 12 observational studies (7 case-control and 5 prospective)
20	459	comparing the highest with the lowest categories of dietary ALA intake demonstrated
21 22	460	overall no significant association between ALA intake and risk of prostate cancer
23	461	• The subgroup analysis of case control studies alone showed a positive non-significant
24 25	462	association, but with substantial heterogeneity. However, upon removal of the studies,
26	463	which reported large odds ratios, the association became weakly protective but remained
27 28	464	non-significant, with decreased heterogeneity
29	465	• The subgroup analysis of case control studies alone showed a positive non-significant
30 31	466	association, but with substantial heterogeneity, which suggests an element of increased
31 32	467	risk dependent on the inclusion of two studies with very high odds ratios, the reasons for
33	468	which are difficult to explain
34 35	469	Strengths and Limitations:
36	470	• This meta-analysis includes both prospective and case control studies to determine the
37 38	471	effect of ALA on prostate cancer
39	472	Possible confounders and sources of heterogeneity were discussed and explored in
40 41	473	relation to the results
41 42	474	• Interpretation of analyses was complicated by considerable heterogeneity among the
43	475	studies, which may be due to lack of randomized controlled trials, study design, and
44 45	476	follow-up durationvariation in ALA sources and dietary patterns, variation in ALA
46	477	exposure levels, differences in FFQs and food databases, variation in adjustment factors,
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ALA is considered a cardioprotective nutrient, however some epidemiological studies have suggested that dietary ALA intake increases the risk of prostate cancer. Although Carayol et al. conducted a meta-analysis on the effect of dietary ALA on prostate cancer in 2010, only prospective studies were analyzed and case-control studies were not included. Overall, we found no significant association between ALA intake and risk of prostate cancer. The results from the prospective studies were similar to those of previously published findings. However, the subgroup analysis of case control studies alone showed a positive non-significant association, but with substantial heterogeneity. The case control studies suggested an element of increased risk, which was dependent on the inclusion of two studies with very high odds ratios, the reasons for which are difficult to explain. Additional research from epidemiological, clinical, and in vitro studies are required to elucidate whether ALA has a promotional, null, or inhibitory effect on prostate cancer risk and development.

Authorship

AUTHORSHIP

All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. Details of Contributors: AJC was involved in the conception and design, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content, and final approval of the version to be published. JLS was involved in the conception and design, some analysis, and revising the article critically for important intellectual content. RS was involved in revising the article critically for important intellectual content. GE was involved in the conception and design and in revising the article critically for important intellectual content. DJAJ was in the conception and design, revising the article critically for important intellectual content, and final approval of the version to be published.

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498	COMPETING INTEREST DECLARATION		yrigh
499	All authors have completed the Unified Competing Interest form at		it, in
500	www.icmje.org/coi disclosure.pdf (available on request from the corresponding author) and		clud
501	declare that (1) AJC, JLS, RS, GE, and DJAJGE have not had financial support from any		ling
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505	submitted work; and (4) AJC, JLS, RS, GE, and DJAJ have no non-financial interests that may		Enseignement Superieur ses related to text and da
506	be relevant to the submitted work."and GE have no non-financial interests that may be relevant		ent :
507	to the submitted work. DJAJ has served on the Scientific Advisory Board of Sanitarium		Supe Supe
508	Company, Agri-Culture and Agri-Food Canada (AAFC), Canadian Agriculture Policy Institute		ment Superieur (ABES) . of to text and data mining, A
509	(CAPI), California Strawberry Commission, Loblaw Supermarket, Herbal Life International,		ır (A data
510	Nutritional Fundamental for Health, Pacific Health Laboratories, Metagenics, Bayer Consumer		min
511	Care, Orafti, Dean Foods, Kellogg's, Quaker Oats, Procter & Gamble, Coca-Cola, NuVal Griffin		ing,
512	Hospital, Abbott, Pulse Canada, Saskatchewan Pulse Growers, and Canola Council of Canada;		_
513	received honoraria for scientific advice from Sanitarium Company, Orafti, the Almond Board of		rain
514	California, the American Peanut Council, International Tree Nut Council Nutrition Research and		ing,
515	Education Foundation and the Peanut Institute, Herbal Life International, Pacific Health		and
516	Laboratories, Nutritional Fundamental for Health, Barilla, Metagenics, Bayer Consumer Care,		l training, and similar te
517	Unilever Canada and Netherlands, Solae, Oldways, Kellogg's, Quaker Oats, Procter & Gamble,		training, and similar technologies
518	Coca-Cola, NuVal Griffin Hospital, Abbott, Canola Council of Canada, Dean Foods, California		techn
519	Strawberry Commission, Haine Celestial, Pepsi, and Alpro Foundation; has been on the speakers		Inol
520	panel for the Almond Board of California; received research grants from Saskatchewan Pulse		ogie
521	Growers, the Agricultural Bioproducts Innovation Program (ABIP) through the Pulse Research		ູ່
522	Network (PURENet), Advanced Food Materials Network (AFMNet), Loblaw, Unilever, Barilla,		ologies.
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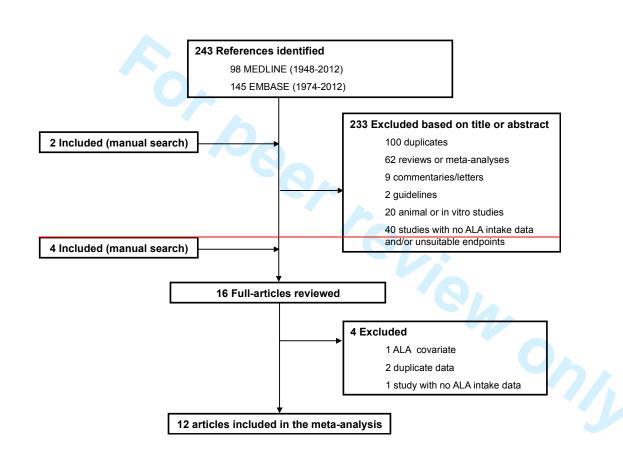
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8 9	523	Almond Board of California, Coca-Cola, Solae, Haine Celestial, Sanitarium Company, Orafti,
9 10	525 524	International Tree Nut Council Nutrition Research and Education Foundation and the Peanut
11	525	Institute, the Canola and Flax Councils of Canada, Calorie Control Council, Canadian Institutes
12 13		
14	526	of Health Research, Canada Foundation for Innovation, and the Ontario Research Fund; and
15	527	received travel support to meetings from the Solae, Sanitarium Company, Orafti, AFMNet,
16 17	528	Coca-Cola, The Canola and Flax Councils of Canada, Oldways Preservation Trust, Kellogg's,
18	529	Quaker Oats, Griffin Hospital, Abbott Laboratories, Dean Foods, the California Strawberry
19	530	Commission, American Peanut Council, Herbal Life International, Nutritional Fundamental for
20 21	531	Health, Metagenics, Bayer Consumer Care, AAFC, CAPI, Pepsi, Almond Board of California,
22	532	Unilever, Alpro Foundation, International Tree Nut Council, Barilla, Pulse Canada, and the
23 24	533	Saskatchewan Pulse Growers. DJAJ's wife is a director of Glycemic Index Laboratories,
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Study	Country of Origin	Study Design	Sample size	Age (years)	Incident Cases	Follow-up (years)	Exposure level (g/d)	Relative Risk or Odds Ratio	95%Cl
Andersson et al. 1996 [38]	Sweden	Case-control	526 cases/536 controls	<80	-	-	0.817 - 1.352	0.93	0.65-1.32
Vleyer et al. 1997 [39]	Canada	Case-control	215 cases/593 controls	<u>≥</u> 45	-	-	-	0.98	0.54-1.78
Schuurman et al. 1999 [18]*	Netherlands	Nested case-cohort	58279 (1525 subcohort)	55-69	642	6.3	0.7 - 2.1	0.76	0.66-1.04
De Stefani et al. 2000 [29]	Uruguay	Case-control	217 cases/431 controls	40-89	-	-	⊴0.8 - ≥1.5	3.91	1. <mark>50-10.1</mark>
Ramon et al. 2000 [40]	Spain	Case-control	217 cases/434 controls	<60-80	-	-	0.72 - 2.1	3.1	2.2-4.7
Mannisto et al. 2003 [22]*	Finland	Nested case-control	198 cases/198 controls	50-69	246	5-8	1.0 - 2.3	1.16	0.64-2.13
Biddi et al. 2005 [41]	Italy	Case-control	1294 cases/1451 controls	45-74	-	-	mean 1.6	0.7	0.6-0.9
Koralek et al. 2006 [20]*	United States	Prospective cohort	29,592	55-74	1898	5.1	1.09 - 1.75	0.94	0.81-1.09
-ledelin et al. 2007 [42]	Sweden	Case-control	1499 cases/1130 controls	mean 67.3	-	-	0.05 - 0.60	1.35	0.99-1.84
Giovannucci et al. 2007 [19]*	United States	Prospective cohort	47,750	40-75	3544	16	<0.79 - ≥1.32	1.12	1.01-1.25
Park et al. 2007 [17]*	United States	Prospective cohort	82,483	<u>≻</u> 45	4404	8	1.1 - 2.14†	0.92	0.84-1.02
Milliams et al. 2011 [43]	United States	Case-control	79 cases/187 controls	≥18	NJ	-	≤1.0 - 4.156†	0.82	0.41-1.65
[*] Prospective studies.									
Hased on a 2000 kcal diet.									
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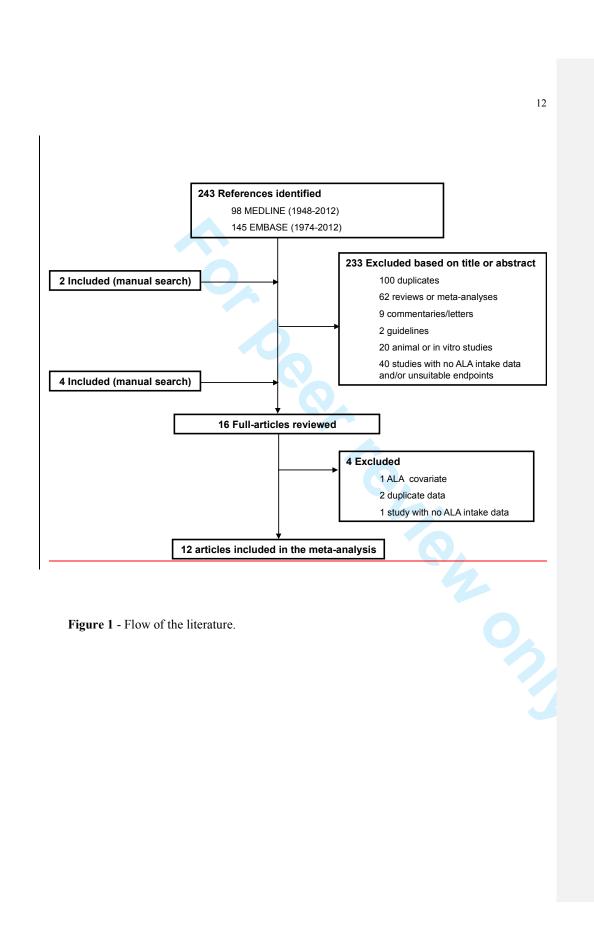
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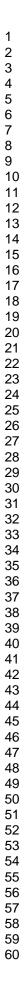
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Risk Ratio

Favours ALA Favours Control



Study or Subgroup	Weight	IV, Random, 95% C	I Year	IV, Random, 95% CI
Andersson 1996 [38]	8.4%	0.93 [0.65, 1.33]	1996	— — —
Meyer 1997 [39]	5.2%	0.98 [0.54, 1.78]	1997	
Schuurman 1999 [18]	10.5%	0.76 [0.61, 0.95]	1999	
De Stefani 2000 [29]	2.7%	3.91 [1.51, 10.15]	2000	
Ramon 2000 [40]	8.0%	3.10 [2.12, 4.53]	2000	
Mannisto 2003 [22]	5.1%	1.16 [0.64, 2.12]	2003	
Bidoli 2005 [41]	10.9%	0.70 [0.57, 0.86]		
Koralek 2006 [20]	11.6%	0.94 0.81, 1.09	2006	
Giovannucci 2007 [19]	12.1%	1.12 [1.01, 1.25]	2007	-
Hedelin 2007 [42]	9.1%	1.35 [0.99, 1.84]	2007	- - -
Park 2007 [17]	12.2%	0.92 [0.83, 1.01]		-
Williams 2011 [43]	4.3%	0.82 [0.41, 1.64]		
			2011	
Total (95% CI)	100.0%	1.08 [0.90, 1.29]		•
Heterogeneity: Tau ² = 0.	06 [.] Chi ² =	71.45 df = 11 (P < 0.0)	$(0001) \cdot 1^2 = 85\%$	+ + + + + + + + + + + + + + + + + + + +
Test for overall effect: Z				0.1 0.2 0.5 1 2 5 10
	0.01 (1	0.10)		Favours ALA Favours Control
		Risk Ratio		Risk Ratio
Study or Subgroup	Weight	Risk Ratio IV, Random, 95% CI	Year	Risk Ratio IV, Random, 95% CI
Study or Subgroup Andersson 1996 [48]	Weight 8.4%		Year 1996	
Andersson 1996 [48] Meyer 1997 [49]	8.4% 5.2%	IV, Random, 95% CI 0.93 [0.65, 1.33] 0.98 [0.54, 1.78]	1996 1997	
Andersson 1996 [48] Meyer 1997 [49] Schuurman 1999 [20]	8.4% 5.2% 10.5%	IV, Random, 95% CI 0.93 [0.65, 1.33] 0.98 [0.54, 1.78] 0.76 [0.61, 0.95]	1996 1997 1999	
Andersson 1996 [48] Meyer 1997 [49] Schuurman 1999 [20] De Stefani 2000 [32]	8.4% 5.2% 10.5% 2.7%	IV, Random, 95% CI 0.93 [0.65, 1.33] 0.98 [0.54, 1.78] 0.76 [0.61, 0.95] 3.91 [1.51, 10.15]	1996 1997 1999 2000	
Andersson 1996 [48] Meyer 1997 [49] Schuurman 1999 [20] De Stefani 2000 [32] Ramon 2000 [45]	8.4% 5.2% 10.5% 2.7% 8.0%	IV, Random, 95% CI 0.93 [0.65, 1.33] 0.98 [0.54, 1.78] 0.76 [0.61, 0.95] 3.91 [1.51, 10.15] 3.10 [2.12, 4.53]	1996 1997 1999 2000 2000	
Andersson 1996 [48] Meyer 1997 [49] Schuurman 1999 [20] De Stefani 2000 [32] Ramon 2000 [45] Mannisto 2003 [24]	8.4% 5.2% 10.5% 2.7% 8.0% 5.1%	IV, Random, 95% CI 0.93 [0.65, 1.33] 0.98 [0.54, 1.78] 0.76 [0.61, 0.95] 3.91 [1.51, 10.15] 3.10 [2.12, 4.53] 1.16 [0.64, 2.12]	1996 1997 1999 2000 2000 2003	
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Andersson 1996 [48] Meyer 1997 [49] Schuurman 1999 [20] De Stefani 2000 [32] Ramon 2000 [45] Mannisto 2003 [24] Bidoli 2005 [50] Koralek 2006 [22]	8.4% 5.2% 10.5% 2.7% 8.0% 5.1% 10.9% 11.6%	IV, Random, 95% CI 0.93 [0.65, 1.33] 0.98 [0.54, 1.78] 0.76 [0.61, 0.95] 3.91 [1.51, 10.15] 3.10 [2.12, 4.53] 1.16 [0.64, 2.12] 0.70 [0.57, 0.86] 0.94 [0.81, 1.09]	1996 1997 1999 2000 2000 2003 2005 2005	
Andersson 1996 [48] Meyer 1997 [49] Schuurman 1999 [20] De Stefani 2000 [32] Ramon 2000 [45] Mannisto 2003 [24] Bidoli 2005 [50] Koralek 2006 [22] Hedelin 2007 [51]	8.4% 5.2% 10.5% 2.7% 8.0% 5.1% 10.9% 11.6% 9.1%	IV, Random, 95% CI 0.93 [0.65, 1.33] 0.98 [0.54, 1.78] 0.76 [0.61, 0.95] 3.91 [1.51, 10.15] 3.10 [2.12, 4.53] 1.16 [0.64, 2.12] 0.70 [0.57, 0.86] 0.94 [0.81, 1.09] 1.35 [0.99, 1.84]	1996 1997 1999 2000 2000 2003 2005 2005 2006 2007	
Andersson 1996 [48] Meyer 1997 [49] Schuurman 1999 [20] De Stefani 2000 [32] Ramon 2000 [45] Mannisto 2003 [24] Bidoli 2005 [50] Koralek 2006 [22] Hedelin 2007 [51] Park 2007 [19]	8.4% 5.2% 10.5% 2.7% 8.0% 5.1% 10.9% 11.6% 9.1% 12.2%	IV, Random, 95% CI 0.93 [0.65, 1.33] 0.98 [0.54, 1.78] 0.76 [0.61, 0.95] 3.91 [1.51, 10.15] 3.10 [2.12, 4.53] 1.16 [0.64, 2.12] 0.70 [0.57, 0.86] 0.94 [0.81, 1.09] 1.35 [0.99, 1.84] 0.92 [0.83, 1.01]	1996 1997 1999 2000 2000 2003 2005 2006 2007 2007	
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Andersson 1996 [48] Meyer 1997 [49] Schuurman 1999 [20] De Stefani 2000 [32] Ramon 2000 [45] Mannisto 2003 [24] Bidoli 2005 [50] Koralek 2006 [22] Hedelin 2007 [51] Park 2007 [19] Giovannucci 2007 [21] Williams 2011 [52]	8.4% 5.2% 10.5% 2.7% 8.0% 5.1% 10.9% 11.6% 9.1% 12.2% 12.1% 4.3% 100.0%	IV, Random, 95% CI 0.93 [0.65, 1.33] 0.98 [0.54, 1.78] 0.76 [0.61, 0.95] 3.91 [1.51, 10.15] 3.10 [2.12, 4.53] 1.16 [0.64, 2.12] 0.70 [0.57, 0.86] 0.94 [0.81, 1.09] 1.35 [0.99, 1.84] 0.92 [0.83, 1.01] 1.12 [1.01, 1.25] 0.82 [0.41, 1.64] 1.08 [0.90, 1.29]	1996 1997 1999 2000 2000 2003 2005 2005 2006 2007 2007 2007 2011	IV, Random, 95% CI

Risk Ratio

Figure 2 – Pooled effect of dietary ALA intake on prostate cancer risk in case-control, nested case-control, nested case-cohort, and cohort studies. Relative Risk (RR) with 95% CI, study weights, and pooled effect estimates were generated using the general inverse variance method with random effects models (RevMan 5.1, Cochrane Library software, Oxford, UK). Inter-study heterogeneity was tested by Cochrane's Q (Chi²) at a significance level of P<0.10 and quantified by I², where I² \geq 50 % is considered to be evidence of substantial heterogeneity and \geq 75%, considerable heterogeneity $^{3455}_{*}$.

Test for overall effect: Z = 0.84 (P = 0.40)

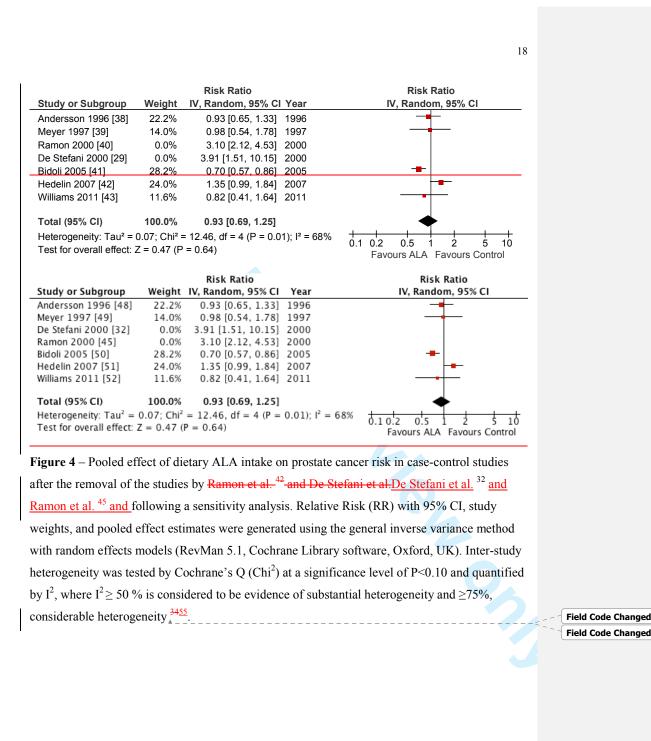
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		Risk Ratio		Risk Ratio
Study or Subgroup	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% CI
Andersson 1996 [38]	15.7%	0.93 [0.65, 1.33]	1996	
Meyer 1997 [39]	13.5%	0.98 [0.54, 1.78]	1997	_
Ramon 2000 [40]	15.5%	3.10 [2.12, 4.53]	2000	_
De Stefani 2000 [29]	10.0%	3.91 [1.51, 10.15]	2000	
Bidoli 2005 [41]	16.7%	0.70 [0.57. 0.86]	2005	
Hedelin 2007 [42]	16.1%	1.35 [0.99, 1.84]	2007	
Williams 2011 [43]	12.5%	0.82 [0.41, 1.64]	2011	
Total (95% Cl)	100.0%	1.30 [0.81, 2.07]		•
Heterogeneity: Tau ² = (0.33; Chi² =	= 57.44, df = 6 (P < 0.0	0001); l ² = 90% +	
Test for overall effect: 2	,	, ,	0.	1 0.2 0.5 1 2 5 10
	,	,		Favours ALA Favours Control
		Risk Ratio		Risk Ratio
Study or Subgroup	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
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Hedelin 2007 [51]	16.1%	1.35 [0.99, 1.84]	2007	
Williams 2011 [52]	12.5%	0.82 [0.41, 1.64]	2011	
Total (95% CI)	100.0%	1.30 [0.81, 2.07]		•
Heterogeneity: Tau ² =	0.33; Chi ²	= 57.44, df = 6 (P <	0.00001 ; $I^2 = 90\%$	0.10.2 0.5 1 2 5 10
Test for overall effect: 2	Z = 1.10 (F	P = 0.27)		Favours ALA Favours Control
Figure 3 – Pooled et	ffect of d	ietary ALA intake	on prostate cance	r risk in case-control studies.
Dolotivo Diele (DD) -	with 050/	CL study waishts	and needed offer	t actimates were concreted
Relative KISK (KK) V	viiii 93%	Ci, study weights	, and pooled effec	t estimates were generated

Relative Risk (RR) with 95% CI, study weights, and pooled effect estimates were generated using the general inverse variance method with random effects models (RevMan 5.1, Cochrane Library software, Oxford, UK). Inter-study heterogeneity was tested by Cochrane's Q (Chi²) at a significance level of P<0.10 and quantified by I², where I² \geq 50 % is considered to be evidence of substantial heterogeneity and \geq 75%, considerable heterogeneity $\frac{3455}{2}$.

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		Rate Ratio	Rate Ratio
Study or Subgroup	Weight	IV, Random, 95% CI Year	IV, Random, 95% CI
Schuurman 1999 [18]	16.6%	0.76 [0.61, 0.95] 1999	
Mannisto 2003 [22]	4.1%	1.16 [0.64, 2.12] 2003	
Koralek 2006 [20]	23.4%	0.94 [0.81, 1.09] 2006	
Giovannucci 2007 [19]	27.5%	1.12 [1.01, 1.25] 2007	
Park 2007 [17]	28.4%	0.92 [0.83, 1.01] 2007	•
Total (95% CI)	100.0%	0.95 [0.84, 1.09]	•
Heterogeneity: Tau ² = 0.	.01; Chi² = 1	13.03, df = 4 (P = 0.01); l ² = 69%	+ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$
Test for overall effect: Z	= 0.70 (P =	0.48)	Favours ALA Favours Control

Figure 5 Pooled effect of dietary ALA intake on prostate cancer risk in prospective studies. Relative Risk (RR) with 95% CL study weights, and pooled effect estimates were generated using the general inverse variance method with random effects models (RevMan 5.1, Cochrane Library software, Oxford, UK). Inter-study heterogeneity was tested by Cochrane's Q (Chi²) at a significance level of P<0.10 and quantified by I^2 , where $I^2 \ge 50$ % is considered to be evidence of substantial heterogeneity and \ge 75%, considerable heterogeneity.³⁴.

		Rate Ratio	Rate Ratio
Study or Subgroup	Weight	IV, Random, 95% CI Year	IV, Random, 95% Cl
Schuurman 1999 [18]	12.8%	0.76 [0.61, 0.95] 1999	
Mannisto 2003 [22]	1.9%	1.16 [0.64, 2.12] 2003	
Koralek 2006 [20]	28.1%	0.94 [0.81, 1.09] 2006	+
Park 2007 [17]	57.1%	0.92 [0.83, 1.01] 2007	
Giovannucci 2007 [19]	0.0%	1.12 [1.01, 1.25] 2007	
Total (95% CI)	100.0%	0.91 [0.83, 0.99]	♦
Heterogeneity: Tau ² = 0.00; Chi ² = 3.27, df = 3 (P = 0.35); l ² = 8% Test for overall effect: Z = 2.28 (P = 0.02)			0.1 0.2 0.5 1 2 5 10 Favours ALA Favours Control

Figure 6

0		Risk Ratio		Risk Ratio
Study or Subgroup	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Andersson 1996 [48]	34.1%	0.93 [0.65, 1.33]	1996	
Meyer 1997 [49]	13.4%	0.98 [0.54, 1.78]	1997	
De Stefani 2000 [32]	0.0%	3.91 [1.51, 10.15]	2000	
Ramon 2000 [45]	0.0%	3.10 [2.12, 4.53]	2000	
Bidoli 2005 [50]	0.0%	0.70 [0.57, 0.86]	2005	
Hedelin 2007 [51]	42.5%	1.35 [0.99, 1.84]	2007	⊢∎ -
Williams 2011 [52]	10.0%	0.82 [0.41, 1.64]	2011	
Total (95% CI)	100.0%	1.08 [0.86, 1.36]		+
Heterogeneity: Tau ² = 0	0.01; Chi ²	= 3.37, df = 3 (P = 0)	$(.34); I^2 = 11\%$	
Test for overall effect: 2	Z = 0.70 (P	P = 0.49)		Favours ALA Favours Control

Figure 5 – Pooled effect of dietary ALA intake on prostate cancer risk in case-control studies after the removal of the studies by De Stefani et al. ³², Ramon et al. ⁴⁵, and Bidoli et al. ⁵⁰ and following a sensitivity analysis. Relative Risk (RR) with 95% CI, study weights, and pooled effect estimates were generated using the general inverse variance method with random effects models (RevMan 5.1, Cochrane Library software, Oxford, UK). Inter-study heterogeneity was tested by Cochrane's Q (Chi²) at a significance level of P<0.10 and quantified by I², where I² ≥ 50 % is considered to be evidence of substantial heterogeneity and ≥75%, considerable heterogeneity ⁵⁵.

		Rate Ratio		Rate Ratio
Study or Subgroup	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Schuurman 1999 [20]	16.6%	0.76 [0.61, 0.95]	1999	
Mannisto 2003 [24]	4.1%	1.16 [0.64, 2.12]	2003	-
Koralek 2006 [22]	23.4%	0.94 [0.81, 1.09]	2006	+
Park 2007 [19]	28.4%	0.92 [0.83, 1.01]	2007	
Giovannucci 2007 [21]	27.5%	1.12 [1.01, 1.25]	2007	-
Total (95% CI)	100.0%	0.95 [0.84, 1.09]		•
Heterogeneity: Tau ² = 0.	.01; Chi ² =	= 13.03, df = 4 (P = 0).01); I ² = 69%	
Test for overall effect: Z	= 0.70 (P	= 0.48)		Favours ALA Favours Control

Figure 6 – Pooled effect of dietary ALA intake on prostate cancer risk in prospective studies. Relative Risk (RR) with 95% CI, study weights, and pooled effect estimates were generated using the general inverse variance method with random effects models (RevMan 5.1, Cochrane Library software, Oxford, UK). Inter-study heterogeneity was tested by Cochrane's Q (Chi²) at a significance level of P<0.10 and quantified by I², where I² \geq 50 % is considered to be evidence of substantial heterogeneity and \geq 75%, considerable heterogeneity ⁵⁵.

		Rate Ratio		Rate Ratio
Study or Subgroup	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Schuurman 1999 [20]	12.8%	0.76 [0.61, 0.95]	1999	
Mannisto 2003 [24]	1.9%	1.16 [0.64, 2.12]	2003	
Koralek 2006 [22]	28.1%	0.94 [0.81, 1.09]	2006	↓
Park 2007 [19]	57.1%	0.92 [0.83, 1.01]	2007	–
Giovannucci 2007 [21]	0.0%	1.12 [1.01, 1.25]	2007	
Total (95% CI)	100.0%	0.91 [0.83, 0.99]		•
Heterogeneity: Tau ² = 0	.00: Chi ² =		35 : $I^2 = 8\%$	
Test for overall effect: Z				0.10.2 0.5 1 2 5 10 Favours ALA Favours Control

<u>Figure 7</u> – Pooled effect of dietary ALA intake on prostate cancer risk in prospective studies after the systematic removal of the study by Giovannucci et al. ²¹ following a sensitivity analysis.

Relative Risk (RR) with 95% CI, study weights, and pooled effect estimates were generated using the general inverse variance method with random effects models (RevMan 5.1, Cochrane Library software, Oxford, UK). Inter-study heterogeneity was tested by Cochrane's Q (Chi²) at a significance level of P<0.10 and quantified by I², where I² \ge 50 % is considered to be evidence of substantial heterogeneity and \ge 75%, considerable heterogeneity ³⁴⁵⁵.

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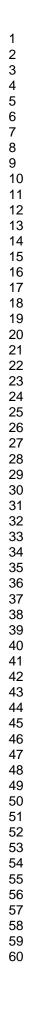
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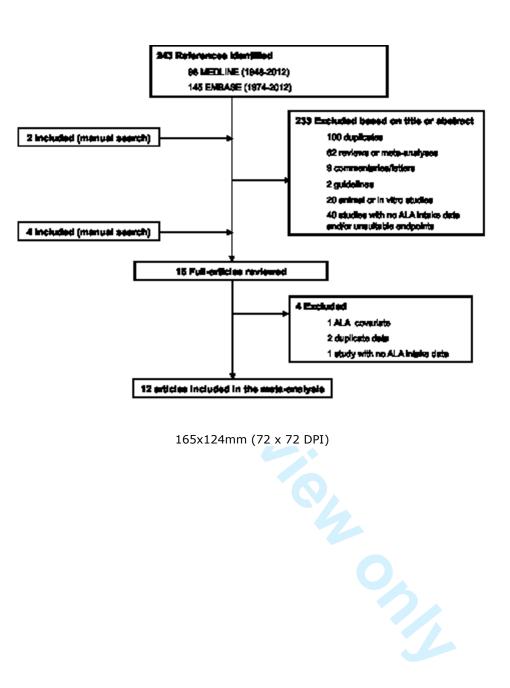
Stady	Country of Origin	Study Design	Bampio alco	Age (pears)	Cames	Pallan-ap (pears)	Expense level (g/d)	Relative Nation Odde Radio	MTK CI
Andersson al al. 1998 [25]	Svedan	Case-control	528 cares/638 carbole	<\$0		•	0.617 - 1.552	0.98	0.65-1.32
Neyer et al. 1997 [39]	Canada	Case-control	215 ceses/893 controls	546		•		0.98	0.54-1.76
Schaarmen at al. 1999 [18]*	Natharkanda	Nasted case cohort	58278 (1525 missolant)	55-64	842	8.3	67-21	0.76	0.66-1.04
De Stelani et al. 2000 [29]	Unguay	Case-control	217 cases/431 canbols	40-58	-	-	10.8-21.5	2.91	1.60-10.1
Remon et el. 2000 (40)	Spein	Case-control	217 ceses/434 controls	<80-80		•	0.72-2.1	3.1	2.34.7
Marmisto at al. 2006 [22]*	Finland	Neutral case-control	190 cases/198 cantrols	50-68	248	5-8	1.0 - 2.5	1.18	0.64-2.15
Bidol at al. 2005 [41]	liniy	Case-control	1284 cover/1451 controls	45-74	-	-	maan 1.8	0.7	0.60.8
Konsleik el al. 2006 [20]*	United States	Prospective exhert	29,692	68-74	1598	8.1	1.09 - 1.70	0.94	0.81-1.04
Heddelin at al. 2007 (42)	Sweden	Case-control	1489 curren/1130 controls	mean 67.2	-	-	0.05 - 0.60	1.35	0.89-1.84
Observed of al. 2007 [19]*	Unlind States	Prospective other:	47,750	40-75	3544	18	<0.79-21.52	1.12	1.01-1.20
Perk et el. 2007 [17]*	United States	Prospective echort	62,483	346	4404	8	1.1 - 2.14	0.92	0.54-1.02
Williams at al. 2011 [42]	Unlied States	Case-control	79 cases/187 cardrain	218	-	-	s1.0 - 4.168†	0.82	0.41-1.00
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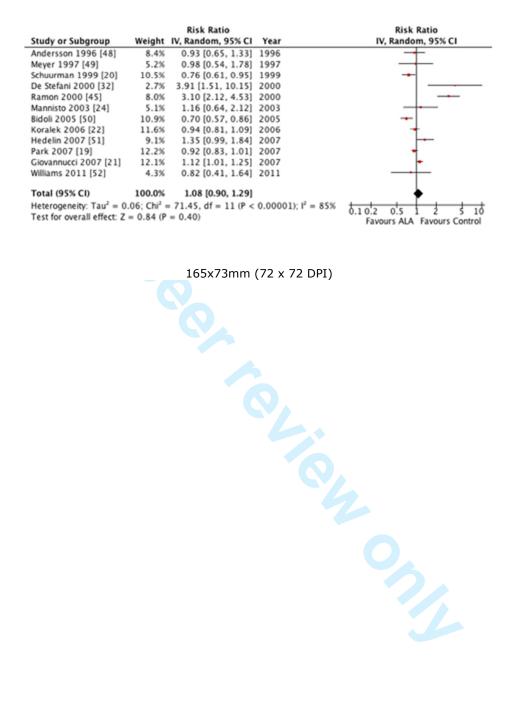
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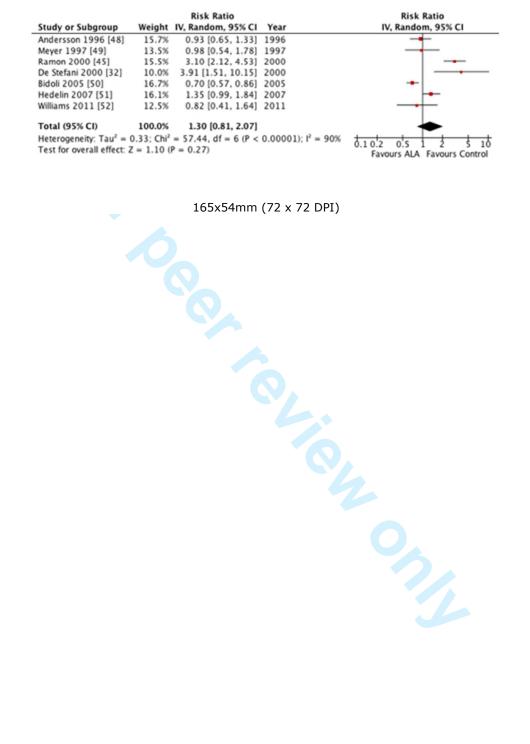


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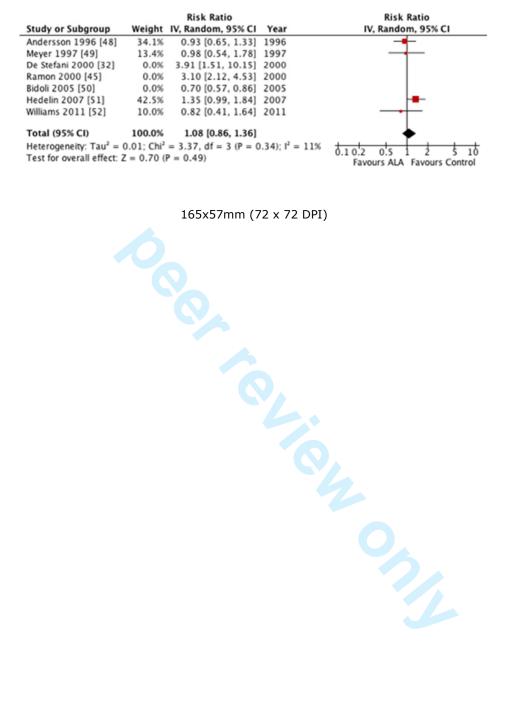
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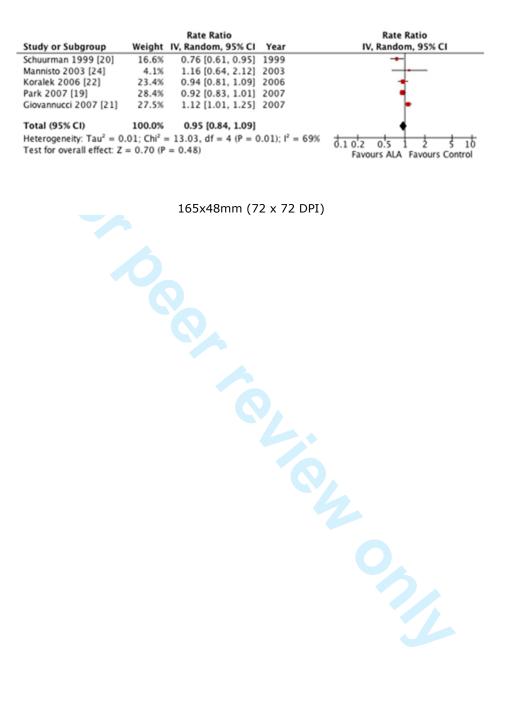
Study or Subgroup	Weight	Risk Ratio IV, Random, 95% CI	Year	Risk Ratio IV, Random, 95% CI
Andersson 1996 [48]	22.2%	0.93 [0.65, 1.33]	1996	
Meyer 1997 [49]	14.0%	0.98 [0.54, 1.78]	1997	
De Stefani 2000 [32]	0.0%	3.91 [1.51, 10.15]	2000	
Ramon 2000 [45]	0.0%	3.10 [2.12, 4.53]	2000	
Bidoli 2005 [50]	28.2%	0.70 [0.57, 0.86]	2005	
Hedelin 2007 [51]	24.0%	1.35 [0.99, 1.84]	2007	
Williams 2011 [52]	11.6%	0.82 [0.41, 1.64]	2011	
Total (95% CI)	100.0%	0.93 [0.69, 1.25]		
Heterogeneity: Tau ² = Test for overall effect: 2			0.01); I ² = 68%	0.1 0.2 0.5 1 2 5 10 Fayours ALA Fayours Control

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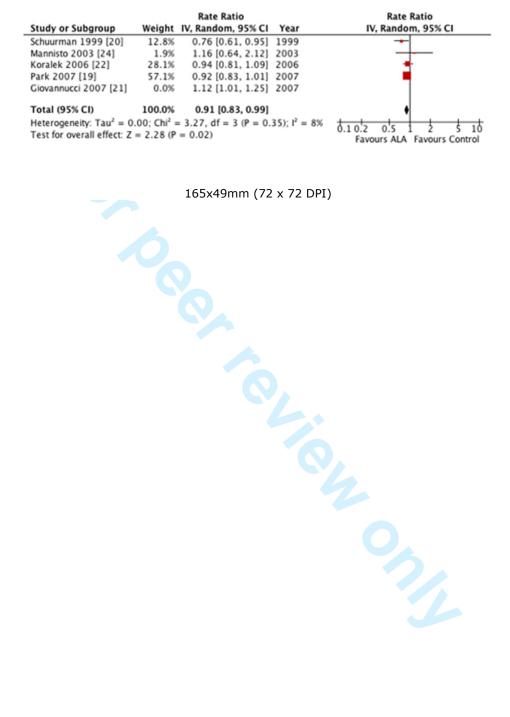


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Case-Control and Prospective Studies of Dietary Alpha-Linolenic Acid Intake and Prostate Cancer Risk: a Meta-Analysis

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10 11	4	Amanda J Carleton, MSc ^{1,2,3} ; John L Sievenpiper ^{1,2,4} , MD, PhD; Russell de Souza, ScD,
12	5	RD ^{1,2,5,7} ; Gail McKeown-Eyssen, PhD ^{2,6} ; David JA Jenkins, MD, PhD ^{1,2,3} .
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52 53	28	Text word count: 5300;
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56 57	30	Tables: 1; Figures: 5;
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2 3 4	32	ARTICLE SUMMARY
5 6 7	33	Article Focus
	34	• ALA is considered a cardioprotective nutrient, however some epidemiological studies
8 9	35	have suggested that dietary ALA intake increases the risk of prostate cancer
10 11	36	• A systematic review and meta-analysis of case-control and prospective studies was
12 13	37	conducted to investigate the association between dietary ALA intake and prostate cancer
14 15	38	risk
16	39	Key Messages
17 18	40	• The present meta-analysis of 12 observational studies (7 case-control and 5 prospective)
19 20	41	comparing the highest with the lowest categories of dietary ALA intake demonstrated
21 22	42	overall no significant association between ALA intake and risk of prostate cancer
23	43	• The subgroup analysis of case control studies alone showed a positive non-significant
24 25	44	association, but with substantial heterogeneity. However, upon removal of the studies,
26 27	45	which reported large odds ratios, the association became non-significantly protective with
28 29	46	decreased heterogeneity. The reasons for this result may be explained by the differing
30 31	47	sources of ALA
32	48	• The subgroup analysis of prospective studies alone showed a protective non-significant
33 34	49	association, but with substantial heterogeneity. However, removal of the study by
35 36	50	Giovannucci et al. ²¹ eliminated heterogeneity and the association became significantly
37 38	51	protective
39 40	52	
41	53	Strengths and Limitations:
42 43	54	• This meta-analysis includes both prospective and case control studies to determine the
44 45	55	effect of ALA on prostate cancer
46 47	56	• Possible confounders and sources of heterogeneity were discussed and explored in
48 49	57	relation to the results
50	58	• Interpretation of analyses was complicated by considerable heterogeneity among the
51 52	59	studies, which may be due to lack of randomized controlled trials, variation in ALA
53 54	60	sources and dietary patterns, variation in ALA exposure levels, differences in FFQs and
55 56	61	food databases, variation in adjustment factors, follow-up duration, and study design
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3 4	62	ABSTRACT
5 6	63	Background: ALA is considered a cardioprotective nutrient, however some epidemiological
7 8	64	studies have suggested that dietary ALA intake increases the risk of prostate cancer.
9 10	65	Objective: To conduct a systematic review and meta-analysis of case-control and prospective
11	66	studies investigating the association between dietary ALA intake and prostate cancer risk.
12 13	67	Data Sources: MEDLINE and EMBASE were searched for relevant prospective and case-
14 15	68	control studies.
16 17	69	Eligibility Criteria for Selecting Studies: We included all prospective cohort, case-control,
18	70	nested case-cohort, and nested case-control studies that investigated the effect of dietary ALA
19 20	71	intake on the incidence (or diagnosis) of prostate cancer and provided relative risk (RR), hazard
21 22	72	ratios (HR), or odds ratios (OR) estimates.
23 24	73	Design: Data were pooled using the generic inverse variance method with a random-effects
25 26	74	model from studies that compared the highest ALA quantile with the lowest ALA quantile. Risk
27	75	estimates were expressed as relative risk (RR) with 95% confidence intervals (CI). Heterogeneity
28 29	76	was assessed by χ^2 and quantified by I ² .
30 31	77	Results: Data from 5 prospective and 7 case-control studies were pooled. The overall RR
32 33 34	78	estimate showed ALA intake to be positively, but non-significantly associated with prostate
	79	cancer risk (1.08 [0.90 to 1.29], P=0.40, I ² =85%), but the interpretation was complicated by
35 36	80	evidence of heterogeneity not explained by study design. A weak non-significant protective
37 38	81	effect of ALA intake on prostate cancer risk in the prospective studies became significant (0.91
39 40	82	[0.83 to 0.99], P=0.02) without evidence of heterogeneity ($I^2=8\%$, P=0.35) on removal of one
41 42	83	study during sensitivity analyses.
43	84	Conclusions: This analysis failed to confirm an association between dietary ALA intake and
44 45 46 47 48 49 50 51 52	85	prostate cancer risk. Larger and longer observational and interventional studies are needed to
	86	define the role of ALA and prostate cancer.
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53 54	90	
55 56	91	Key Words: Alpha-linolenic acid, prostate cancer, omega-3 fatty acid, meta-analysis
57 58 59	92	
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2 3 4 5 6 7	93	INTRODUCTION
6	94	Prostate cancer is the second most common cancer in men worldwide ¹ . Prostate cancer
8	95	incidence rates vary widely among countries, populations, and races. Incidence rates vary by
9 10	96	more than 25-fold worldwide, with the highest rates documented in the developed countries of
11 12	97	North America, Europe, and Oceania, which may be due largely to the wide utilization of
13 14	98	prostate- specific antigen (PSA) testing that detects clinically important tumors that might
15	99	otherwise escape diagnosis ² . In contrast, males of African descent in the Caribbean region have
16 17	100	the highest prostate cancer mortality rates in the world ² , which is thought to reflect partly a
18 19	101	difference in genetic susceptibility ^{3 4} . The large differences in prostate cancer incidence rates
20 21	102	have led to many migration and ecologic studies, which have provided strong evidence for the
22	103	role of environmental factors, such as diet, in the etiology of prostate cancer ⁵⁻¹⁴ . In 1975,
23 24	104	Armstrong and Doll first hypothesized that there was an association between dietary fat and
25 26	105	death from prostate cancer ¹² , and many studies have examined this connection ¹⁵⁻¹⁸ , but in recent
27 28	106	years more attention has been focused on specific fatty acids. Several studies have examined the
29 30	107	association between polyunsaturated fatty acids (PUFAs) and risk of prostate cancer ¹⁹⁻²⁵ . There
31	108	has been particular interest in alpha-linolenic acid (ALA), the parent fatty acid for the ω -3
32 33	109	PUFAs, since increased consumption of ω -3 fatty acids is advised for cardiovascular disease risk
34 35	110	reduction ²⁶⁻²⁹ despite a possible association with prostate cancer ³⁰ .
36 37 38 39	111	Dietary ALA occurs mainly in plants and vegetable oils with certain seed oils (flaxseed,
	112	perilla, chia seed, and canola), beans (soybeans, navy beans), and nuts (walnuts) singled out as
40	113	examples of healthy foods due to their high ALA content ³¹ . However, in the United States, the
41 42	114	important sources of ALA are animal-based foods high in saturated fats, such as red meats, beef,
43 44	115	pork, and lamb, rather than ALA-rich vegetable sources, such as walnuts. ²⁵ . The largest
45 46	116	proportion of ALA (53.8%) comes from red meat in Uruguay ³² , but comes from margarine
47	117	(25%) in the Netherlands ³³ . Furthermore, foods such as bread, eggs, and margarine are now
48 49	118	being enriched with ALA to increase their healthfulness.
50 51	119	There are currently divergent health views on ALA. Numerous epidemiological ³⁴⁻³⁹ and
52	120	clinical studies ⁴⁰⁻⁴² have shown that ALA is associated with a reduction in coronary heart

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ergent health views on ALA. Numerous epidemiological ³⁴⁻³⁹ and clinical studies ⁴⁰⁻⁴² have shown that ALA is associated with a reduction in coronary heart 120 disease (CHD) incidence and heart disease mortality. However, since ALA has also been 121 associated with an increased risk of prostate cancer, ^{25 30 32 43-47} the seriousness of this potential 122

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association requires that any favourable effects of ALA on CHD be weighed against its possible adverse effects on prostate cancer. Numerous prospective cohort ^{19-22 24} and case-control studies ^{32 45 48-52} have investigated the association between ALA and prostate cancer risk. While previous meta-analyses ^{30 53 54} have been conducted to determine whether a relationship exists, there has been no meta-analysis since 2010, examining the specific effect of dietary ALA on prostate cancer risk and none since 2009, that included in both prospective cohort and case-control studies. Therefore, it appears timely to determine whether there are associations between dietary ALA from ω -3 fatty acid-rich foods, generally believed to be healthy, and prostate cancer risk. **METHODS** We followed the Cochrane handbook for systematic reviews of interventions version 5.1.0 updated March 2011 for the planning and conduct of this meta-analysis ⁵⁵. The reporting followed the QUOROM (Quality of Reporting of Meta-analyses) guidelines ⁵⁶. **Study Selection** We first conducted a search of MEDLINE (1948-April 17, 2009) and EMBASE (1974-April 17, 2009) using the following search terms and Boolean operators: prostate AND (cancer OR adenoma OR adenocarcinoma OR neoplasia OR gleason score) AND (alpha-linolenic acid OR n-3 fatty acids OR omega-3 fatty acids) and this literature search was last updated on August 28, 2012. The search was restricted to human research studies. No limit was placed on language. Manual searches of references cited by the published original studies and review articles supplemented the database search strategy. We included all prospective cohort, retrospective case-control, nested case-cohort, and nested case-control studies that investigated the effect of dietary ALA intake on the incidence (or diagnosis) of prostate cancer and provided relative risk (RR), hazard ratios (HR), or odds ratios (OR) estimates. No randomized controlled trials were identified. No lone abstracts or unpublished studies were identified. In cases where multiple publications existed for the same study, the article with the most recent information was included.

149Data Extraction

Two investigators (AJC, JLS) independently extracted relevant data on study
 characteristics and outcomes using a standardized proforma. These data included information

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about study design (prospective cohort, case-control, etc.), sample size and participant characteristics (nationality, race, named cohort, country of residence, gender, age, disease status, preexisting medical conditions), follow-up duration, sources of ALA, method of ALA status assessment, endpoints (incidence of prostate cancer, prostate specific antigen (PSA), Gleason score etc.), endpoint assessment (self-reporting, medical records, biopsy, etc.), and number of new incident cases. Bounds of intake categories, quartiles or quintiles, were also recorded. RR, HR, or OR with the greatest degree of control for other environmental and dietary risk factors, and their corresponding 95% CIs for incident prostate cancer risk were extracted as the main endpoint. Disagreements were reconciled by consensus and where necessary by discussion with another investigator (DJAJ). Authors were not contacted to request any additional information or translation.

Statistical Analysis

Data were analyzed using Review Manager (RevMan) 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and STATA v. 11.2 (StataCorp, College Station, TX). We used the reported RR or OR of the highest versus lowest intake category, as the measure of the relation between ALA intake and prostate cancer risk. The primary pooled analysis of all reports was conducted using the Generic Inverse Variance method using random effects weighting ⁵⁷ where the log RRs for cohort studies or log ORs for case-control studies were weighted by the inverse of the variance to obtain a pooled RR estimate. Since nested case-cohort and nested case-control studies are temporally prospective, we analyzed data from these studies with the prospective studies. As in other meta-analyses that have examined prostate cancer ^{30 54 58}, ORs were considered as approximations of RRs. Since prostate cancer is a rare disease, ORs were treated as unbiased approximations of RRs. ⁵⁹ Inter-study heterogeneity was assessed by Cochrane's Q (Chi² P<0.10) and quantified by I². An I² \geq 50% indicated "substantial" heterogeneity and \geq 75% indicated "considerable" heterogeneity. ⁶⁰ Sources of heterogeneity were explored by sensitivity analyses whereby the influence of individual studies was investigated by systematic removal of each study followed by recalculation of the pooled effect estimate and heterogeneity, as well as removal of outlier studies with risk estimates larger than 2 standard deviations from the mean risk estimate and recalculation of the pooled effect estimate and heterogeneity. We also performed *a priori* subgroup analyses to assess effect modification

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by study design (prospective versus case-control). Effect modification by study characteristics was explored using meta-regression. Publication bias was formally tested using Begg's and Egger's tests. RESULTS **Search Results** Figure 1 shows the flow of the literature selection applying the systematic search and selection strategies to identify eligible reports. Two hundred and forty three reports were identified by the search and two reports were manually included after a database search. Of these, 233 were determined to be irrelevant on review of the titles and abstracts. Four additional reports were then manually included. The remaining 16 reports were retrieved and reviewed in full, of which 4 were excluded. Results for The Health Professionals' Follow-up Study were published in three separate publications at different times of follow-up ^{21 23 25}. Only the most recent publication of the results, by Giovannucci et al. in 2007, was included in the analyses as representing the cumulative experience of the earlier assessments of this cohort ²¹. A total of 12 reports, 5 prospective and 7 case-control studies, were included in the pooled analyses. **Study Characteristics** Table 1 shows the characteristics of the 12 included studies, which were composed of 7 case-control studies ^{32 45 48-52} and 5 prospective studies ^{19-22 24} that used 3 designs: cohort, nested case-cohort, and nested case-control. Five studies were conducted in North America, 1 in South America, and 6 in Europe. The 12 included studies contained a total of 14,795 cases of prostate cancer and 231,143 controls. All studies obtained dietary data using food frequency questionnaires (FFQ). Individual and average dietary ALA intake in these studies ranged from ≈ 0.05 to 4.16 g/d) and the reported relative risk or odds ratio of the highest versus the lowest intake category ranged from 0.7 to 3.91.

Primary Analysis

The overall analysis of the 12 studies examined prostate cancer, comparing the highest with the lowest ALA intake category. Seven studies reported a protective effect of ALA intake on prostate cancer, one of which was significant, and the remaining five studies reported a

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 positive association, of which 3 were significant. Overall, high exposure to ALA was not
associated with increased risk of prostate cancer (pooled RR: 1.08; 95%CI: 0.90, 1.29, P=0.40)
(Figure 2). However, there was evidence of considerable inter-study heterogeneity (I²=85%,
P<0.00001). Systematic removal of each study, and recalculation of the pooled effect during
sensitivity analyses did not identify an influential outlier.

215 Subgroup Analyses

216 Case-Control Studies

In an *a priori* meta-regression, we found no evidence of effect measure modification according to study design (P=0.331). There remained significant unexplained heterogeneity within each type of study design. In case-control studies (n=7; 4,047 cases and 4,762 controls), the summary RR was 1.30 (95%CI: 0.81, 2.07, P=0.27), with considerable inter-study heterogeneity ($I^2=90\%$, P<0.00001) (Figure 3). Systematic removal of each individual study during sensitivity analyses did not explain the heterogeneity. Removal of the 2 case-control studies by Ramon et al.⁴⁵, De Stefani et al.³² that reported risk estimates larger than 2 standard deviations from the pooled RR estimate reduced the inter-study heterogeneity ($I^2=68\%$, P=0.01) but did not eliminate it. The overall association became protective, but was not significant (RR=0.93; 95%CI: 0.69, 1.25, P=0.64).

228 Prospective Studies

In prospective studies alone (n=5; 10,748 cases and 207,752 controls), no association between ALA intake and prostate cancer risk was found (RR: 0.95; 95%CI: 0.84, 1.09, P=0.48) (**Figure 4**) but there existed substantial inter-study heterogeneity (I^2 =69%, P=0.01). Sensitivity analyses showed that removal of the study by Giovannucci et al. ²¹ eliminated heterogeneity with prospective studies (I^2 =8%, P=0.35) and made the protective effect significant (RR=0.91; 95%CI: 0.83,0.99, P=0.02) (**Figure 5**).

236 Publication Bias

Neither Begg's (P>0.165) nor Egger's (P>0.527) tests revealed evidence of publication
 bias, however, one study by Ramon et al. ⁴⁵ had an unusually large effect with a small standard
 error.

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40 DISCUSSION41 Summary of Results

42 The present meta-analysis of 12 observational studies (7 case-control and 5 prospective) 43 comparing the highest with the lowest categories of dietary ALA intake demonstrated non-44 significant heterogeneous effects of ALA on prostate cancer risk. Overall, there was no 45 significant association between ALA intake and risk of prostate cancer. The subgroup analysis of 46 case control studies alone showed a positive non-significant association, but with substantial heterogeneity. However, upon removal of the studies by De Stefani et al. ³² and Ramon et al. ⁴⁵, 47 which reported large odds ratios greater than 3 but were still within 2 standard deviations of the 48 49 mean effect, the association became non-significantly protective with decreased heterogeneity. 50 When examining the prospective studies alone, the association between ALA intake and prostate 51 cancer risk was non-significantly protective and after removal of the study by Giovannucci et al. ²¹ became weakly, but significantly, protective with no heterogeneity. 52

53 The results from the prospective studies are similar to those of previously published findings that examined only prospective studies ⁵³. Our study additionally investigated the 54 55 association between dietary ALA intake and prostate cancer risk among case-control studies and 56 reached the conclusion of non-significantly increased risk with high heterogeneity, particularly 57 due to the inclusion of two studies with very high odds ratios. We explore whether these 58 heterogeneous results can be explained by a number of factors, such as the variation in ALA 59 consumption, sources, or population dietary patterns. However, this heterogeneity among the 60 case-control studies may serve to highlight the less reliable nature of case-control study design as 61 it inherently involves recall bias since dietary information is collected after disease development. 62

Heterogeneity and the Effect of ALA between Studies

In our study, different findings reviewed and inter-study heterogeneity may be explained by a number of factors: variation in ALA consumption and sources of ALA as a result of the population's dietary patterns, variation in ALA exposure levels, use of different FFQs and food databases, variation in adjustment factors, and difference in follow-up times among prospective studies.

70 Variation in ALA Consumption and Sources, and Population Dietary Patterns

6

 In the Netherlands, the chief sources of ALA include margarine (25% of daily intake), meat (11%), bread (10%), and vegetables $(8\%)^{33}$, whereas in the United States, major sources of ALA come from mayonnaise, creamy salad dressings, margarine, butter, beef, pork, lamb, and oil and vinegar-based dressings²⁵. Interestingly, the prospective study from the Netherlands reported a weak protective effect of ALA intake on prostate cancer risk²⁰, but the most recent study from the United States reported a 25% increase in risk ²¹. This difference may be due to the nature of the foods that contain ALA since in the United States, the sources of ALA are not the "healthy" sources where ALA is naturally found (e.g. flaxseed, walnuts, and canola oil), but rather profiled an unhealthy diet (e.g. canola oil in the form of mayonnaise and creamy salad dressings), which may be indicative of a less healthy lifestyle and this in itself may contribute to an increased risk of prostate cancer independent of ALA intake levels ^{61 62}. In addition, in the case-control studies from Uruguay ³² and Spain ⁴⁵ that showed the largest increases in prostate cancer risk demonstrated that meat, and not vegetable, was the major source of ALA. When these two studies were removed from the analysis of the case-control studies, the effect of ALA intake on prostate cancer changed from a non-significantly positive to a non-significantly protective effect. Compared with the other studies from Europe and the United States, there is a much higher consumption of meat in Spain⁶³ and Uruguay, with Uruguay having the highest meat consumption per capita in the world ⁶⁴. An earlier analysis of the Health Professionals Follow-up Study cohort²⁵ supports this positive association between red meat consumption and prostate cancer risk. Furthermore, the two studies from Spanish-speaking countries also investigated the effect of animal fat on prostate cancer and both found significant positive associations. The Uruguayan study ³² observed that at the highest level of ALA intake derived from animal sources resulted in almost 3 times the risk of developing prostate cancer and the Spanish study ⁴⁵ revealed that the highest level of animal fat intake was associated with 2

times the risk. These findings indicate that high meat intake rather than high ALA may explain ALA's apparent adverse effect on prostate cancer. In further support of this idea, the study by Bidoli et al.⁵⁰ demonstrated a significant protective association between ALA and prostate cancer risk in an Italian population where ALA is mainly derived from olive oil ⁶⁵ and the diet is rich in raw vegetables ⁵⁰ rather than meat, profiling an overall more "healthy" diet.

An explanation for the apparent association of prostate cancer incidence with vegetable sources of ALA may be that in addition those who follow healthy lifestyles with increased plant

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ALA sources may undergo more frequent prostate specific antigen (PSA) testing and therefore have early prostate cancer detection. In this respect it has been found that higher whole grain intake was also associated with increased prostate cancer risk. However, when frequency of PSA screening was accounted for, the association of whole grains with prostate cancer incidence disappeared ⁶⁶. These studies indicate the importance of not only identifying the dietary sources of ALA, but taking into account what the nature of the foods may indicate in terms of diet and lifestyle since these also may affect prostate cancer risk.

310 Variation in ALA Exposure Levels

Another important aspect to consider is the differing exposure levels between the studies. Each study had different cut-offs for each quantile, which makes a true comparison of ALA intake exposure difficult since some studies had higher levels of ALA in their highest intake quantile than others. Further, some studies did not adequately define the absolute upper and/or lower limits of ALA intake ^{21 32 50} and one study did not report numerical exposure levels ⁴⁹. Two studies, one from Spain⁴⁵ and one from the Netherlands²⁰, with the largest adequately defined upper and lower limits of ALA exposure ranges, paradoxically reported the second highest and the second lowest risk of developing prostate cancer, respectively. Since the studies with the greatest range of exposure do not necessarily show the greatest effects, dietary variation in the levels of exposure does not appear to explain differences among the studies, thereby making differences in dietary sources of ALA of more importance especially in relation to meat consumption in Western countries.

Variation in FFQs and Food Databases

In terms of utilizing different FFQs and food databases, each study used a different dietary FFQ. ALA content of processed food can vary, which can be of concern when using food databases to translate food intake into fatty acid intake. For example, the ALA content of 12 margarines available in Australia range from 0.2% to 5.9% ⁶⁷.

330 Variation in Adjustment Factors

Although all the studies reported adjusted RRs or ORs, the adjustment factors were not
 consistent among the studies. Some of the adjustment factors in these studies included age,

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smoking history, physical activity level, BMI, family history of prostate cancer, history of diabetes mellitus, race, education, socioeconomic status, area of residence and intakes of total calories, fat, processed meat, fish, lycopene, and vitamin E supplements. Currently, the most well-established risk factors for prostate cancer are age, family history of the disease, and race/ethnicity ⁶⁸ and consequently are the most important adjustment factors. Only 4 ^{20-22 52} of the 12 included studies adjusted for all of these 3 factors. The studies conducted by Park et al.¹⁹ and Mannisto et al.²⁴ did not adjust for age, which is by far the strongest predictor of prostate cancer incidence and death ⁶⁸. A family history of prostate cancer has been shown to increase the risk of diagnosis and death and this factor was not adjusted for in studies by Hedelin et al.⁵¹, Andersson et al.⁴⁸, and Mannisto et al.²⁴ Race is a prostate cancer risk factor and prognostic factor, with African-American or Black men being at increased risk, and this was not adjusted for in the studies by Bidoli et al. ⁵⁰, De Stefani et al. ³², Ramon et al. ⁴⁵, and Meyer et al. ⁴⁹ Differences in adjustment among the included studies, particularly with respect to the important factors of age, family history of prostate cancer, and race could result in differences in risk estimates, thereby contributing to inter-study heterogeneity.

349 Variation in Follow-up Duration

Follow-up time may also have an effect on heterogeneity, especially since the study by Giovannucci et al.²¹ had the longest follow-up duration (16 years). Comparing previous prospective studies following the same cohort ^{23 25} with this most recent study ²¹, demonstrates a shift over time (total of 12 years) from a non-significant to a significant positive association between ALA intake and prostate cancer. So, it can be hypothesized that the heterogeneity induced by this study may indicate that follow-up duration is positively related to the strength of the association between ALA and prostate cancer risk. This association may relate to the development of cancer over a longer period of time and therefore stronger association in the cohort between agents that may cause cancer and tumour occurrence. Alternatively, this relationship may reflect changes in diagnostic effectiveness over time.

51 360

361 Reasons for the Lack of Effect of ALA

The overall effect of ALA on prostate cancer was found to be non-significant but may result from a number of factors including ALA exposure levels that are within health guidelines, Page 13 of 61

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364 confounding from other polyunsaturated fatty acids, and the difference in effect of ALA on365 prostate cancer mortality versus incidence.

The mean dietary ALA intake levels observed in these studies were all within the dietary reference intake (DRI) range of 1.1 to 1.6 g/d⁶⁹, suggesting that ALA may not increase the risk of cancer more than any other nutrient promoting cell growth. Rather, since ALA is a nutrient deficient in the Western diet⁷⁰, it may be that a deficiency inhibits all cell growth, including tumour growth, instead of adequate or excess levels causing prostate cancer growth.

Another issue to consider is confounding from other polyunsaturated fatty acids such as omega-6 or other omega-3 fatty acids (eicosapentaenoic and docosahexaenoic fatty acids) that might affect ALA metabolism ⁷¹ and consequently may introduce bias. The case-control study from the United States ⁵² demonstrated this as there was no significant association between ALA, omega-3, or omega-6 fatty acids and prostate cancer risk individually, but the highest dietary ratio of omega-6/omega-3 fatty acids was significantly associated with increased risk of high grade prostate cancer.

Finally, our analysis involved cancer incidence rather than mortality and ALA, among other factors such as energy intake, height, body mass index, calcium, and smoking, are also associated with cancer mortality²¹. The study by De Stefani et al.³², which was the only study that defined cases solely as advanced prostate cancer, had the highest risk estimate of prostate cancer, indicating that ALA may be strongly associated with disease progression rather than incidence. In support of this point, the prospective study by Giovannucci et al.²¹ found that higher ALA intake was more strongly associated with increased risk of fatal prostate cancer than with incident. However, three other prospective studies did not find any difference between the effects of ALA on incident or advanced prostate cancer cases ^{19 20 22}. From these mixed findings, it is unclear whether ALA is associated with severity of prostate cancer, but determining whether ALA impacts prostate cancer incidence or progression is an important distinction that should be investigated in the future. Furthermore, the picture of ALA's effect on prostate cancer is complicated by the positive association of incident prostate cancer with either serum or adipose tissue ALA levels ^{24 43 44 46 47 72} despite the in vitro evidence which suggests that ALA may suppress prostate cancer cell growth ^{73 74}. However, there appears to be some correlation between ALA intake and serum ALA levels. In terms of intake, Gann et al. ⁴³ found that plasma ALA levels were significantly positively correlated with meat and dairy product intake, and similar to

the prospective analysis from the Health Professionals Follow-Up Study ²⁵, they found that red meat was positively associated with advanced prostate cancer, whereas diary foods were not. This corroboration not only suggests a correlation between ALA intake and serum ALA levels, but enforces the positive association between ALA from red meat and prostate cancer as seen in the studies from Uruguay ³² and Spain ⁴⁵, rather than from plant foods.

401 Limitations

The first limitation of the meta-analysis is that all data currently available for inclusion come from epidemiological studies since there are no data from randomized controlled trials due to ethical concerns. Second, interpretation of the analyses was complicated by the evidence of considerable heterogeneity among the studies, which as discussed above may have resulted from differences in ALA sources and population dietary patterns, ALA exposure levels, FFQs and food databases, adjustment factors, and duration of follow-up. There are also inherent limitations in the studies included based on study design. For example, there is the possibility of recall bias in case-control studies, as dietary intake information is collected after disease development.

411 CONCLUSION

In conclusion, these findings provide no clear evidence of an association between dietary ALA intake and prostate cancer risk. Further, since these observational studies can only show association between ALA intake and prostate cancer, possible causation would be difficult to establish. Therefore, additional research from epidemiological, clinical, and in vitro studies are required to elucidate whether ALA has a promotional, inhibitory, or no effect on prostate cancer risk and development. For the present, no significant association has been found and where any support of a positive effect was seen, red meat sources have been strongly implicated. The source of ALA appears to be of importance, particularly identifying whether it is from animal or vegetable sources, as ALA may be a marker for higher meat and fat intake in some countries both of which have been associated with increased prostate cancer risk. Attention should also be paid to the effect of ALA on prostate cancer progression to address the issues of specific vulnerability identified in the studies of Giovannucci et al. and De Stefani et al.²¹³². However, resolving the relation of dietary ALA to prostate cancer risk through randomized controlled trials will likely continue to be difficult due to the significant public health implications of

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26 reducing/eliminating a dietary fatty acid which is essential and has suggested heart health 27 benefits. Of probably greater importance is determination of the sources of the fatty acid since 28 ALA is associated in the North American diet with meat membranes and creamy salad dressings, 29 which themselves may be markers of a suboptimal dietary pattern and lifestyle 130

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133 AUTHORSHIP

All authors, external and internal, had full access to all of the data (including statistical reports 434 435 and tables) in the study and can take responsibility for the integrity of the data and the accuracy 436 of the data analysis.

Details of Contributors: AJC was involved in the conception and design, analysis and 437 438 interpretation of data, drafting the article and revising it critically for important intellectual 139 content, and final approval of the version to be published. JLS was involved in the conception 140 and design, some analysis, and revising the article critically for important intellectual content. RS 441 was involved in revising the article critically for important intellectual content. GE was involved

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3 4	442	in the conception and design and in revising the article critically for important intellectual
5 6	443	content. DJAJ was in the conception and design, revising the article critically for important
7 8	444	intellectual content, and final approval of the version to be published.
9 10	445	DATA SHARING
11 12 13	446	There is no additional data available.
14 15	447	COMPETING INTEREST DECLARATION
16 17	448	All authors have completed the Unified Competing Interest form at
18	449	www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and
19 20	450	declare that (1) AJC, JLS, RdS, and GE have not had financial support from any company for the
21 22	451	submitted work; (2) AJC, JLS, RdS, and GE have no relationships with any companies that
23 24	452	might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners,
25	453	or children have no financial relationships that may be relevant to the submitted work; and (4)
26 27	454	AJC, JLS, RdS, and GE have no non-financial interests that may be relevant to the submitted
28 29	455	work. DJAJ has served on the Scientific Advisory Board of Sanitarium Company, Agri-Culture
30 31	456	and Agri-Food Canada (AAFC), Canadian Agriculture Policy Institute (CAPI), California
32	457	Strawberry Commission, Loblaw Supermarket, Herbal Life International, Nutritional
33 34	458	Fundamental for Health, Pacific Health Laboratories, Metagenics, Bayer Consumer Care, Orafti,
35 36	459	Dean Foods, Kellogg's, Quaker Oats, Procter & Gamble, Coca-Cola, NuVal Griffin Hospital,
37 38	460	Abbott, Pulse Canada, Saskatchewan Pulse Growers, and Canola Council of Canada; received
39 40	461	honoraria for scientific advice from Sanitarium Company, Orafti, the Almond Board of
41	462	California, the American Peanut Council, International Tree Nut Council Nutrition Research and
42 43	463	Education Foundation and the Peanut Institute, Herbal Life International, Pacific Health
44 45	464	Laboratories, Nutritional Fundamental for Health, Barilla, Metagenics, Bayer Consumer Care,
46 47	465	Unilever Canada and Netherlands, Solae, Oldways, Kellogg's, Quaker Oats, Procter & Gamble,
48	466	Coca-Cola, NuVal Griffin Hospital, Abbott, Canola Council of Canada, Dean Foods, California
49 50	467	Strawberry Commission, Haine Celestial, Pepsi, and Alpro Foundation; has been on the speakers
51 52	468	panel for the Almond Board of California; received research grants from Saskatchewan Pulse
53 54	469	Growers, the Agricultural Bioproducts Innovation Program (ABIP) through the Pulse Research
55	470	Network (PURENet), Advanced Food Materials Network (AFMNet), Loblaw, Unilever, Barilla,
56 57 58 59	471	Almond Board of California, Coca-Cola, Solae, Haine Celestial, Sanitarium Company, Orafti,

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3 4	472	International Tree Nut Council Nutrition Research and Education Foundation and the Peanut
5 6	473	Institute, the Canola and Flax Councils of Canada, Calorie Control Council, Canadian Institutes
7	474	of Health Research, Canada Foundation for Innovation, and the Ontario Research Fund; and
8 9	475	received travel support to meetings from the Solae, Sanitarium Company, Orafti, AFMNet,
10 11	476	Coca-Cola, The Canola and Flax Councils of Canada, Oldways Preservation Trust, Kellogg's,
12 13	477	Quaker Oats, Griffin Hospital, Abbott Laboratories, Dean Foods, the California Strawberry
14	478	Commission, American Peanut Council, Herbal Life International, Nutritional Fundamental for
15 16	479	Health, Metagenics, Bayer Consumer Care, AAFC, CAPI, Pepsi, Almond Board of California,
17 18	480	Unilever, Alpro Foundation, International Tree Nut Council, Barilla, Pulse Canada, and the
19 20	481	Saskatchewan Pulse Growers. DJAJ's wife is a director of Glycemic Index Laboratories,
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22 23		
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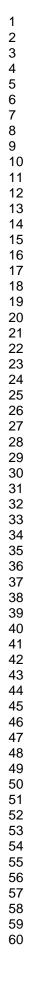
Table 1 - Characteristics of studies included in the meta-analysis of alpha-linolenic acid intake and prostate cancer

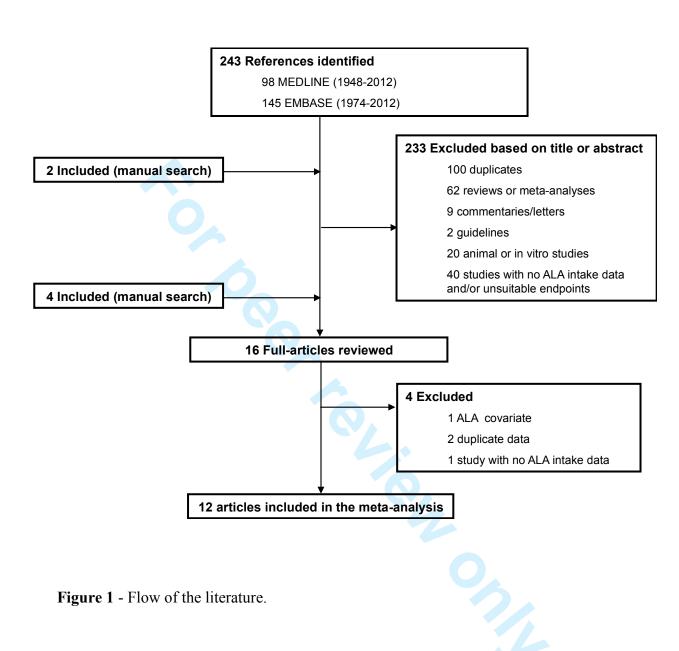
Study	Country of Origin	Study Design	Sample size	Age (years)	Incident Cases	Follow-up (years)	Exposure level (g/d)	Relative Risk or Odds Ratio	95% CI
Andersson et al. 1996 [38]	Sweden	Case-control	526 cases/536 controls	<80	-	-	0.817 - 1.352	0.93	0.65-1.32
Neyer et al. 1997 [39]	Canada	Case-control	215 cases/593 controls	≥45	-	-	-	0.98	0.54-1.78
Schuurman et al. 1999 [18]*	Netherlands	Nested case-cohort	58,279 (1525 subcohort)	55-69	642	6.3	0.7 - 2.1	0.76	0.66-1.04
De Stefani et al. 2000 [29]	Uruguay	Case-control	217 cases/431 controls	40-89	-	-	≤0.8 - ≥1.5	3.91	1.50-10.1
Ramon et al. 2000 [40]	Spain	Case-control	217 cases/434 controls	<60-80	-	-	0.72 - 2.1	3.1	2.2-4.7
Mannisto et al. 2003 [22]*	Finland	Nested case-control	198 cases/198 controls	50-69	246	5-8	1.0 - 2.3	1.16	0.64-2.13
Bidoli et al. 2005 [41]	Italy	Case-control	1294 cases/1451 controls	45-74	-	-	mean 1.6	0.7	0.6-0.9
Koralek et al. 2006 [20]*	United States	Prospective cohort	29,592	55-74	1898	5.1	1.09 - 1.75	0.94	0.81-1.09
Hedelin et al. 2007 [42]	Sweden	Case-control	1499 cases/1130 controls	mean 67.3	-	-	0.05 - 0.60	1.35	0.99-1.84
Giovannucci et al. 2007 [19]*	United States	Prospective cohort	47,750	40-75	3544	16	<0.79 - ≥1.32	1.12	1.01-1.25
Park et al. 2007 [17]*	United States	Prospective cohort	82,483	≥45	4404	8	1.1 - 2.14†	0.92	0.84-1.02
Williams et al. 2011 [43]	United States	Case-control	79 cases/187 controls	≥18	-	-	≤1.0 - 4.156 †	0.82	0.41-1.65

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		Risk Ratio		Risk Ratio
Study or Subgroup	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Andersson 1996 [48]	8.4%	0.93 [0.65, 1.33]	1996	
Meyer 1997 [49]	5.2%	0.98 [0.54, 1.78]	1997	+
Schuurman 1999 [20]	10.5%	0.76 [0.61, 0.95]	1999	
De Stefani 2000 [32]	2.7%	3.91 [1.51, 10.15]		
Ramon 2000 [45]	8.0%	3.10 [2.12, 4.53]		
Mannisto 2003 [24]	5.1%	1.16 [0.64, 2.12]		
Bidoli 2005 [50]	10.9%	0.70 [0.57, 0.86]		
Koralek 2006 [22]	11.6%	0.94 [0.81, 1.09]		
Hedelin 2007 [51]	9.1%	1.35 [0.99, 1.84]		
Park 2007 [19] Giovannucci 2007 [21]	12.2% 12.1%	0.92 [0.83, 1.01] 1.12 [1.01, 1.25]		_
Williams 2011 [52]	4.3%	0.82 [0.41, 1.64]		
Williams 2011 [52]	4.370	0.02 [0.41, 1.04]	2011	
Total (95% CI)	100.0%	1.08 [0.90, 1.29]		•
Heterogeneity: $Tau^2 = 0$).06: Chi ² =	= 71.45. df = 11 (P <	0.000	(1): $ ^2 = 85\%$
Test for overall effect: Z				(1); I' = 85% 0.10.2 0.5 1 2 5 10 Favours ALA Favours Control
				ravours ALA Favours control
Figure 2 – Pooled ef	fect of di	ietary ALA intake	on pro	state cancer risk in case-control, nested
case-control, nested of	case-coho	ort, and cohort stud	dies. R	elative Risk (RR) with 95% CI, study
weights, and pooled a	effect est	imates were gener	rated us	sing the general inverse variance method
with random effects i	models (1	RevMan 5.1, Coch	irane L	ibrary software, Oxford, UK). Inter-study
heterogeneity was tes	sted by C	cochrane's Q (Chi ²) at a s	significance level of P<0.10 and quantified
by I^2 , where $I^2 \ge 50$ %	6 is cons	idered to be evider	nce of	substantial heterogeneity and \geq 75%,
considerable heteroge	eneity 55.			
		Risk Ratio		Risk Ratio
Study or Subgroup	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Andersson 1996 [48]	15.7%	0.93 [0.65, 1.33]		-+-
Meyer 1997 [49]	13.5%	0.98 [0.54, 1.78]		
Ramon 2000 [45]	15.5%	3.10 [2.12, 4.53]		_
De Stefani 2000 [32]	10.0%	3.91 [1.51, 10.15]		· · · · · · · · · · · · · · · · · · ·
Bidoli 2005 [50]	16.7%	0.70 [0.57, 0.86]		
Hedelin 2007 [51]	16.1%	1.35 [0.99, 1.84]		⊢ ■−
Williams 2011 [52]	12.5%	0.82 [0.41, 1.64]	2011	

1.30 [0.81, 2.07] Total (95% CI) 100.0% Heterogeneity: Tau² = 0.33; Chi² = 57.44, df = 6 (P < 0.00001); I² = 90% 0.1 0.2 0.5 Test for overall effect: Z = 1.10 (P = 0.27) Favours ALA Favours Control

Figure 3 – Pooled effect of dietary ALA intake on prostate cancer risk in case-control studies. Relative Risk (RR) with 95% CI, study weights, and pooled effect estimates were generated using the general inverse variance method with random effects models (RevMan 5.1, Cochrane Library software, Oxford, UK). Inter-study heterogeneity was tested by Cochrane's Q (Chi²) at a

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significance level of P<0.10 and quantified by I², where I² \geq 50 % is considered to be evidence of substantial heterogeneity and \geq 75%, considerable heterogeneity ⁵⁵.

		Rate Ratio		Rate Ratio
Study or Subgroup	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Schuurman 1999 [20]	16.6%	0.76 [0.61, 0.95]	1999	
Mannisto 2003 [24]	4.1%	1.16 [0.64, 2.12]	2003	
Koralek 2006 [22]	23.4%	0.94 [0.81, 1.09]	2006	-
Park 2007 [19]	28.4%	0.92 [0.83, 1.01]	2007	-
Giovannucci 2007 [21]	27.5%	1.12 [1.01, 1.25]	2007	-
Total (95% CI)	100.0%	0.95 [0.84, 1.09]		•
Heterogeneity: Tau ² = 0	.01; Chi ² =	= 13.03, df = 4 (P = 0	.01); I ² = 69%	
Test for overall effect: Z	= 0.70 (P	= 0.48)		Favours ALA Favours Control

Figure 4 – Pooled effect of dietary ALA intake on prostate cancer risk in prospective studies. Relative Risk (RR) with 95% CI, study weights, and pooled effect estimates were generated using the general inverse variance method with random effects models (RevMan 5.1, Cochrane Library software, Oxford, UK). Inter-study heterogeneity was tested by Cochrane's Q (Chi²) at a significance level of P<0.10 and quantified by I², where I² \geq 50 % is considered to be evidence of substantial heterogeneity and \geq 75%, considerable heterogeneity ⁵⁵.

		Rate Ratio		Rate Ratio
Study or Subgroup	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Schuurman 1999 [20]	12.8%	0.76 [0.61, 0.95]	1999	
Mannisto 2003 [24]	1.9%	1.16 [0.64, 2.12]	2003	
Koralek 2006 [22]	28.1%	0.94 [0.81, 1.09]	2006	+
Park 2007 [19]	57.1%	0.92 [0.83, 1.01]	2007	•
Total (95% CI) Heterogeneity: Tau ² = 0	100.0%	0.91 [0.83, 0.99] = 3.27, df = 3 (P = 0	.35): l ² = 8%	<u>↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ </u>
Test for overall effect: Z				0.1 0.2 0.5 1 2 5 10 Favours ALA Favours Control

Figure 5 – Pooled effect of dietary ALA intake on prostate cancer risk in prospective studies after the systematic removal of the study by Giovannucci et al. ²¹ following a sensitivity analysis. Relative Risk (RR) with 95% CI, study weights, and pooled effect estimates were generated using the general inverse variance method with random effects models (RevMan 5.1, Cochrane Library software, Oxford, UK). Inter-study heterogeneity was tested by Cochrane's Q (Chi²) at a significance level of P<0.10 and quantified by I², where I² \geq 50 % is considered to be evidence of substantial heterogeneity and \geq 75%, considerable heterogeneity ⁵⁵.

1 2 3 4 **Contributorship** 5 AJC was involved in the conception and design, analysis and interpretation of data, drafting the 6 7 article and revising it critically for important intellectual content, and final approval of the 8 version to be published. JLS was involved in the conception and design, some analysis, and 9 revising the article critically for important intellectual content. RS was involved in revising the 10 article critically for important intellectual content. GE was involved in the conception and design 11 and in revising the article critically for important intellectual content. DJAJ was in the 12 conception and design, revising the article critically for important intellectual content, and final 13 14 approval of the version to be published. 15 16 Funding 17 None 18 19 **Competing Interests** 20 21 None 22 23 **Data sharing** 24 No additional data available 25 26 27 28 References 29 30 1. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. CA Cancer J Clin 31 2005;55(2):74-108. 32 2. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011;61(2):69-33 34 90 35 3. Bock CH, Schwartz AG, Ruterbusch JJ, et al. Results from a prostate cancer admixture 36 mapping study in African-American men. Hum Genet 2009;126(5):637-42. 37 4. Miller DC, Zheng SL, Dunn RL, et al. Germ-line mutations of the macrophage scavenger 38 receptor 1 gene: association with prostate cancer risk in African-American men. Cancer 39 40 Res 2003;63(13):3486-9. 41 5. Sim HG, Cheng CW. Changing demography of prostate cancer in Asia. Eur J Cancer 42 2005;41(6):834-45. 43 6. Shimizu H, Ross RK, Bernstein L, et al. Cancers of the prostate and breast among Japanese 44 and white immigrants in Los Angeles County. Br J Cancer 1991;63(6):963-6. 45 46 47 48 49 50 51 52 53 54 55 56 47. 57 58 59

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1	Case-Control and Prospective Studies of Dietary Alpha-Linolenic Acid Intake
2	and Prostate Cancer Risk: a Meta-Analysis
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ABSTRACT

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35 Objective: To conduct a systematic review and meta-analysis of case-control and prospective 36 studies investigating the association between dietary ALA intake and prostate cancer risk. Data Sources: MEDLINE and EMBASE were searched for relevant prospective and case-37 38 control studies. 39 Eligibility Criteria for Selecting Studies: We included all prospective cohort, case-control, 40 nested case-cohort, and nested case-control studies that investigated the effect of dietary ALA 41 intake on the incidence (or diagnosis) of prostate cancer and provided relative risk (RR), hazard 42 ratios (HR), or odds ratios (OR) estimates. 43 Design: Data were pooled using the generic inverse variance method with a random-effects 44 model from studies that compared the highest ALA quantile with the lowest ALA quantile. Risk 45 estimates were expressed as relative risk (RR) with 95% confidence intervals (CI). Heterogeneity 46 was assessed by χ^2 and quantified by I^2 . 47 **Results:** Data from 5 prospective and 7 case-control studies were pooled. The overall RR 48 estimate showed ALA intake to be positively, but non-significantly associated with prostate cancer risk (1.08 [0.90 to 1.29], P=0.40, I²=85%), but the interpretation was complicated by 49 50 evidence of heterogeneity not explained by study design. A weak non-significant protective 51 effect of ALA intake on prostate cancer risk in the prospective studies became significant (0.91

Background: ALA is considered a cardioprotective nutrient, however some epidemiological

studies have suggested that dietary ALA intake increases the risk of prostate cancer.

52 [0.83 to 0.99], P=0.02) without evidence of heterogeneity (I^2 =8%, P=0.35) on removal of one 53 study during sensitivity analyses.

54 Conclusions: This analysis failed to confirm an association between dietary ALA intake and
55 prostate cancer risk. Larger and longer observational and interventional studies are needed to
56 define the role of ALA and prostate cancer.

61 Key Words: Alpha-linolenic acid, prostate cancer, omega-3 fatty acid, meta-analysis

63 INTRODUCTION

Prostate cancer is the second most common cancer in men worldwide¹. Prostate cancer incidence rates vary widely among countries, populations, and races. Incidence rates vary by more than 25-fold worldwide, with the highest rates documented in the developed countries of North America, Europe, and Oceania, which may be due largely to the wide utilization of prostate- specific antigen (PSA) testing that detects clinically important tumors that might otherwise escape diagnosis². In contrast, males of African descent in the Caribbean region have the highest prostate cancer mortality rates in the world², which is thought to reflect partly a difference in genetic susceptibility ³⁴. The large differences in prostate cancer incidence rates have led to many migration and ecologic studies, which have provided strong evidence for the role of environmental factors, such as diet, in the etiology of prostate cancer ⁵⁻¹⁴. In 1975, Armstrong and Doll first hypothesized that there was an association between dietary fat and death from prostate cancer¹², and many studies have examined this connection¹⁵⁻¹⁸, but in recent vears more attention has been focused on specific fatty acids. Several studies have examined the association between polyunsaturated fatty acids (PUFAs) and risk of prostate cancer ¹⁹⁻²⁵. There has been particular interest in alpha-linolenic acid (ALA), the parent fatty acid for the ω -3 PUFAs, since increased consumption of ω -3 fatty acids is advised for cardiovascular disease risk reduction $^{26-29}$ despite a possible association with prostate cancer 30 . Dietary ALA occurs mainly in plants and vegetable oils with certain seed oils (flaxseed, perilla, chia seed, and canola), beans (soybeans, navy beans), and nuts (walnuts) singled out as

examples of healthy foods due to their high ALA content ³¹. However, in the United States, the important sources of ALA are animal-based foods high in saturated fats, such as red meats, beef, pork, and lamb, rather than ALA-rich vegetable sources, such as walnuts. ²⁵. The largest proportion of ALA (53.8%) comes from red meat in Uruguay ³², but comes from margarine (25%) in the Netherlands ³³. Furthermore, foods such as bread, eggs, and margarine are now being enriched with ALA to increase their healthfulness.

89 There are currently divergent health views on ALA. Numerous epidemiological ³⁴⁻³⁹ and 90 clinical studies ⁴⁰⁻⁴² have shown that ALA is associated with a reduction in coronary heart 91 disease (CHD) incidence and heart disease mortality. However, since ALA has also been 92 associated with an increased risk of prostate cancer, ^{25 30 32 43-47} the seriousness of this potential

association requires that any favourable effects of ALA on CHD be weighed against its possible adverse effects on prostate cancer. Numerous prospective cohort ^{19-22 24} and case-control studies ^{32 45 48-52} have investigated the association between ALA and prostate cancer risk. While previous meta-analyses ^{30 53 54} have been conducted to determine whether a relationship exists, there has been no meta-analysis since 2010, examining the specific effect of dietary ALA on prostate cancer risk and none since 2009, that included in both prospective cohort and case-control studies. Therefore, it appears timely to determine whether there are associations between dietary ALA from ω -3 fatty acid-rich foods, generally believed to be healthy, and prostate cancer risk.

101 METHODS

We followed the Cochrane handbook for systematic reviews of interventions version 5.1.0 updated March 2011 for the planning and conduct of this meta-analysis ⁵⁵. The reporting followed the QUOROM (Quality of Reporting of Meta-analyses) guidelines ⁵⁶.

Study Selection

We first conducted a search of MEDLINE (1948-April 17, 2009) and EMBASE (1974-April 17, 2009) using the following search terms and Boolean operators: prostate AND (cancer OR adenoma OR adenocarcinoma OR neoplasia OR gleason score) AND (alpha-linolenic acid OR n-3 fatty acids OR omega-3 fatty acids) and this literature search was last updated on August 28, 2012. The search was restricted to human research studies. No limit was placed on language. Manual searches of references cited by the published original studies and review articles supplemented the database search strategy. This search strategy was last updated on August 28. 2012. We included all prospective cohort, retrospective case-control, nested case-cohort, and nested case-control studies that investigated the effect of dietary ALA intake on the incidence (or diagnosis) of prostate cancer and provided relative risk (RR), hazard ratios (HR), or odds ratios (OR) estimates. No randomized controlled trials were identified. No lone abstracts or unpublished studies were identified. In cases where multiple publications existed for the same study, the article with the most recent information was included.

Data Extraction

Two investigators (AJC, JLS) independently extracted relevant data on study
 characteristics and outcomes using a standardized proforma. These data included information

about study design (prospective cohort, case-control, etc.), sample size and participant characteristics (nationality, race, named cohort, country of residence, gender, age, disease status, preexisting medical conditions), follow-up duration, sources of ALA, method of ALA status assessment, endpoints (incidence of prostate cancer, prostate specific antigen (PSA), Gleason score etc.), endpoint assessment (self-reporting, medical records, biopsy, etc.), and number of new incident cases. Bounds of intake categories, quartiles or quintiles, were also recorded. RR, HR, or OR with the greatest degree of control for other environmental and dietary risk factors, and their corresponding 95% CIs for incident prostate cancer risk were extracted as the main endpoint. Disagreements were reconciled by consensus and where necessary by discussion with another investigator (DJAJ). Authors were not contacted to request any additional information or translation.

Statistical Analysis

Data were analyzed using Review Manager (RevMan) 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and STATA v. 11.2 (StataCorp, College Station, TX). We used the reported RR or OR of the highest versus lowest intake category, as the measure of the relation between ALA intake and prostate cancer risk. A-The primary pooled analysis of all reports was conducted using the Generic Inverse Variance method using random effects models weighting 57 where the log RRs for cohort studies or log ORs for case-control studies were weighted by the inverse of the variance to obtain a pooled RR estimate. Since nested case-cohort and nested case-control studies are temporally prospective, we analyzed data from these studies with the prospective studies. As in other meta-analyses that have examined prostate cancer ^{30 54 58}, ORs were considered as approximations of RRs. Since the initial risk of prostate cancer is lowSince prostate cancer is a rare disease, it is unlikely that there will be a substantial discrepancy in approximating ORs were treated as unbiased approximations of to RRs. ⁵⁹ Inter-study heterogeneity was assessed by Cochrane's Q (Chi² P<0.10) and quantified by I^2 . An $I^2 \ge 50\%$ indicated "substantial" heterogeneity and $\ge 75\%$ indicated "considerable" heterogeneity.⁶⁰ Sources of heterogeneity were explored by sensitivity analyses whereby the influence of individual studies was investigated by systematic removal of each study followed by recalculation of the pooled effect estimate and heterogeneity, as well as removal of outlier studies with risk estimates larger than 2 standard deviations from the mean risk estimate and

recalculation of the pooled effect estimate and heterogeneity. We also performed a priori subgroup analyses to assess effect modification by study design (prospective versus casecontrol). Effect modification by study characteristics was explored using meta-regression Posthoe analyses included dichotomous subgroup analyses to assess effect modification by study design (STATA 11.2., College Station, USA) and continuous analyses to assess the effect of the duration of follow-up on relative risk among prospective studies. Publication bias-that was formally tested using Begg's and Egger's tests.

RESULTS

Search Results

Figure 1 shows the flow of the literature selection applying the systematic search and selection strategies to identify eligible reports. Two hundred and forty three reports were identified by the search and two reports were manually included after a database search. Of these, 233 were determined to be irrelevant on review of the titles and abstracts. Four additional reports were then manually included. The remaining 16 reports were retrieved and reviewed in full, of which 4 were excluded. Results for The Health Professionals' Follow-up Study were published in three separate publications at different times of follow-up^{21 23 25}. Only the most recent publication of the results, by Giovannucci et al. in 2007, was included in the analyses as representing the cumulative experience of the earlier assessments of this cohort ²¹. A total of 12 reports, 5 prospective and 7 case-control studies, were included in the pooled analyses.

Study Characteristics

Table 1 shows the characteristics of the 12 included studies, which were composed of 7 case-control studies ^{32 45 48-52} and 5 prospective studies ^{19-22 24} that used 3 designs: cohort, nested case-cohort, and nested case-control. Five studies were conducted in North America, 1 in South America, and 6 in Europe. The 12 included studies contained a total of 14,795 cases of prostate cancer and 231,143 controls. All studies obtained dietary data using food frequency questionnaires (FFQ). Individual and average dietary ALA intake in these studies ranged from ≈ 0.05 to 4.16 g/d) and the reported relative risk or odds ratio of the highest versus the lowest intake category ranged from 0.7 to 3.91.

Primary Analysis

The overall analysis of the 12 studies examined prostate cancer, comparing the highest with the lowest ALA intake category. Seven studies reported a protective effect of ALA intake on prostate cancer, one of which was significant, and the remaining five studies reported a positive association, of which 3 were significant. Overall, although the relative risk was increased numerically by 8%, Overall, high exposure to ALA was not associated with increased risk of prostate cancer this increase in prostate cancer risk was not significant (pooled RR: 1.08; 95%CI: 0.90, 1.29, P=0.40) (Figure 2). However, there was evidence of considerable inter-study heterogeneity (1²=85%, P<0.00001). Systematic removal of each study, and recalculation of the pooled effect- during sensitivity analyses did not suggest identify any single study was an influential outlier.

Subgroup Analyses

Case-Control Studies

In an *a priori* meta-regression, we found no evidence of effect measure modification according to study design (P-value of the associated beta coefficient for study design P for heterogeneity = 0.331). There remained significant unexplained heterogeneity within each type of study design. In case-control studies (n=7; 4,047 n-cases and 4,762n controls), the summary RR was 1.30 (95%CI: 0.81, 2.07, P=0.27), with considerable inter-study heterogeneity (I²=90%, P<0.00001) (Figure 3). Systematic removal of each individual study during sensitivity analyses did not explain the heterogeneity. Removal of the 2 case-control studies by Ramon et al.⁴⁵, De Stefani et al.³² that reported risk estimates larger than 2 standard deviations from the pooled RR estimate reduced the inter-study heterogeneity (I²=68%, P=0.01) but did not eliminate it (Figure 4). The overall association became weakly protective, but was not significant (RR=0.93; 95%CI: 0.69,1.25, P=0.64) (Figure 4), Removal of the 3 case control studies by Ramon et al.⁴⁵ De Stefani et al.³², and Bidoli et al.⁵⁰ that had risk estimates outside the 95% CI of the pooled RR estimate, eliminated heterogeneity in the case control studies (I²=11%, P=0.34), but the overall non-significant association between ALA intake and prostate cancer risk remained (RR=1.08; 95%CI: 0.86,1.36, P=0.49) (Figure 5).

Prospective Studies

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210	In prospective studies alone ($n=5$; 10,748 n cases and 207,752n controls), no association
211	between ALA intake and prostate cancer risk was revealed found (RR: 0.95; 95%CI: 0.84, 1.09,
212	P=0.48) (Figure 46) but there existed substantial inter-study heterogeneity (I^2 =69%, P=0.01).
213	Sensitivity analyses showed that removal of the study by Giovannucci et al. ²¹ eliminated
214	heterogeneity with prospective studies ($I^2=8\%$, P=0.35) and made the protective effect
215	significant (RR=0.91; 95%CI: 0.83,0.99, P=0.02) (Figure <u>5</u> 7).
216	Duration of follow-up in prospective studies was found to be positively but not
217	significantly associated with the magnitude of relative risk (r=0.47).
218	
219	Publication Bias
220	Neither Begg's (P>0.165) nor Egger's (P>0.527) tests revealed evidence of publication
221	bias, however, one study by Ramon et al. ⁴⁵ had an unusually large effect with a small standard
222	error.
222	DISCUSSION
223	
224	Summary of Results
225	The present meta-analysis of 12 observational studies (7 case-control and 5 prospective)
226	comparing the highest with the lowest categories of dietary ALA intake demonstrated non-
227	significant heterogeneous effects of ALA on prostate cancer risk. Overall, there was no
228	significant association between ALA intake and risk of prostate cancer. The subgroup analysis of
229	case control studies alone showed a positive non-significant association, but with substantial
230	heterogeneity. However, upon removal of the studies by De Stefani et al. ³² and Ramon et al. ⁴⁵ ,
231	which reported large odds ratios greater than 3 but were still within 2 standard deviations of the
232	mean effect, the association became weakly non-significantly protective with decreased
233	heterogeneity. When examining the prospective studies alone, the association between ALA
234	intake and prostate cancer risk was weakly-non-significantly protective and after removal of the
235	study by Giovannucci et al. ²¹ became <u>weakly, but</u> significantly, protective with no
236	heterogeneity.
237	The results from the prospective studies are similar to those of previously published
238	findings that examined only prospective studies ⁵³ . Our study additionally investigated the
239	association between dietary ALA intake and prostate cancer risk among case-control studies and

reached a similarthe conclusion of non-significantly increased risk with high heterogeneity, particularly due to the inclusion of two studies with very high odds ratios. We explore whether these heterogeneous results can be explained by a number of factors, such as the variation in ALA consumption, sources, or population dietary patterns. However, this heterogeneity among the case-control studies may serve to highlight the less reliable nature of case-control study design as it inherently involves recall bias since dietary information is collected after disease development.

although the case control studies suggested an element of increased risk, which was dependent on the inclusion of two studies with very high odds ratios, the reasons for which are difficult to explain.

Heterogeneity and the Effect of ALA between Studies

In our study, different findings reviewed and inter-study heterogeneity may be explained by a number of factors: variation in ALA consumption and sources of ALA as a result of the population's dietary patterns, variation in ALA exposure levels, use of different FFQs and food databases, variation in adjustment factors, and difference in follow-up times among prospective studies.

Variation in ALA Consumption and Sources, and Population Dietary Patterns-

In the Netherlands, the chief sources of ALA include margarine (25% of daily intake), meat (11%), bread (10%), and vegetables (8%)³³, whereas in the United States, major sources of ALA come from mayonnaise, creamy salad dressings, margarine, butter, beef, pork, lamb, and oil and vinegar-based dressings²⁵. Interestingly, the prospective study from the Netherlands reported a weak protective effect of ALA intake on prostate cancer risk²⁰, but the most recent study from the United States reported a 25% increase in risk²¹. This difference may be due to the nature of the foods that contain ALA since in the United States, the sources of ALA are not the "healthy" sources where ALA is naturally found (e.g. flaxseed, walnuts, and canola oil), but rather profiled an unhealthy diet (e.g. canola oil in the form of mayonnaise and creamy salad dressings), which may be indicative of a less healthy lifestyle and this in itself may contribute to an increased risk of prostate cancer independent of ALA intake levels^{61 62}.

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In addition, in the case-control studies from Uruguay ³² and Spain ⁴⁵ that showed the largest increases in prostate cancer risk demonstrated that meat, and not vegetable, was the major source of ALA. When these two studies were removed from the analysis of the case-control studies, the effect of ALA intake on prostate cancer changed from a non-significantly weakly positive to a non-significantly weakly protective effect. Compared with the other studies from Europe and the United States, there is a much higher consumption of meat in Spain⁶³ and Uruguay, with Uruguay having the highest meat consumption per capita in the world ⁶⁴. An earlier analysis of the Health Professionals Follow-up Study cohort²⁵ supports this positive association between red meat consumption and prostate cancer risk. Furthermore, the two studies from Spanish-speaking countries also investigated the effect of animal fat on prostate cancer and both found significant positive associations. The Uruguayan study ³² observed that at the highest level of ALA intake derived from animal sources resulted in almost 3 times the risk of developing prostate cancer and the Spanish study ⁴⁵ revealed that the highest level of animal fat intake was associated with 2 times the risk. These findings indicate that high meat intake rather than high ALA may explain ALA's apparent adverse effect on prostate cancer. In further support of this idea, the study by Bidoli et al.⁵⁰ demonstrated a significant protective association between ALA and prostate cancer risk in an Italian population where ALA is mainly derived from olive oil ⁶⁵ and the diet is rich in raw vegetables ⁵⁰ rather than meat, profiling an overall more "healthy" diet. An explanation for the apparent association of prostate cancer incidence with vegetable

sources of ALA may be that in addition those who follow healthy lifestyles with increased plant ALA sources may undergo more frequent prostate specific antigen (PSA) testing and therefore have early prostate cancer detection. In this respect it has been found that higher whole grain intake was also associated with increased prostate cancer risk. However, when frequency of PSA screening was accounted for, the association of whole grains with prostate cancer incidence disappeared ⁶⁶. These studies indicate the importance of not only identifying the dietary sources of ALA, but taking into account what the nature of the foods may indicate in terms of diet and lifestyle since these also may affect prostate cancer risk.

299 Variation in ALA Exposure Levels.

 Another important aspect to consider is the differing exposure levels between the studies. Each study had different cut-offs for each quantile, which makes a true comparison of ALA intake exposure difficult since some studies had higher levels of ALA in their highest intake quantile than others. Further, some studies did not adequately define the absolute upper and/or lower limits of ALA intake ^{21 32 50} and one study did not report numerical exposure levels ⁴⁹. Two studies, one from Spain⁴⁵ and one from the Netherlands²⁰, with the largest adequately defined upper and lower limits of ALA exposure ranges, paradoxically reported the second highest and the second lowest risk of developing prostate cancer, respectively. Since the studies with the greatest range of exposure do not necessarily show the greatest effects, dietary variation in the levels of exposure does not appear to explain differences among the studies, thereby making differences in dietary sources of ALA of more importance especially in relation to meat consumption in Western countries.

Variation in FFQs and Food Databases-

In terms of utilizing different FFQs and food databases, each study used a different dietary FFQ. ALA content of processed food can vary, which can be of concern when using food databases to translate food intake into fatty acid intake. For example, the ALA content of 12 margarines available in Australia range from 0.2% to 5.9% ⁶⁷.

Variation in Adjustment Factors-

Although all the studies reported adjusted RRs or ORs, the adjustment factors were not consistent among the studies. Some of the adjustment factors in these studies included age, smoking history, physical activity level, BMI, family history of prostate cancer, history of diabetes mellitus, race, education, socioeconomic status, area of residence and intakes of total calories, fat, processed meat, fish, lycopene, and vitamin E supplements. Currently, the most well-established risk factors for prostate cancer are age, family history of the disease, and race/ethnicity ⁶⁸ and consequently are the most important adjustment factors. Only 4 ^{20-22 52} of the 12 included studies adjusted for all of these 3 factors. The studies conducted by Park et al. ¹⁹ and Mannisto et al.²⁴ did not adjust for age, which is by far the strongest predictor of prostate cancer incidence and death ⁶⁸. A family history of prostate cancer has been shown to increase the risk of diagnosis and death and this factor was not adjusted for in studies by Hedelin et al. ⁵¹, Andersson

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et al.⁴⁸, and Mannisto et al.²⁴ Race is a prostate cancer risk factor and prognostic factor, with African-American or Black men being at increased risk, and this was not adjusted for in the studies by Bidoli et al. ⁵⁰, De Stefani et al. ³², Ramon et al. ⁴⁵, and Meyer et al. ⁴⁹ Differences in adjustment among the included studies, particularly with respect to the important factors of age, family history of prostate cancer, and race could result in differences in risk estimates, thereby contributing to inter-study heterogeneity.

Variation in Follow-up Duration,

Follow-up time may also have an effect on heterogeneity, especially since the study by Giovannucci et al.²¹ had the longest follow-up duration (16 years). Comparing previous prospective studies following the same cohort ^{23 25} with this most recent study ²¹, demonstrates a shift over time (total of 12 years) from a non-significant to a significant positive association between ALA intake and prostate cancer. So, it can be hypothesized that the heterogeneity induced by this study may indicate that follow-up duration is positively related to the strength of the association between ALA and prostate cancer risk. This association may relate to the development of cancer over a longer period of time and therefore stronger association in the cohort between agents that may cause cancer and tumour occurrence. Alternatively, this relationship may reflect changes in diagnostic effectiveness over time. After investigating this suggestion, the effect of follow up duration on relative risk among the prospective studies was found to be positively, but not significantly correlated (r=0.47).

Reasons for the Lack of Effect of ALA

The overall effect of ALA on prostate cancer was found to be non-significant but may result from a number of factors including ALA exposure levels that are within health guidelines, confounding from other polyunsaturated fatty acids, and the difference in effect of ALA on prostate cancer mortality versus incidence.

The mean dietary ALA intake levels observed in these studies were all within the dietary reference intake (DRI) range of 1.1 to 1.6 g/d⁶⁹, suggesting that ALA may not increase the risk of cancer more than any other nutrient promoting cell growth. Rather, since ALA is a nutrient deficient in the Western diet ⁷⁰, it may be that a deficiency inhibits all cell growth, including tumour growth, instead of adequate or excess levels causing prostate cancer growth.

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Another issue to consider is confounding from other polyunsaturated fatty acids such as omega-6 or other omega-3 fatty acids (eicosapentaenoic and docosahexaenoic fatty acids) that might affect ALA metabolism ⁷¹ and consequently may introduce bias. The case-control study from the United States ⁵² demonstrated this as there was no significant association between ALA, omega-3, or omega-6 fatty acids and prostate cancer risk individually, but the highest dietary ratio of omega-6/omega-3 fatty acids was significantly associated with increased risk of high grade prostate cancer.

Finally, our analysis involved cancer incidence rather than mortality and ALA, among other factors such as energy intake, height, body mass index, calcium, and smoking, are also associated with cancer mortality²¹. The study by De Stefani et al. ³², which was the only study that defined cases solely as advanced prostate cancer, had the highest risk estimate of prostate cancer, indicating that ALA may be strongly associated with disease severity progression rather than incidence. In support of this point, the prospective study by Giovannucci et al.²¹ found that higher ALA intake was more strongly associated with increased risk of fatal prostate cancer than with incident. However, three other prospective studies did not find any difference between the effects of ALA on incident or advanced prostate cancer cases ^{19 20 22}. From these mixed findings, it is unclear whether ALA is associated with severity of prostate cancer, but determining whether ALA impacts prostate cancer incidence or progression is an important distinction that should be investigated in the future. Furthermore, the picture of ALA's effect on prostate cancer is complicated by the positive association of incident prostate cancer with either serum or adipose tissue ALA levels ^{24 43 44 46 47 72} despite the in vitro evidence which suggests that ALA may suppress prostate cancer cell growth ^{73 74}. However, there appears to be some correlation between ALA intake and serum ALA levels. In terms of intake, Gann et al. 43 found that plasma ALA levels were significantly positively correlated with meat and dairy product intake, and similar to the prospective analysis from the Health Professionals Follow-Up Study ²⁵, they found that red meat was positively associated with advanced prostate cancer, whereas diary foods were not. This corroboration not only suggests a correlation between ALA intake and serum ALA levels, but enforces the positive association between ALA from red meat and prostate cancer as seen in the studies from Uruguay ³² and Spain ⁴⁵, rather than from plant foods.

392 Limitations

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The first limitation of the meta-analysis is that all data currently available for inclusion come from epidemiological studies since there are no data from randomized controlled trials due to ethical concerns. Second, interpretation of the analyses was complicated by the evidence of considerable heterogeneity among the studies, which as discussed above may have resulted from differences in ALA sources and population dietary patterns, ALA exposure levels, FFQs and food databases, adjustment factors, and duration of follow-up. There are also inherent limitations in the studies included based on study design. The association between ALA intake and prostate eancer risk was stronger overall in the case-control studies than in the prospective studies. HoweverFor example, there is the possibility of recall bias in case-control studies, as dietary intake information is collected after disease development.

CONCLUSION

In conclusion, these findings provide no clear evidence of an association between dietary ALA intake and prostate cancer risk. Further, since these observational studies can only show association between ALA intake and prostate cancer, possible causation would be difficult to establish. Therefore, additional research from epidemiological, clinical, and in vitro studies are required to elucidate whether ALA has a promotional, inhibitory, or no effect on prostate cancer risk and development. For the present, no significant association has been found and where any support of a positive effect was seen, red meat sources have been strongly implicated. The source of ALA appears to be of importance, particularly identifying whether it is from animal or vegetable sources, as ALA may be a marker for higher meat and fat intake in some countries both of which have been associated with increased prostate cancer risk. Attention should also be paid to the effect of ALA on prostate cancer progression to address the issues of specific vulnerability identified in the studies of Giovannucci et al. and De Stefani et al. 21 32. However, resolving the relation of dietary ALA to prostate cancer risk through randomized controlled trials will likely continue to be difficult due to the significant public health implications of reducing/eliminating a dietary fatty acid which is essential and has suggested heart health benefits. Of probably greater importance is determination of the sources of the fatty acid since ALA is associated in the North American diet with meat membranes and creamy salad dressings, which themselves may be markers of a suboptimal dietary pattern and lifestyle

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sources and dietary patterns, variation in ALA exposure levels, differences in FFQs and food databases, variation in adjustment factors, follow-up duration, and study design

"What this Paper Adds"

ALA is considered a cardioprotective nutrient, however some epidemiological studies have suggested that dietary ALA intake increases the risk of prostate cancer. Although Carayol et al. conducted a meta-analysis on the effect of dietary ALA on prostate cancer in 2010, only prospective studies were analyzed and case-control studies were not included. Overall, we found no significant association between ALA intake and risk of prostate cancer. The results from the prospective studies were similar to those of previously published findings. However, the subgroup analysis of case control studies alone showed a positive non-significant association, but with substantial heterogeneity. The case control studies suggested an element of increased risk, which was dependent on the inclusion of two studies with very high odds ratios, the reasons for which are difficult to explain. Additional research from epidemiological, clinical, and in vitro studies are required to elucidate whether ALA has a promotional, null, or inhibitory effect on prostate cancer risk and development.

459 AUTHORSHIP

All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. Details of Contributors: AJC was involved in the conception and design, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content, and final approval of the version to be published. JLS was involved in the conception and design, some analysis, and revising the article critically for important intellectual content. RS was involved in revising the article critically for important intellectual content. GE was involved in the conception and design and in revising the article critically for important intellectual content. DJAJ was in the conception and design, revising the article critically for important intellectual content, and final approval of the version to be published.

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9	471	DATA SHARING	
10 11	472	There is no additional data available.	
12	473	COMPETING INTEREST DECLARATION	
13 14	474	All authors have completed the Unified Competing Interest form at	
15	475	www.icmje.org/coi disclosure.pdf (available on request from the corresponding author) and	
16 17	476	declare that (1) AJC, JLS, RdS, and GE have not had financial support from any company for the	
18	477	submitted work; (2) AJC, JLS, RdS, and GE have no relationships with any companies that	Ű
19	478	might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners,	Comment [R2]: May want to confirm Joh
20 21	479	or children have no financial relationships that may be relevant to the submitted work; and (4)	okay with this—his wife works for Unilever. I generally disclose our Coke ties, but might r
22	480	AJC, JLS, RdS, and GE have no non-financial interests that may be relevant to the submitted	relevant for this—we like to err on the side of "overidsclosure"
23 24	481	work. DJAJ has served on the Scientific Advisory Board of Sanitarium Company, Agri-Culture	
25	482	and Agri-Food Canada (AAFC), Canadian Agriculture Policy Institute (CAPI), California	
26 27	483	Strawberry Commission, Loblaw Supermarket, Herbal Life International, Nutritional	
28	484	Fundamental for Health, Pacific Health Laboratories, Metagenics, Bayer Consumer Care, Orafti,	
29 30	485	Dean Foods, Kellogg's, Quaker Oats, Procter & Gamble, Coca-Cola, NuVal Griffin Hospital,	
30 31	486	Abbott, Pulse Canada, Saskatchewan Pulse Growers, and Canola Council of Canada; received	
32	487	honoraria for scientific advice from Sanitarium Company, Orafti, the Almond Board of	
33 34	488	California, the American Peanut Council, International Tree Nut Council Nutrition Research and	
35	489	Education Foundation and the Peanut Institute, Herbal Life International, Pacific Health	
36 37	490	Laboratories, Nutritional Fundamental for Health, Barilla, Metagenics, Bayer Consumer Care,	
38	491	Unilever Canada and Netherlands, Solae, Oldways, Kellogg's, Quaker Oats, Procter & Gamble,	
39 40	492	Coca-Cola, NuVal Griffin Hospital, Abbott, Canola Council of Canada, Dean Foods, California	
40	493	Strawberry Commission, Haine Celestial, Pepsi, and Alpro Foundation; has been on the speakers	
42	494	panel for the Almond Board of California; received research grants from Saskatchewan Pulse	
43 44	495	Growers, the Agricultural Bioproducts Innovation Program (ABIP) through the Pulse Research	
45	496	Network (PURENet), Advanced Food Materials Network (AFMNet), Loblaw, Unilever, Barilla,	
46 47	497	Almond Board of California, Coca-Cola, Solae, Haine Celestial, Sanitarium Company, Orafti,	
48	498	International Tree Nut Council Nutrition Research and Education Foundation and the Peanut	
49 50	499	Institute, the Canola and Flax Councils of Canada, Calorie Control Council, Canadian Institutes	
50 51	500	of Health Research, Canada Foundation for Innovation, and the Ontario Research Fund; and	
52	501	received travel support to meetings from the Solae, Sanitarium Company, Orafti, AFMNet,	
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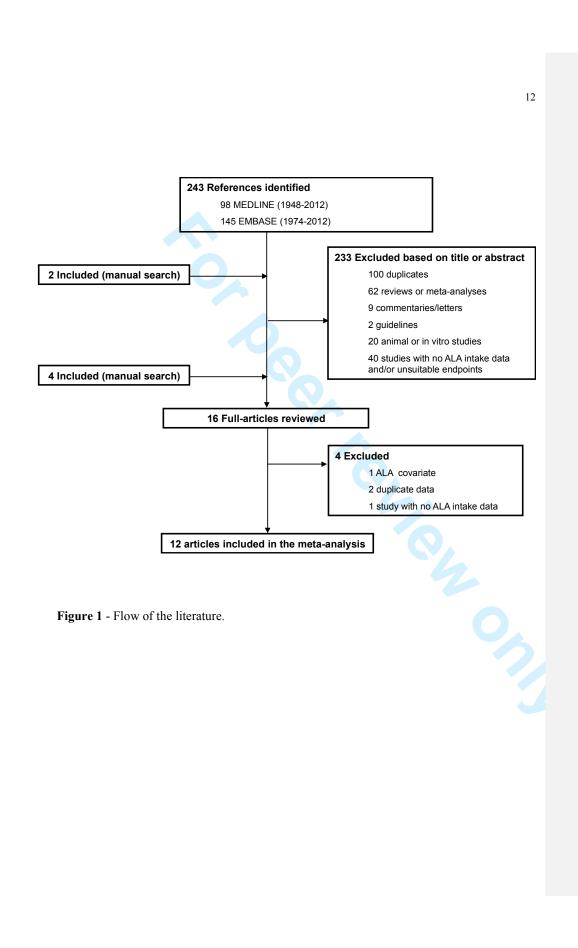
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Study	Country of Origin	Study Design	Sample size	Age (years)	Incident Cases	Follow-up (years)	Exposure level (g/d)	Relative Risk or Odds Ratio	95% CI
Andersson et al. 1996 [38]	Sweden	Case-control	526 cases/536 controls	<80	-	-	0.817 - 1.352	0.93	0.65-1.32
Vleyer et al. 1997 [39]	Canada	Case-control	215 cases/593 controls	≥45	-	-	-	0.98	0.54-1.78
Schuurman et al. 1999 [18]*	Netherlands	Nested case-cohort	58,279 (1525 subcohort)	55-69	642	6.3	0.7 - 2.1	0.76	0.66-1.04
De Stefani et al. 2000 [29]	Uruguay	Case-control	217 cases/431 controls	40-89	-	-	≤0.8 - ≥1.5	3.91	1.50-10.1
Ramon et al. 2000 [40]	Spain	Case-control	217 cases/434 controls	<60-80	-	-	0.72 - 2.1	3.1	2.2-4.7
Vannisto et al. 2003 [22]*	Finland	Nested case-control	198 cases/198 controls	50-69	246	5-8	1.0 - 2.3	1.16	0.64-2.13
Bidoli et al. 2005 [41]	Italy	Case-control	1294 cases/1451 controls	45-74	-	-	mean 1.6	0.7	0.6-0.9
Koralek et al. 2006 [20]*	United States	Prospective cohort	29,592	55-74	1898	5.1	1.09 - 1.75	0.94	0.81-1.09
Hedelin et al. 2007 [42]	Sweden	Case-control	1499 cases/1130 controls	mean 67.3	-	-	0.05 - 0.60	1.35	0.99-1.84
Giovannucci et al. 2007 [19]*	United States	Prospective cohort	47,750	40-75	3544	16	<0.79 - ≥1.32	1.12	1.01-1.25
Park et al. 2007 [17]*	United States	Prospective cohort	82,483	≥45	4404	8	1.1 - 2.14†	0.92	0.84-1.02
Williams et al. 2011 [43]	United States	Case-control	79 cases/187 controls	≥18	-	-	≤1.0 - 4.156†	0.82	0.41-1.6

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Meyer et al. 1997 [39]	Canada	Case-control	215 cases/593 controls	<u>≥</u> 45	-		-	0.98	0.54-1.78
Schuurman et al. 1999 [18]*	Netherlands	Nested case-cohort	58279 (1525 subcohort)	55-69	642	6.3	0.7 - 2.1	0.76	0.66-1.04
De Stefani et al. 2000 [29]	Uruguay	Case-control	217 cases/431 controls	40-89	-	-	⊴0.8 - ≥1.5	3.91	1.50-10.1
Ramon et al. 2000 [40]	Spain	Case-control	217 cases/434 controls	<60-80	-	-	0.72 - 2.1	3.1	2.2-4.7
Mannisto et al. 2003 [22]*	Finland	Nested case-control	198 cases/198 controls	50-69	246	5-8	1.0 - 2.3	1.16	0.64-2.13
Biddi et al. 2005 [41]	Italy	Case-control	1294 cases/1451 controls	45-74	-	-	mean 1.6	0.7	0.6-0.9
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* Prospective studies.									
† Based on a 2000 kcal diet.									

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		Risk Ratio		Risk Ratio
Study or Subgroup	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Andersson 1996 [48]	8.4%	0.93 [0.65, 1.33]	1996	
Meyer 1997 [49]	5.2%	0.98 [0.54, 1.78]	1997	
Schuurman 1999 [20]	10.5%	0.76 [0.61, 0.95]	1999	
De Stefani 2000 [32]	2.7%	3.91 [1.51, 10.15]	2000	
Ramon 2000 [45]	8.0%	3.10 [2.12, 4.53]	2000	_
Mannisto 2003 [24]	5.1%	1.16 [0.64, 2.12]	2003	_
Bidoli 2005 [50]	10.9%	0.70 [0.57, 0.86]	2005	
Koralek 2006 [22]	11.6%	0.94 [0.81, 1.09]	2006	-
Hedelin 2007 [51]	9.1%	1.35 [0.99, 1.84]	2007	
Park 2007 [19]	12.2%	0.92 [0.83, 1.01]	2007	-
Giovannucci 2007 [21]	12.1%	1.12 [1.01, 1.25]	2007	-
Williams 2011 [52]	4.3%	0.82 [0.41, 1.64]	2011	
Total (95% CI)	100.0%	1.08 [0.90, 1.29]		•
Heterogeneity: Tau ² = 0	.06; Chi ² =	= 71.45, df = 11 (P <	0.00001 ; $I^2 = 85\%$	0.10.2 0.5 1 2 5 10
Test for overall effect: Z				0.10.2 0.5 1 2 5 10 Favours ALA Favours Control

Figure 2 – Pooled effect of dietary ALA intake on prostate cancer risk in case-control, nested case-cohort, and cohort studies. Relative Risk (RR) with 95% CI, study weights, and pooled effect estimates were generated using the general inverse variance method with random effects models (RevMan 5.1, Cochrane Library software, Oxford, UK). Inter-study heterogeneity was tested by Cochrane's Q (Chi²) at a significance level of P<0.10 and quantified by I², where I² \geq 50 % is considered to be evidence of substantial heterogeneity and \geq 75%, considerable heterogeneity ⁵⁵.

		Risk Ratio		Risk Ratio
Study or Subgroup	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Andersson 1996 [48]	15.7%	0.93 [0.65, 1.33]	1996	
Meyer 1997 [49]	13.5%	0.98 [0.54, 1.78]	1997	_
Ramon 2000 [45]	15.5%	3.10 [2.12, 4.53]	2000	_
De Stefani 2000 [32]	10.0%	3.91 [1.51, 10.15]	2000	—
Bidoli 2005 [50]	16.7%	0.70 [0.57, 0.86]	2005	
Hedelin 2007 [51]	16.1%	1.35 [0.99, 1.84]	2007	
Williams 2011 [52]	12.5%	0.82 [0.41, 1.64]	2011	
Total (95% CI)	100.0%	1.30 [0.81, 2.07]		★
Heterogeneity: Tau ² = (0.33; Chi ²	= 57.44, df = 6 (P <	0.00001); I ² = 90%	
Test for overall effect: 2	z = 1.10 (P = 0.27)		Favours ALA Favours Control

Figure 3 – Pooled effect of dietary ALA intake on prostate cancer risk in case-control studies. Relative Risk (RR) with 95% CI, study weights, and pooled effect estimates were generated using the general inverse variance method with random effects models (RevMan 5.1, Cochrane Library software, Oxford, UK). Inter-study heterogeneity was tested by Cochrane's Q (Chi²) at a



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significance level of P<0.10 and quantified by I², where I² \geq 50 % is considered to be evidence of substantial heterogeneity and \geq 75%, considerable heterogeneity ⁵⁵.

Study or Subgroup	Weight	Risk Ratio IV, Random, 95% CI	Year	Risk Ratio IV, Random, 95% CI
Andersson 1996 [48]	22.2%	0.93 [0.65, 1.33]	1996	
Meyer 1997 [49]	14.0%	0.98 [0.54, 1.78]	1997	
De Stefani 2000 [32]	0.0%	3.91 [1.51, 10.15]	2000	
Ramon 2000 [45]	0.0%	3.10 [2.12, 4.53]	2000	
Bidoli 2005 [50]	28.2%	0.70 [0.57, 0.86]	2005	
Hedelin 2007 [51]	24.0%	1.35 [0.99, 1.84]	2007	`
Williams 2011 [52]	11.6%	0.82 [0.41, 1.64]	2011	
Total (95% CI)	100.0%	0.93 [0.69, 1.25]		•
Heterogeneity: Tau ² =	0.07; Chi ²	= 12.46, df = 4 (P =	0.01 ; $I^2 = 68\%$	
Test for overall effect: 2	Z = 0.47 (P = 0.64)		Favours ALA Favours Control

Figure 4 – Pooled effect of dietary ALA intake on prostate cancer risk in case control studies after the removal of the studies by De Stefani et al. ³² and Ramon et al. ⁴⁵ and following a sensitivity analysis. Relative Risk (RR) with 95% CI, study weights, and pooled effect estimates were generated using the general inverse variance method with random effects models (RevMan 5.1, Cochrane Library software, Oxford, UK). Inter study heterogeneity was tested by Cochrane's Q (Chi²) at a significance level of P<0.10 and quantified by I², where I² \geq 50 % is considered to be evidence of substantial heterogeneity and \geq 75%, considerable heterogeneity.⁵⁵.

		Risk Ratio		Risk Ratio
Study or Subgroup	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Andersson 1996 [48]	34.1%	0.93 [0.65, 1.33]	1996	
Meyer 1997 [49]	13.4%	0.98 [0.54, 1.78]	1997	
De Stefani 2000 [32]	0.0%	3.91 [1.51, 10.15]	2000	
Ramon 2000 [45]	0.0%	3.10 [2.12, 4.53]	2000	
Bidoli 2005 [50]	0.0%	0.70 [0.57, 0.86]	2005	
Hedelin 2007 [51]	42.5%	1.35 [0.99, 1.84]	2007	⊢∎
Williams 2011 [52]	10.0%	0.82 [0.41, 1.64]	2011	
Total (95% CI)	100.0%	1.08 [0.86, 1.36]		•
Heterogeneity: Tau ² =	0.01; Chi ²	= 3.37, df = 3 (P = 0)	$(.34); I^2 = 11\%$	
Test for overall effect: 2				Favours ALA Favours Control

Figure 5 – Pooled effect of dietary ALA intake on prostate cancer risk in case-control studies after the removal of the studies by De Stefani et al.³², Ramon et al.⁴⁵, and Bidoli et al.⁵⁰ and following a sensitivity analysis. Relative Risk (RR) with 95% CI, study weights, and pooled effect estimates were generated using the general inverse variance method with random effects

models (RevMan 5.1, Cochrane Library software, Oxford, UK). Inter-study heterogeneity was tested by Cochrane's Q (Chi²) at a significance level of P<0.10 and quantified by I^2 , where $I^2 \ge 50$ % is considered to be evidence of substantial heterogeneity and $\ge 75\%$, considerable heterogeneity.⁵⁵.

		Rate Ratio	Rate Ratio
Study or Subgroup	Weight	IV, Random, 95% CI Year	IV, Random, 95% CI
Schuurman 1999 [20]	16.6%	0.76 [0.61, 0.95] 1999	
Mannisto 2003 [24]	4.1%	1.16 [0.64, 2.12] 2003	
Koralek 2006 [22]	23.4%	0.94 [0.81, 1.09] 2006	+
Park 2007 [19]	28.4%	0.92 [0.83, 1.01] 2007	=
Giovannucci 2007 [21]	27.5%	1.12 [1.01, 1.25] 2007	-
Total (95% CI)	100.0%	0.95 [0.84, 1.09]	•
Heterogeneity: Tau ² = 0	.01; Chi ² =	= 13.03, df = 4 (P = 0.01); $I^2 = 69\%$	
Test for overall effect: Z			Favours ALA Favours Control

Figure 46 – Pooled effect of dietary ALA intake on prostate cancer risk in prospective studies. Relative Risk (RR) with 95% CI, study weights, and pooled effect estimates were generated using the general inverse variance method with random effects models (RevMan 5.1, Cochrane Library software, Oxford, UK). Inter-study heterogeneity was tested by Cochrane's Q (Chi²) at a significance level of P<0.10 and quantified by I², where I² \geq 50 % is considered to be evidence of substantial heterogeneity and \geq 75%, considerable heterogeneity ⁵⁵.

		Rate Ratio	Rate Ratio
Study or Subgroup	Weight I	IV, Random, 95% Cl Year	IV, Random, 95% CI
Schuurman 1999 [20]	12.8%	0.76 [0.61, 0.95] 1999	
Mannisto 2003 [24]	1.9%	1.16 [0.64, 2.12] 2003	
Koralek 2006 [22]	28.1%	0.94 [0.81, 1.09] 2006	+
Park 2007 [19]	57.1%	0.92 [0.83, 1.01] 2007	•
Total (95% CI)	100.0%	0.91 [0.83, 0.99]	•
Heterogeneity: $Tau^2 = 0$.00; Chi ² =	= 3.27, df = 3 (P = 0.35); l ² = 8%	
Test for overall effect: Z	= 2.28 (P	= 0.02)	Favours ALA Favours Control
			Tavours ALA Tavours Control
		Rate Ratio	Rate Ratio
Study or Subgroup	Weight	Rate Ratio IV, Random, 95% Cl Year	Rate Ratio IV, Random, 95% CI
Study or Subgroup Schuurman 1999 [20]	Weight 12.8%		
, ,	-	IV, Random, 95% Cl Year 0.76 [0.61, 0.95] 1999	
Schuurman 1999 [20]	12.8%	IV, Random, 95% CI Year 0.76 [0.61, 0.95] 1999 1.16 [0.64, 2.12] 2003	
Schuurman 1999 [20] Mannisto 2003 [24]	12.8% 1.9%	IV, Random, 95% CI Year 0.76 [0.61, 0.95] 1999 1.16 [0.64, 2.12] 2003 0.94 [0.81, 1.09] 2006	
Schuurman 1999 [20] Mannisto 2003 [24] Koralek 2006 [22]	12.8% 1.9% 28.1%	IV, Random, 95% CI Year 0.76 [0.61, 0.95] 1999 1.16 [0.64, 2.12] 2003 0.94 [0.81, 1.09] 2006	
Schuurman 1999 [20] Mannisto 2003 [24] Koralek 2006 [22] Park 2007 [19] Giovannucci 2007 [21]	12.8% 1.9% 28.1% 57.1% 0.0%	IV, Random, 95% Cl Year 0.76 [0.61, 0.95] 1999 1.16 [0.64, 2.12] 2003 0.94 [0.81, 1.09] 2006 0.92 [0.83, 1.01] 2007 1.12 [1.01, 1.25] 2007	
Schuurman 1999 [20] Mannisto 2003 [24] Koralek 2006 [22] Park 2007 [19] Giovannucci 2007 [21] Total (95% CI)	12.8% 1.9% 28.1% 57.1% 0.0% 100.0%	IV, Random, 95% CI Year 0.76 [0.61, 0.95] 1999 1.16 [0.64, 2.12] 2003 0.94 [0.81, 1.09] 2006 0.92 [0.83, 1.01] 2007 1.12 [1.01, 1.25] 2007 0.91 [0.83, 0.99]	
Schuurman 1999 [20] Mannisto 2003 [24] Koralek 2006 [22] Park 2007 [19] Giovannucci 2007 [21] Total (95% CI)	12.8% 1.9% 28.1% 57.1% 0.0% 100.0%	IV, Random, 95% Cl Year 0.76 [0.61, 0.95] 1999 1.16 [0.64, 2.12] 2003 0.94 [0.81, 1.09] 2006 0.92 [0.83, 1.01] 2007 1.12 [1.01, 1.25] 2007	

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Figure 57 – Pooled effect of dietary ALA intake on prostate cancer risk in prospective studies after the systematic removal of the study by Giovannucci et al. ²¹ following a sensitivity analysis. Relative Risk (RR) with 95% CI, study weights, and pooled effect estimates were generated using the general inverse variance method with random effects models (RevMan 5.1, Cochrane Library software, Oxford, UK). Inter-study heterogeneity was tested by Cochrane's Q (Chi²) at a significance level of P<0.10 and quantified by I², where I² \geq 50% is considered to be evidence of substantial heterogeneity and \geq 75%, considerable heterogeneity ⁵⁵.

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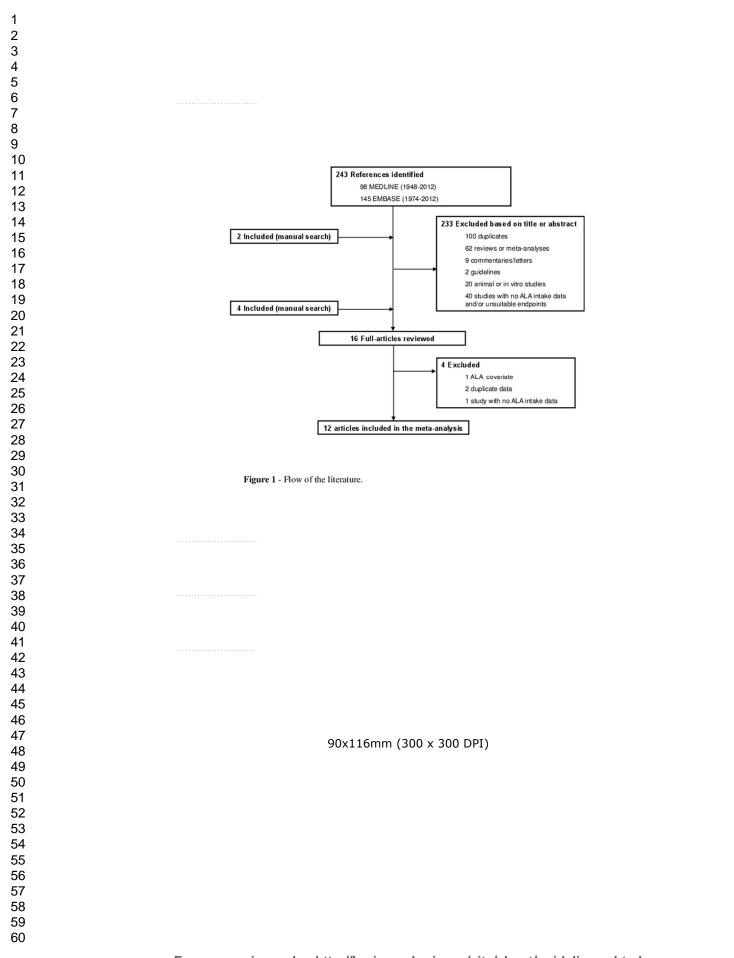
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		Risk Ratio		Risk Ratio
Study or Subgroup	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Andersson 1996 [48]	8.4%	0.93 [0.65, 1.33]	1996	
Meyer 1997 [49]	5.2%	0.98 [0.54, 1.78]	1997	
Schuurman 1999 [20]	10.5%	0.76 [0.61, 0.95]	1999	
De Stefani 2000 [32]	2.7%	3.91 [1.51, 10.15]	2000	
Ramon 2000 [45]	8.0%	3.10 [2.12, 4.53]	2000	
Mannisto 2003 [24]	5.1%	1.16 [0.64, 2.12]	2003	
Bidoli 2005 [50]	10.9%	0.70 [0.57, 0.86]	2005	-
Koralek 2006 [22]	11.6%	0.94 [0.81, 1.09]	2006	-
Hedelin 2007 [51]	9.1%	1.35 [0.99, 1.84]	2007	
Park 2007 [19]	12.2%	0.92 [0.83, 1.01]	2007	-
Giovannucci 2007 [21]	12.1%	1.12 [1.01, 1.25]	2007	-
Williams 2011 [52]	4.3%	0.82 [0.41, 1.64]	2011	
Total (95% CI)	100.0%	1.08 [0.90, 1.29]		•
Heterogeneity: Tau ² = 0	.06; Chi ² =	= 71.45, df = 11 (P <	0.00001 ; $I^2 = 85\%$	
Test for overall effect: Z	= 0.84 (P	= 0.40)		Favours ALA Favours Contro

Figure 2 – Pooled effect of dietary ALA intake on prostate cancer risk in case-control, nested case-control, nested case-cohort, and cohort studies. Relative Risk (RR) with 95% CI, study weights, and pooled effect estimates were generated using the general inverse variance method with random effects models (RevMan 5.1, Cochrane Library software, Oxford, UK). Inter-study heterogeneity was tested by Cochrane's Q (Chi²) at a significance level of P<0.10 and quantified by l^2 , where $l^2 \ge 50$ % is considered to be evidence of substantial heterogeneity and $\ge 75\%$, considerable heterogeneity.

		Risk Ratio		Risk Ratio
Study or Subgroup	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Andersson 1996 [48]	15.7%	0.93 [0.65, 1.33]	1996	
Meyer 1997 [49]	13.5%	0.98 [0.54, 1.78]	1997	
Ramon 2000 [45]	15.5%	3.10 [2.12, 4.53]	2000	
De Stefani 2000 [32]	10.0%	3.91 [1.51, 10.15]	2000	
Bidoli 2005 [50]	16.7%	0.70 [0.57, 0.86]	2005	
Hedelin 2007 [51]	16.1%	1.35 [0.99, 1.84]	2007	
Williams 2011 [52]	12.5%	0.82 [0.41, 1.64]	2011	
Total (95% CI)	100.0%	1.30 [0.81, 2.07]		•
Heterogeneity: $Tau^2 =$	0.33: Chi ²	= 57.44, df = 6 (P <	0.00001 ; $I^2 = 90\%$	
Test for overall effect: 2	Z = 1.10 (P = 0.27)		Favours ALA Favours Control

Figure 3 – Pooled effect of dietary ALA intake on prostate cancer risk in case-control studies. Relative Risk (RR) with 95% CI, study weights, and pooled effect estimates were generated using the general inverse variance method with random effects models (RevMan 5.1, Cochrane Library software, Oxford, UK). Inter-study heterogeneity was tested by Cochrane's Q (Chi^2) at a significance level of P<0.10 and quantified by I^2 , where $I^2 \ge 50$ % is considered to be evidence of substantial heterogeneity and $\ge 75\%$. considerable heterogeneity ⁵⁵.

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Rate Ratio			Rate Ratio	
Study or Subgroup	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Schuurman 1999 [20]	16.6%	0.76 [0.61, 0.95]	1999	
Mannisto 2003 [24]	4.1%	1.16 [0.64, 2.12]	2003	
Koralek 2006 [22]	23.4%	0.94 [0.81, 1.09]	2006	+
Park 2007 [19]	28.4%	0.92 [0.83, 1.01]	2007	-
Giovannucci 2007 [21]	27.5%	1.12 [1.01, 1.25]	2007	-
Total (95% CI)	100.0%	0.95 [0.84, 1.09]		•
Heterogeneity: Tau ² = 0	.01; Chi ² =	= 13.03, df = 4 (P = 0	0.01 ; $I^2 = 69\%$	
Test for overall effect: Z	= 0.70 (P	= 0.48)		Favours ALA Favours Control

Figure 4 – Pooled effect of dietary ALA intake on prostate cancer risk in prospective studies. Relative Risk (RR) with 95% CI, study weights, and pooled effect estimates were generated using the general inverse variance method with random effects models (RevMan 5.1, Cochrane Library software, Oxford, UK). Inter-study heterogeneity was tested by Cochrane's Q (Chi²) at a significance level of P<0.10 and quantified by I², where I² \ge 50% is considered to be evidence of substantial heterogeneity and \ge 75%, considerable heterogeneity ⁵⁵.

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Study or Subgroup	Weight	Rate Ratio IV, Random, 95% CI	Year	Rate Ratio IV, Random, 95% CI
Schuurman 1999 [20]	12.8%	0.76 [0.61, 0.95]	1999	
Mannisto 2003 [24]	1.9%	1.16 [0.64, 2.12]	2003	
Koralek 2006 [22]	28.1%	0.94 [0.81, 1.09]	2006	+
Park 2007 [19]	57.1%	0.92 [0.83, 1.01]	2007	•
Total (95% CI)	100.0%	0.91 [0.83, 0.99]		•
Heterogeneity: Tau ² =			.35); I ² = 8%	5 to 10 2 0 5 1 2 5 10
Test for overall effect:	Z = 2.28 (P	9 = 0.02)		Favours ALA Favours Control

Figure 5 – Pooled effect of dietary ALA intake on prostate cancer risk in prospective studies after the systematic removal of the study by Giovannucci et al. ²¹ following a sensitivity analysis. Relative Risk (RR) with 95% CI, study weights, and pooled effect estimates were generated using the general inverse variance method with random effects models (RevMan 5.1, Cochrane Library software, Oxford, UK). Inter-study heterogeneity was tested by Cochrane's Q (Chi²) at a significance level of P<0.10 and quantified by 1^2 , where $1^2 \ge 50$ % is considered to be evidence of substantial heterogeneity and $\ge 75\%$, considerable heterogeneity ⁵⁵.