Supplementary file for Hanson et al:

Effects of supplementary dietary polyunsaturated fat on cancer incidence: systematic review and meta-analysis of randomised trials

Contents

RESULTS

(in greater detail than the main paper)

From our trials database we included 47 RCTs (49 comparisons, including 108,194 participants) that assessed outcomes of interest to this review. Thirty four trials (including 97,548 participants) assessed effects of LCn3, three (3179 participants) assessed effects of ALA, eight (4976 participants) assessed effects of omega-6 and 9 trials (including 11,573 participants) assessed effects of total PUFA (Supplementary Table 1). Several trials assessed more than one of these interventions, so numbers of trials and participants are not additive. Of the 47 trials, 38 included participants with normal baseline cancer risk (including healthy adults and those with risk factors for other diseases, or existing disease including CVD, diabetes and eye diseases), 3 included participants with cancer risk factors (2 at high risk of breast cancer, 1 at high risk of bowel cancer) and 6 included participants with previously diagnosed cancer (1 postoperative breast cancer, 3 postoperative colorectal cancer, 1 prostate cancer, one skin cancer). Most trials provided supplementary capsules, but trials of omega-6 and total PUFA tended to provide dietary advice with or without supplementary foods, some trials provide supplementary foods (such as enriched margarines, nuts, and one (set in an institution) provided all food. In four trials the intervention was to reduce fat intake, which also reduced PUFA, so for these trials the higher PUFA arm was the study control arm. Mean trial duration was over 30 months, and most trials were conducted in Europe (20 trials) or North America (15 trials), five were conducted in Japan, two in Australia and/or New Zealand, and five were conducted over more than one continent. Seventeen of the 47 trials were at low summary risk of bias (Supplementary Figure 1, Supplementary Table 1).

Effects of long-chain omega-3 fat on risk of any cancer

Effects of LCn3 on all primary and secondary outcomes, along with sensitivity analyses and subgroupings are displayed in Supplementary Tables 2 and 3. The GRADE assessment is shown in Supplementary Table 4.

Meta-analysis of 27 trials (113,557 participants) reporting from 1 to 1784 cancer diagnoses suggested little or no effect on any cancer diagnosis (RR 1.02, 95% CI 0.98 to 1.07, I^2 0%, Figure 1 in the main paper, high quality evidence), and this lack of effect did not alter in fixed effects meta-analysis, when limiting to trials at low summary risk of bias, low risk of compliance issues or larger trials (at least 100 randomised participants). There was no suggestion of heterogeneity between trials and the funnel plot did not suggest small study bias (Supplementary Figure 2). Subgrouping did not suggest differences in effect by duration, dose, nutrients replaced by LCn3, intervention type, age, sex or baseline cancer risk (test for subgroup differences all $p>0.05$). Mean duration of included trials was 32 months (SD 22, range 12 to 88 months) and mean dose of LCn3 was 1.7g/d (SD 1.2g/d, range 0.5 to 4.6g/d). Increasing LCn3 has little or no effect on risk of diagnosis of any cancer (high quality evidence).

Eighteen trials (99,336 participants) provided data on 2277 cancer deaths and meta-analysis suggested little or no effect of increasing LCn3 (RR 0.97, 95% CI 0.90 to 1.06, I^2 0%, Figure 2 in the main paper), and the lack of effect didn't alter in any sensitivity analysis.

Subgrouping did not suggest differential effects by trial duration, LCn3 dose, replacement for LCn3, intervention type, age, sex or baseline cancer risk. There was no suggestion of heterogeneity between trials, and the funnel plot showed no sign of small study bias (Supplementary Figure 3). Mean duration of included trials was 43 months (SD 22, range 12 to 88 months) and mean dose of LCn3 was 1.6g/d (SD 1.5g/d, range 0.4 to 6.0g/d). Increasing LCn3 probably has little or no effect on risk of cancer death (moderate quality evidence, downgraded once for imprecision).

Effects of long-chain omega-3 fat on risk of breast cancer

Meta-analysis of 12 trials (92,736 participants, 44,304 women) reporting from 1 to 246 breast cancer diagnoses (661 diagnoses overall) suggest little or no effect of LCn3 on breast cancer diagnosis (RR 1.03, 95% CI 0.89 to 1.20, I^2 0%, Figure 3 in the main paper), and this lack of effect did not alter in fixed effects meta-analysis, when limiting to trials at low summary risk of bias, low risk of compliance issues or larger trials (at least 100 randomised participants). There was no suggestion of heterogeneity between trials. Subgrouping did not suggest differences in effect by duration, dose, nutrients replaced by LCn3, intervention type, age, sex or baseline cancer risk (test for subgroup differences all $p>0.05$), however trials tended to cluster into specific subgroups rather than be spread evenly across subgroups, so differences would be harder to see. There was no suggestion of small study bias in the funnel plot (Supplementary Figure 4). Mean duration of included trials was 48 months (SD 25, range 12 to 88 months) and mean dose of LCn3 was 1.9g/d (SD 1.5g/d, range 0.6 to 4.6g/d). Increasing LCn3 probably has little or no effect on risk of breast cancer diagnosis (moderate quality evidence, downgraded once for imprecision).

Two trials (including 3322 participants, 102 women) reported breast cancer deaths, but each reported a single death, so there were insufficient data to assess effects (Supplementary Figure 5). One of the included trials is a male only study but we included the data in Supplementary Figure 5 as it reported a single death from breast cancer [1], men are not included in other breast cancer trials. Mean duration of included trials was 60 months (SD 17, range 48 to 72 months) and mean dose of LCn3 was 0.9g/d (SD 0.5g/d, range 0.5 to 1.2g/d). The effect of increasing LCn3 on breast cancer deaths is unclear as the evidence is of very low quality (downgraded once for risk of bias, twice for imprecision).

Lower breast density is associated with lower risk of breast cancer in women. A single trial (not at low summary risk of bias) of 175 women reported on breast density, suggesting a mean difference of 2.06cm^2 (95% CI -4.68 to 8.81, Supplementary Figure 6), a change of less than 10% from the control group baseline of 56cm^2. This did not change in fixed effects sensitivity analysis or retaining trials of at least 100 participants, but the single trial was lost in sensitivity analyses on summary risk of bias and risk from compliance problems. The effect of increasing LCn3 was unclear as the evidence was of very low quality (downgraded once for imprecision and risk of bias, downgraded twice for indirectness).

Effects of long-chain omega-3 fat on prostate cancer

Seven trials (63,460 participants, 38,525 men) reported on 1021 prostate cancer diagnoses, finding higher risk of prostate cancer in men with increased LCn3 (RR 1.10, 95% CI 0.97 to 1.24, I^2 0%, Figure 4 in the main paper). This slight increase in prostate cancer risk was stable to all sensitivity analyses. With so few trials we did not carry out subgrouping or assess funnel plots. However, the suggestion of harm was contradicted by findings on PSA (below). Mean duration of included trials was 51 months (SD 24, range 24 to 88 months) and mean dose of LCn3 was 1.2g/d (SD 1.5g/d, range 0.4 to 4.5g/d). Increasing LCn3 may increase the risk of prostate cancer (low quality evidence, downgraded once each for imprecision and inconsistency).

Prostate cancer deaths were reported in only two trials (5 deaths in 5616 participants, 5101 men, Supplementary Figure 7) so effects of LCn3 on prostate cancer deaths could not be assessed. The trials were of 48 and 72 months duration, doses of LCn3 were 0.5 and 0.6g/d. The effect of increasing LCn3 on prostate cancer death is unclear as the evidence is of very low quality (downgraded once for inconsistency and twice for imprecision).

Prostate specific antigen (PSA) is a marker of prostate cancer risk, and higher PSA is associated with higher risk. PSA was reported as a continuous measure in a single large trial of 1622 participants (at low summary risk of bias, MD -0.13ng/ml, 95% CI -0.25 to 0.01, Supplementary Figure 8), suggesting a fall of 25% from a baseline of 0.53ng/ml in those on higher LCn3. Odds of increased PSA was reported in a single trial (not at low summary risk of bias) of 62 participants, reporting only 12 participants with raised PSA (RR 0.47, 95% CI 0.16 to 1.40, Supplementary Table 2), but also suggesting protective effects of LCn3 on PSA.

Effects of ALA on risk of any cancer

Effects of ALA on all primary and secondary outcomes, along with sensitivity analyses and subgroupings are displayed in Supplementary Tables 5 and 6. The GRADE assessment is shown in Supplementary Table 4.

Meta-analysis of 2 trials (752 participants) reported 16 cancer diagnoses and suggested little or no effect on risk of cancer diagnosis (RR 0.98, 95% CI 0.38 to 2.55, I^2 0%, Figure 1 in the main paper), and this lack of effect did not alter in fixed effects meta-analysis, but no trials were at low summary risk of bias. The single large trial (with >100 participants) was also the single trial at low risk of compliance issues and suggested a slight increase in cancer risk with increased ALA (RR 1.09, 95% CI 0.40 to 2.98) but with very wide confidence intervals. As there were only two trials we did not attempt subgrouping or a funnel plot. Mean duration of included trials was 18 months (12 and 24 months), mean

dose of LCn3 was 4.2g/d (3.3 and 5.0g/d). The effect of increasing ALA on diagnosis of any cancer is unclear as the evidence was of very low quality (downgraded once for risk of bias, twice for imprecision).

Two trials (5545 participants) provided data on 123 cancer deaths and meta-analysis suggested little or no effect of LCn3 (RR 1.05, 95% CI 0.74 to 1.49, I^2 0%, Figure 2 in the main paper), which didn't alter in any sensitivity analysis. Subgrouping and funnel plots re not attempted. Duration of included trials was 24 and 40 months, doses of LCn3 were 2 and 5g/d. Increasing ALA probably has little or no effect on risk of cancer death (moderate quality evidence, downgraded once for imprecision).

Effects of ALA on risk of breast cancer

Two trials (752 participants, 513 women) reported only 4 breast cancer diagnoses, and no trials reported deaths from breast cancer or breast density, so there were insufficient data to assess effects on breast cancer diagnoses, deaths or markers (Figure 3 in the main paper and Supplementary Figure 5). Duration of included trials of breast cancer diagnosis was 12 and 24 months, doses of LCn3 were 3.3 and 5.0g/d. The effect of increasing ALA on risk of breast cancer diagnosis is unclear as the evidence is of very low quality (downgraded once for risk of bias, twice for imprecision),

Effects of ALA on risk of prostate cancer

Meta-analysis of 2 trials (5545 participants, 4010 men) reporting 46 prostate cancer diagnoses suggesting that increasing ALA increases risk of prostate cancer diagnosis (RR 1.30, 95% CI 0.72 to 2.32, I^2 0%, Figure 4 in the main paper). This increase in risk was consistent across all sensitivity analyses, and supported by a rise in PSA with ALA (below). Mean duration of included trials was 32 months (24 and 40 months), mean dose of LCn3 was 3.5g/d (2.0 and 5.0g/d). Increasing ALA may increase the risk of prostate cancer diagnosis (low quality evidence, downgraded twice for imprecision).

No trials reported deaths from prostate cancer (Supplementary Figure 7). A single large trial at low summary risk of bias reported increased risk of raised PSA (>4ng/ml, RR 1.13, 95% CI 0.86 to 1.50) and higher PSA (by 23% from baseline, MD 0.10ng/ml, 95% CI -0.03 to 0.23, Supplementary Figure 8) in those taking more ALA.

Effects of omega-6 on risk of any cancer

Effects of omega-6 on all primary and secondary outcomes, along with sensitivity analyses and subgroupings are displayed in Supplementary Tables 7 and 8. The GRADE assessment is shown in Supplementary Table 9.

Six trials (4272 participants, 262 cancer diagnoses) suggested that increasing omega-6 increased risk of diagnosis of any cancer (RR 1.21, 95% CI 0.96 to 1.53, I^2 0%, Figure 1 in the main paper). The increased risk was consistent between dietary and supplemental interventions, and in all sensitivity analyses except when restricting to the single trial at low summary risk of bias. Mean duration of the included trials was 30 months (SD 25, range 12 to 72 months), mean dose was 10.7%E from omega-6, but varied enormously (SD 13.9, median 6.4%E, range 0.2 to 37.8%E from omega-6). The effect of increasing omega-6 on cancer diagnosis is unclear as the evidence is of very low quality (downgraded twice for risk of bias, once for imprecision).

Meta-analysis of the four trials assessing effects of omega-6 on cancer deaths was heterogeneous, and suggested little or no effect (RR 0.97, 95% CI 0.51 to 1.85, I^2 52%, Figure 2 in the main paper). However, none of the trials were at low summary risk of bias, and fixed effects analysis suggested in increase in risk of cancer death. No subgrouping or funnel plots were run as we included few trials. Mean duration of the included trials was 37 months (SD 12, range 24 to 48 months), mean dose was 14.0%E from omega-6, but varied a great deal (SD 21.0, median 2.8%E, range 1.4 to 37.8%E from omega-6). The effect of omega-6 on cancer deaths is unclear as the evidence is of very low quality (downgraded once each for risk of bias, imprecision and inconsistency).

Effects of omega-6 on risk of breast and prostate cancer

Only one small trial (200 women participants, 4 breast cancer diagnoses, 12 months duration, 2.7%E from omega-6, Figure 3) assessed effects of omega-6 on breast cancer diagnosis, and none on breast cancer deaths or breast density (Supplementary Figures 5 and 6), so there were insufficient data to assess effects. The effect of omega-6 on breast cancer diagnoses is unclear as the evidence is of very low quality (downgraded once for risk of bias, once for indirectness and twice for imprecision).

One trial (2033 male participants, 24 months duration, 2.8% E increase in omega-6) that was not at low summary risk of bias reported 13 prostate cancer diagnoses (RR 2.24, 95% CI 0.69 to 7.26, Figure 4 in the main paper), no trials reported prostate cancer deaths or PSA. The effect of omega-6 on risk of prostate cancer diagnosis is unclear as the evidence is of very low quality (downgraded once each for risk of bias, indirectness and imprecision).

Effects of total PUFA on risk of any cancer

Effects of total PUFA on all primary and secondary outcomes, along with sensitivity analyses and subgroupings are displayed in Supplementary Tables 10 and 11. The GRADE assessment is shown in Supplementary Table 12.

Eight trials (9428 participants, 436 diagnoses) assessed effects of increasing total PUFA on cancer diagnosis, suggesting that increasing total PUFA increases diagnosis risk (RR 1.19, 95% CI 0.99 to 1.42, I^2 0%, Figure 1 in the main paper). This was consistent across all sensitivity analysis (except when limiting to the three trials at low summary risk of bias, where the RR was 1.08). The funnel plot is difficult to assess with only 8 included trials, but does suggest that smaller trials with higher RRs may be missing (Supplementary Figure 9). If such trials were added back in the RR would rise further. Subgrouping did not suggest important differences between subgroups by study duration, PUFA dose (Supplementary Figure 10), replacement, age, sex and baseline cancer risk. Mean duration of the included trials was 39 months (SD 24, range 12 to 72 months), mean dose was 9.6%E from total PUFA, median 3.3%E, and varied considerably (SD 13, range 0.8 to almost 38%E from total PUFA). Increasing total PUFA may increase risk of diagnosis of any cancer (downgraded once each for risk of bias and imprecision).

Four trials reported on cancer deaths (3407 participants, 73 deaths), suggesting that increasing total PUFA increases risk of death from cancer (RR 1.10, 95% CI 0.48 to 2.49, I^2 37%, Figure 2 in the main paper). This increase in risk of cancer death was consistent across all sensitivity analyses. We did not carry out subgrouping or funnel plots as there were only four trials. Mean duration of the included trials was 39 months (SD 27, range 12 to 72 months), mean dose was 13%E from total PUFA, median 7%E, and varied considerably (SD 17, range 0.8 to almost 38%E from total PUFA). Increasing total PUFA may increase the risk of cancer death (downgraded twice for imprecision).

Effects of total PUFA on risk of breast cancer

Meta-analysis of two trials (5198 female participants, 79 diagnoses) suggested that increasing total PUFA increases risk of breast cancer diagnosis, but with very wide confidence intervals (RR 1.11, 95% CI 0.71 to 1.73, I^2 0%, Figure 3 in the main paper). However, this was not supported in sensitivity analysis limiting to the single trial at low summary risk of bias, and neither trial was at low risk of compliance problems. Duration of both trials was 60 months and the dose was 2%E from total PUFA in one trial, unclear in the other. The effect of increasing total PUFA on risk of breast cancer diagnosis is unclear as the evidence is of very low quality (downgraded once for risk of bias and twice for imprecision).

No trials reported breast cancer deaths or breast density (Supplementary Figures 5 & 6).

Effects of total PUFA on risk of prostate cancer

Meta-analysis of two trials (2879 male participants, 32 diagnoses) suggested that increasing total PUFA increases risk of prostate cancer diagnosis, but with the small number of diagnoses, confidence intervals were very wide (RR 1.64, 95% CI 0.80 to 3.36, I^2 0%, Figure 4 in the main paper). No trials were at low summary risk of bias, all other sensitivity analyses suggested increased prostate cancer risk with increased total PUFA. Duration of the included trials was 24 and 72 months, doses 3 and 11%E from total PUFA. The effect of increasing total PUFA on prostate cancer diagnosis is unclear as the evidence is of very low quality (downgraded once for risk of bias and twice for imprecision).

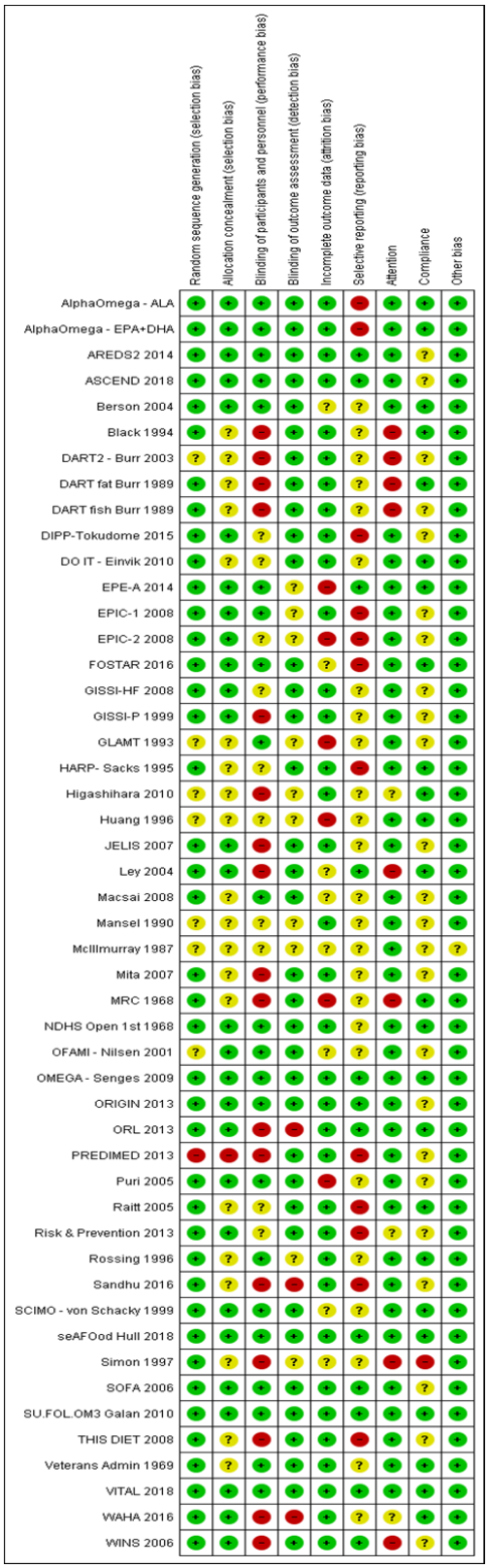
No trials reported prostate cancer deaths or PSA (Supplementary Figures 7 & 8).

Secondary outcomes

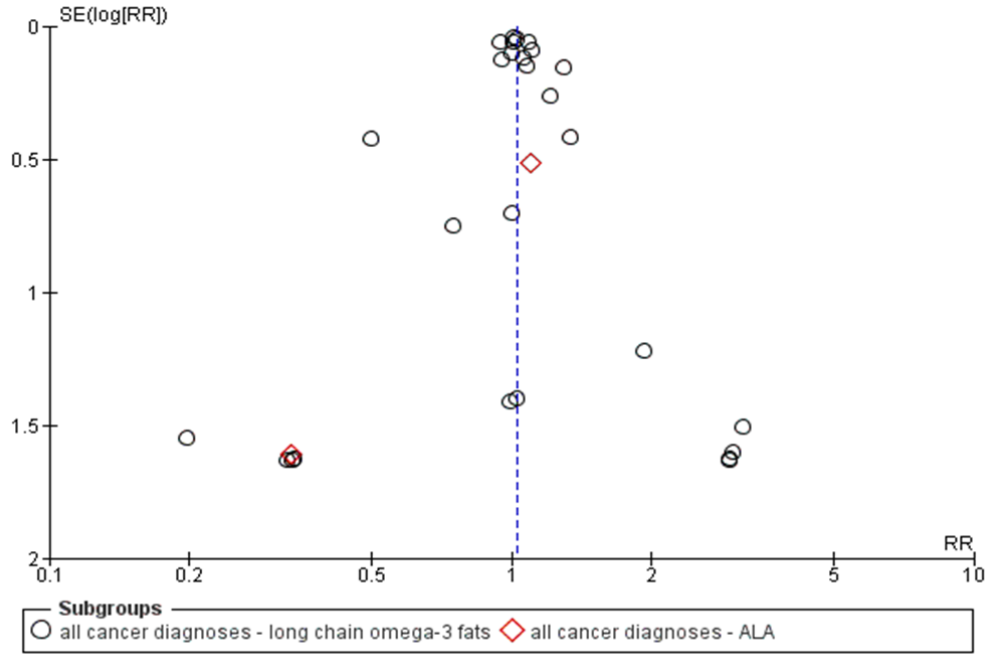
Prostate cancer diagnoses and deaths are reported above. Effects on body weight and measures of adiposity are reported in full (not just in this subset of trials assessing cancer outcomes) in other reviews in this series so are noted in the Supplementary Tables, but not discussed further here.[2-4] We found no trials reporting any measure of quality of life as effects of increases in LCn3, ALA, omega-6 or total PUFA.

When increasing LCn3 risks of gastrointestinal side effects (RR 1.11, 95% CI 0.89 to 1.31, I^2 84%, including effects on nausea, reflux, diarrhoea and hospitalisation for gastrointestinal problems), bleeding (RR 1.09, 95% CI 0.70 to 1.70, I^2 59%), and dropouts due to side effects (RR 1.31, 95% CI 0.98 to 1.76, I^2 19%) appear increased, while risk of headache or migraine (RR 0.81, 95% CI 0.48 to 1.36, I^2 0%), and psychiatric problems (RR 0.70, 95% CI 0.32 to 1.54, I^2 0%), appear reduced (Supplementary Figure 11). Overall giving LCn3 appears to have little or no effect on risk of all side effects combined (RR 1.03, 95% CI 0.93 to 1.15, I^2 85%), or dropouts for any reason (RR 0.98, 95% CI 0.88 to 1.10, I^2 33%, Supplementary Figures 11 and 12).

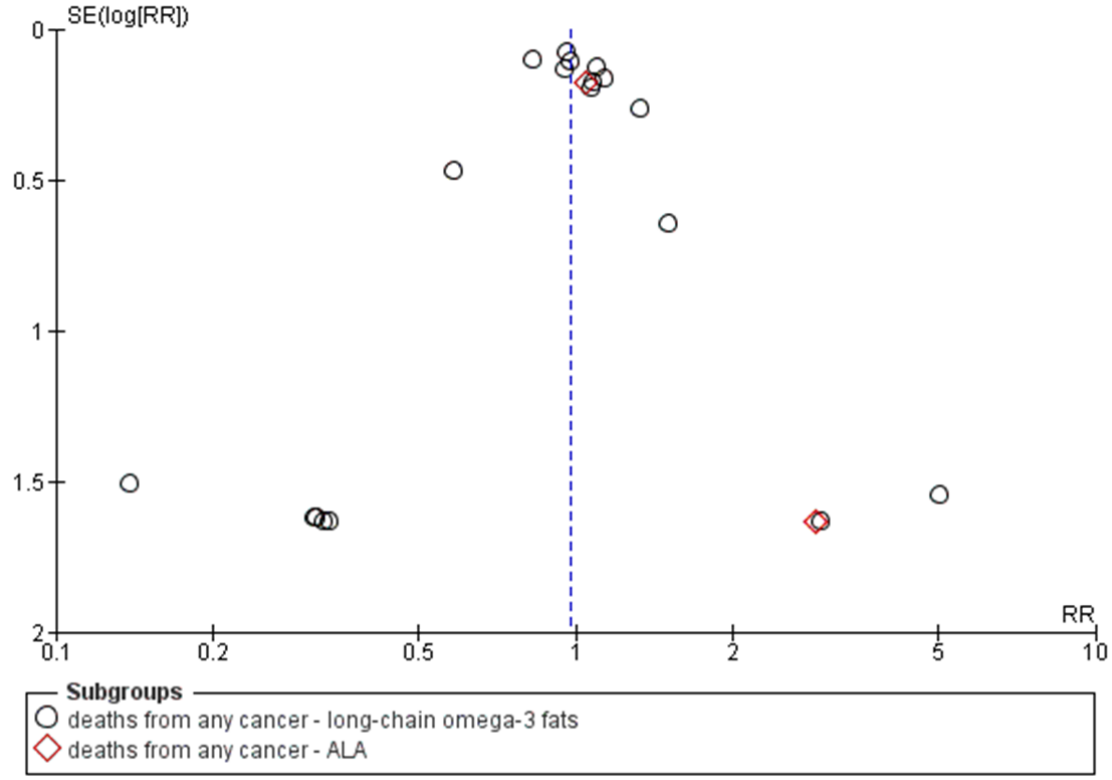
Data on side effects and dropouts are much more limited for ALA (Supplementary Figure 13) and omega-6 (Supplementary Figure 14, all data on side effects and dropouts shown), and no data were available for trials of total PUFA.



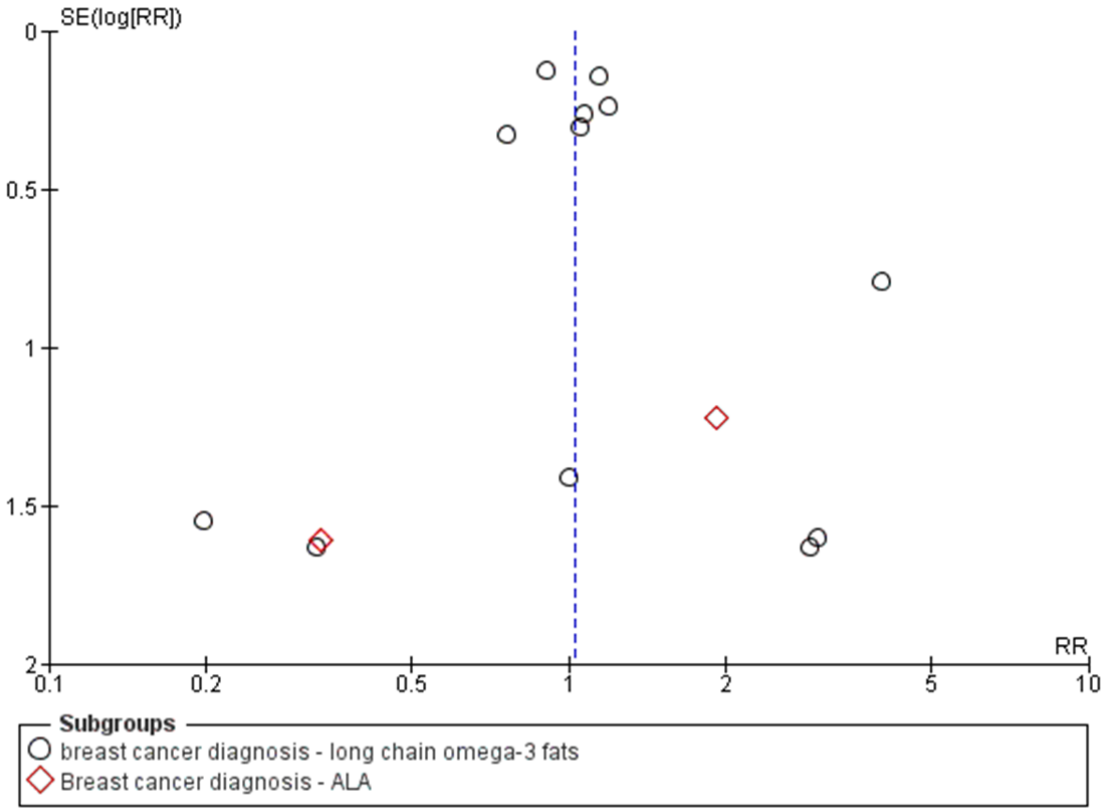
Supplementary Figure 1: Summary risk of bias of included comparisons by domain as assessed by reviewers.



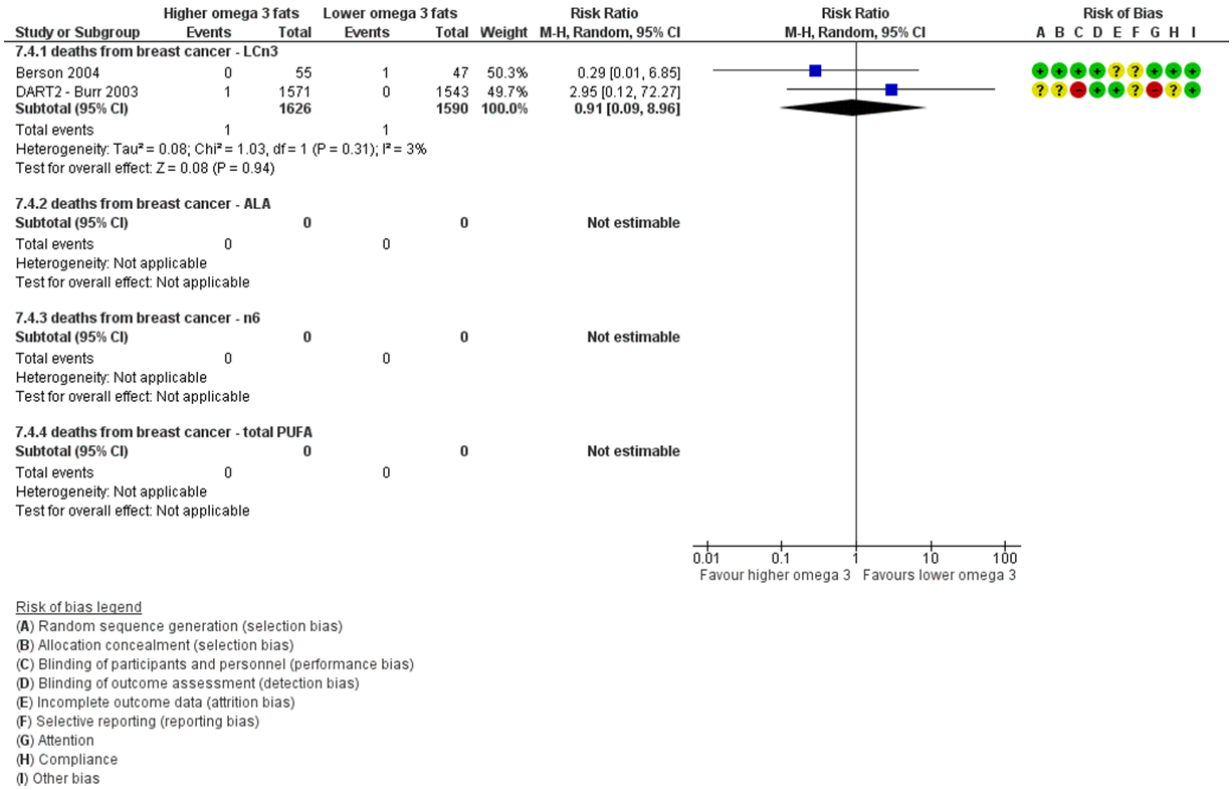
Supplementary Figure 2. Funnel plot for effects of LCn3 on diagnosis of any cancer.



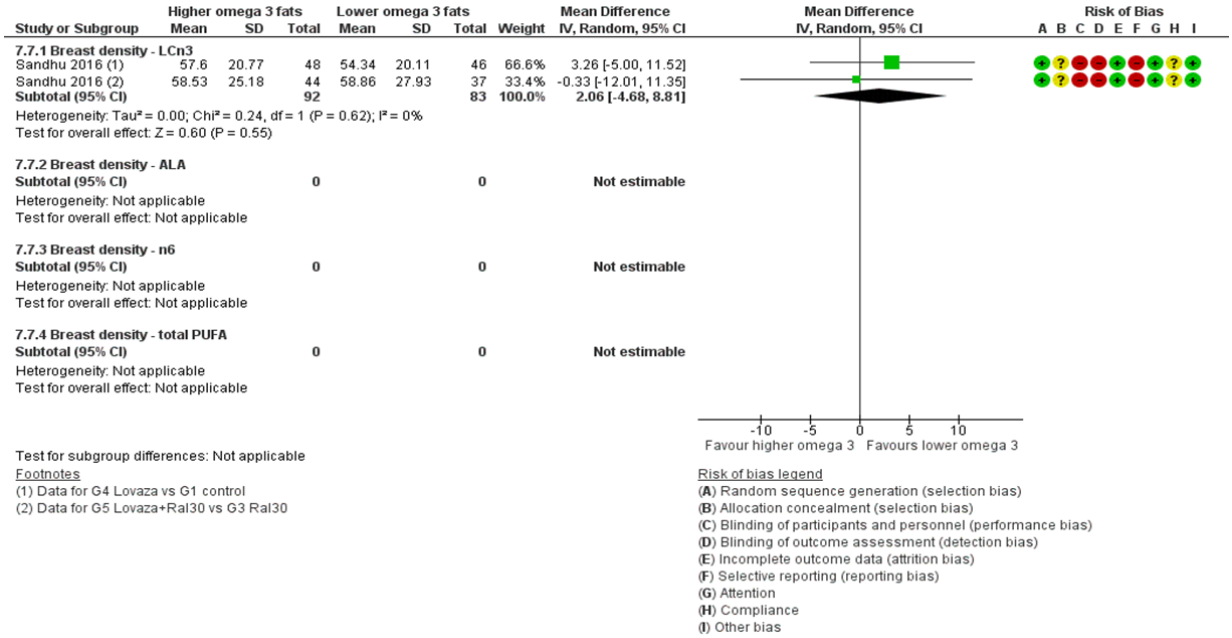
Supplementary Figure 3. Funnel plot for effects of LCn3 on death from any cancer.



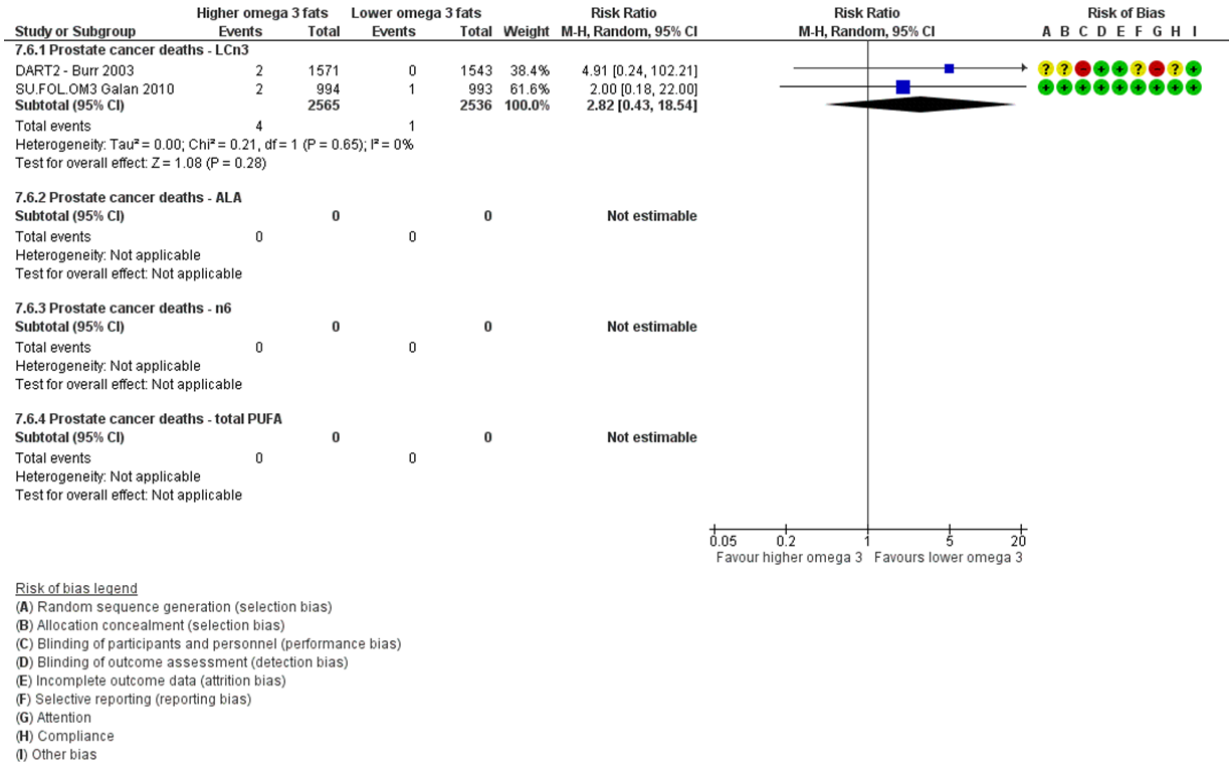
Supplementary Figure 4. Funnel plot for effects of LCn3 on diagnosis of breast cancer.



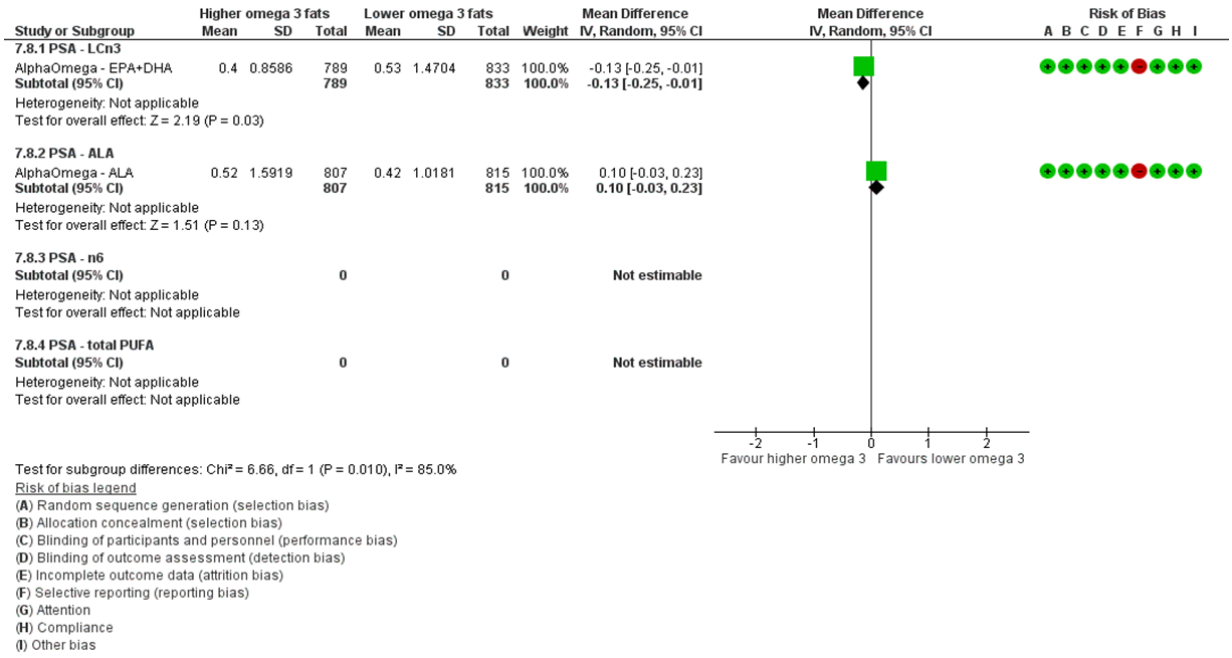
Supplementary Figure 5. Forest plot showing effects of increasing omega-3, omega-6 and total PUFA on deaths from breast cancer in women participants, using random-effects meta-analyses.



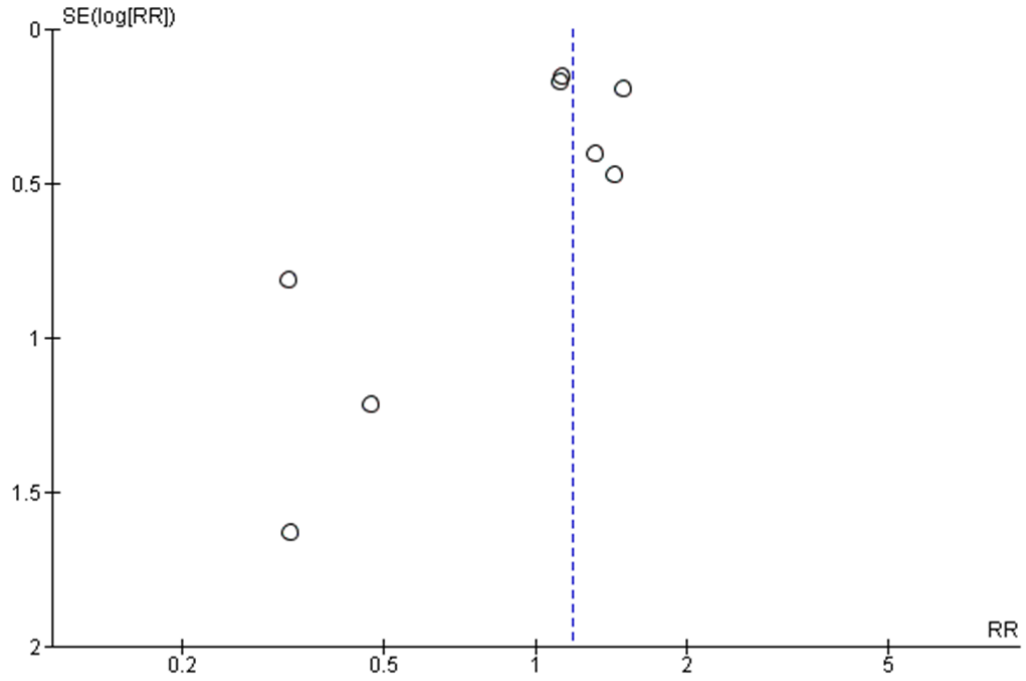
Supplementary Figure 6. Forest plot showing effects of increasing omega-3, omega-6 and total PUFA on breast density in cm^2, using random-effects meta-analyses.



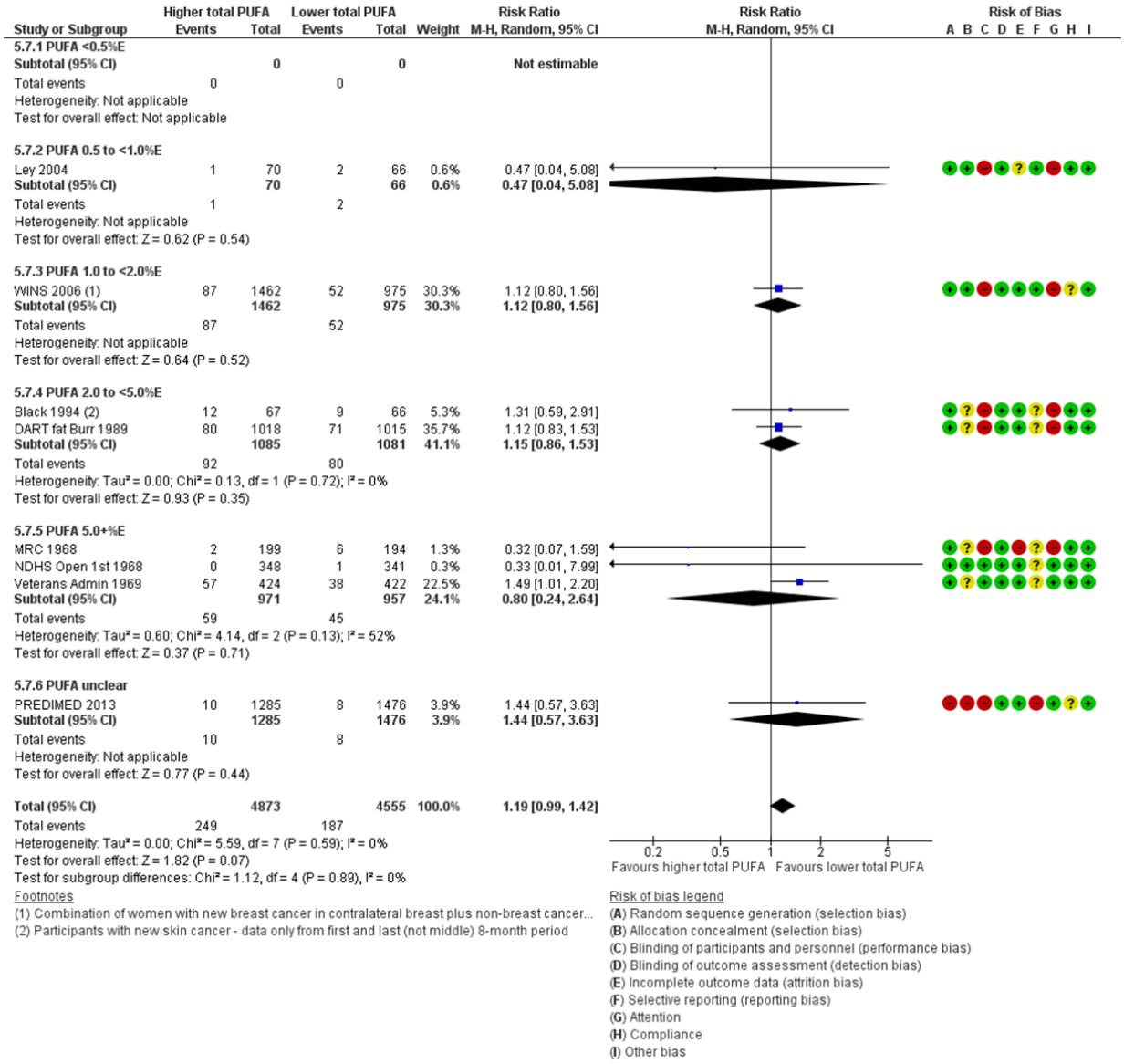
Supplementary Figure 7. Forest plot showing effects of increasing omega-3, omega-6 and total PUFA on deaths from prostate cancer in male participants, using random-effects meta-analyses.



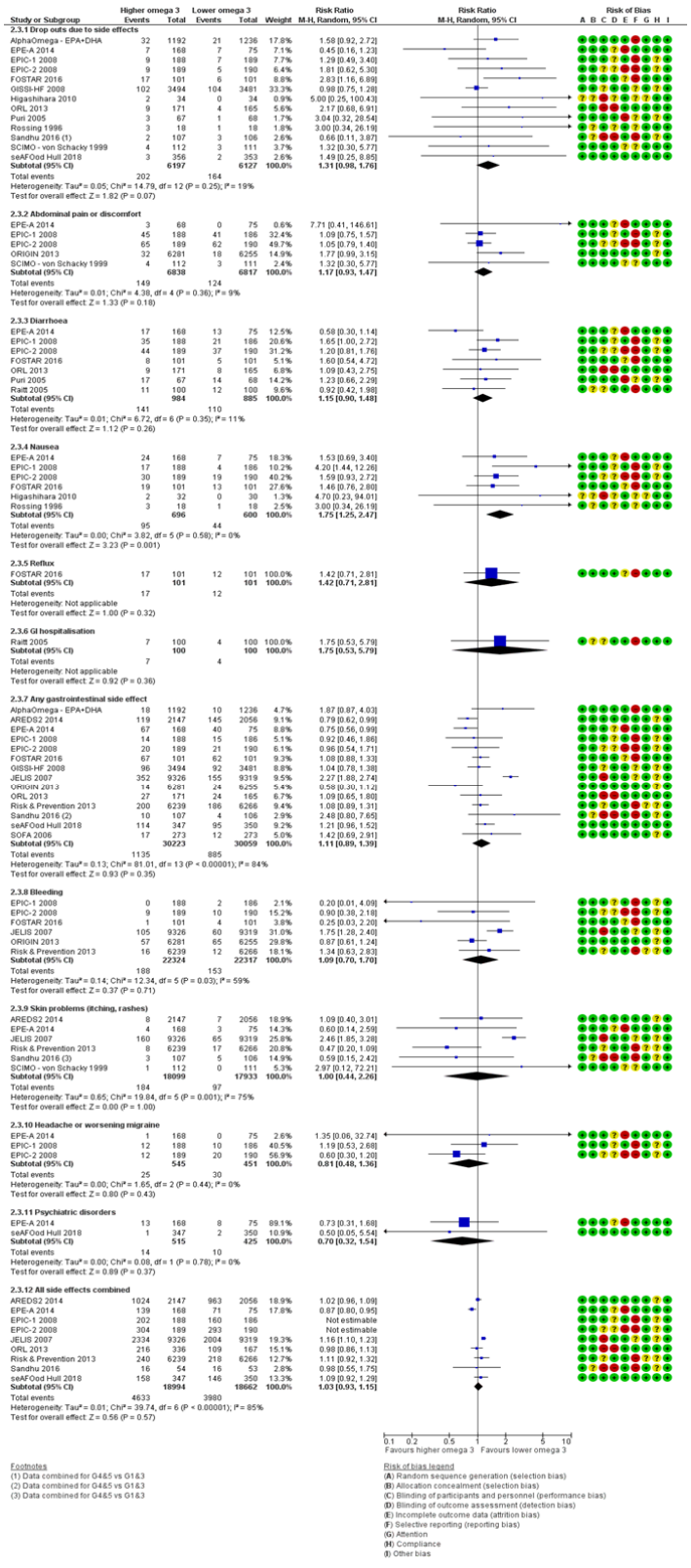
Supplementary Figure 8. Forest plot showing effects of increasing omega-3, omega-6 and total PUFA on prostate specific antigen (PSA, ng/ml), using random-effects meta-analyses.



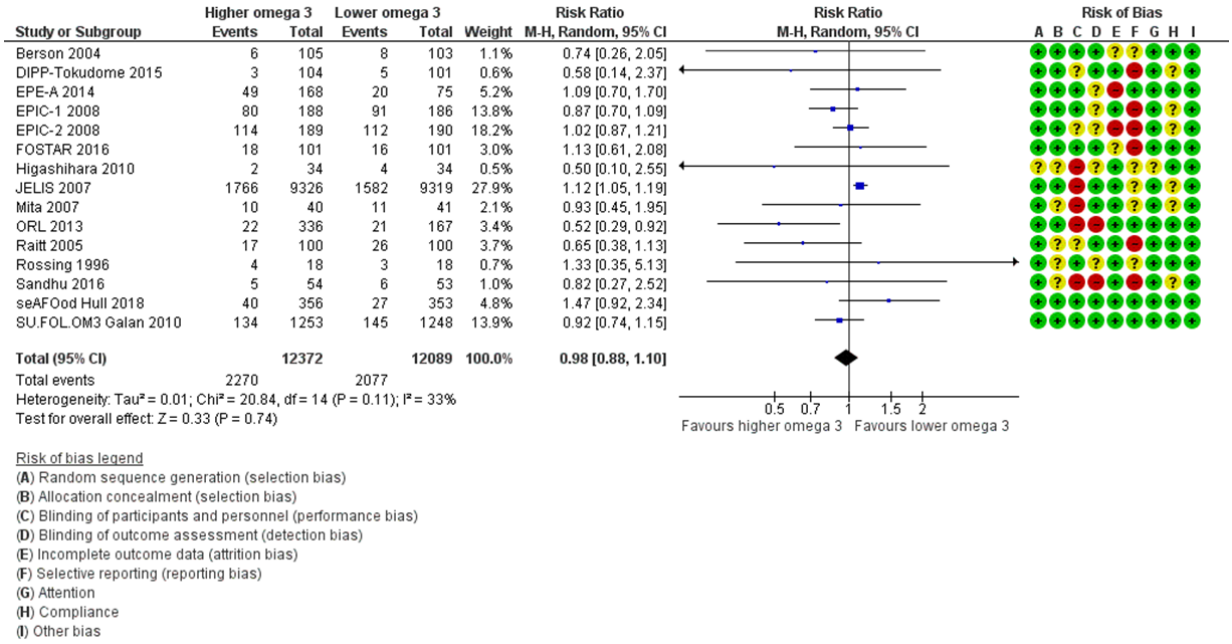
Supplementary Figure 9. Funnel plot for effects of total PUFA on diagnosis of any cancer.



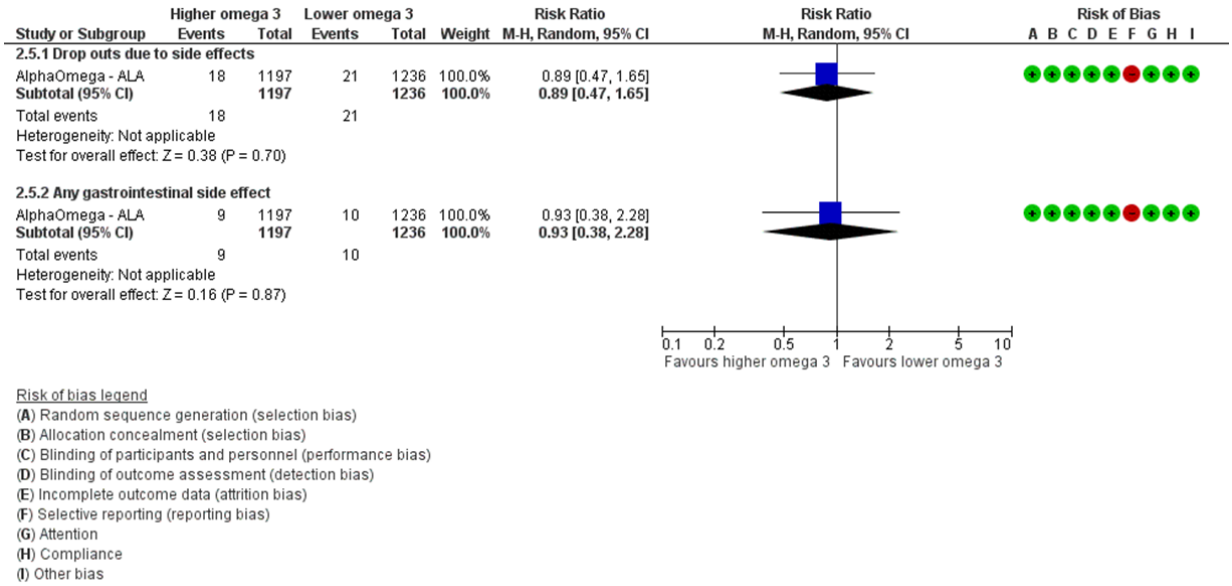
Supplementary Figure 10. Meta-analysis assessing effects of increasing total PUFA on diagnosis of any cancer, subgrouping by dose of PUFA (as percentage of energy intake).



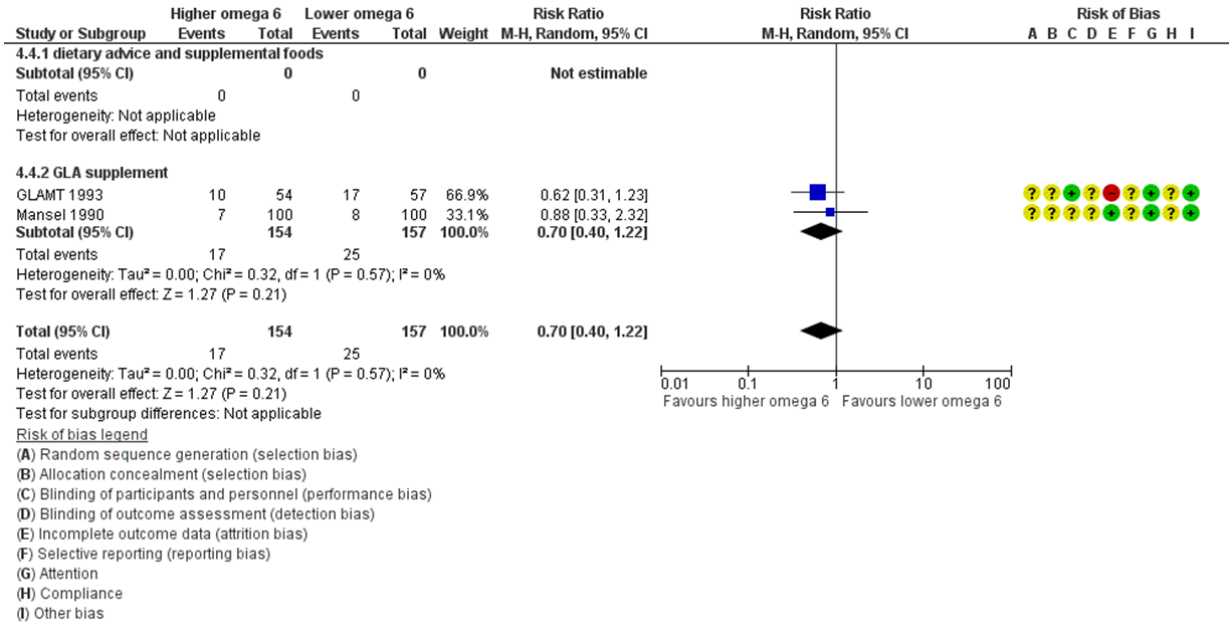
Supplementary Figure 11. Forest plot showing effects of increasing LCn3 on side effects using random-effects meta-analyses.



Supplementary Figure 12. Forest plot showing effects of increasing LCn3 on dropouts using random-effects meta-analyses.



Supplementary Figure 13. Forest plot showing effects of increasing ALA on side effects using random-effects meta-analyses.



Supplementary Figure 14. Forest plot showing effects of increasing omega-6 on dropouts using random-effects meta-analyses.

Supplementary Table 1. Table of characteristics, risk of bias and references for included trials

Trial name & reference	Comparison	Participants	Number randomised	Intervention	Duration of intervention	Summary risk of bias	Location
AlphaOmega – ALA [5-8]	n3 ALA vs MUFA	60-80 year olds with previous MI	1197 ALA intervention, 1236 control	Supplementary margarine, 20g/d enriched margarine incorporating 2g/d ALA	40 months	Low	The Netherlands
AlphaOmega - EPA+DHA [5-8]	n3 EPA+DHA vs MUFA	60-80 year olds with previous MI	1192 EPA/DHA intervention, 1236 control	Supplementary Margarine, 20g/d enriched margarine incorporating 400mg/d LCn3 (240mg/d EPA, 160mg/d DHA)	40 months	Low	The Netherlands
AREDS2 2014 [9-11]	n3 EPA+DHA vs nil	50-85 year olds at high risk of age-related macular degeneration	2147 DHA/EPA, 2056 placebo	Supplement (capsule), 350 mg/d DHA plus 650 mg/d EPA added to standard AREDS supplement	60 months	Low	USA
ASCEND 2018 [12, 13]	n3 EPA + DHA vs MUFA	Patients with DM, without apparent vascular disease	7740 intervention, 7740 control	Supplement (capsule), 840mg/d EPA+DHA (460mg/d EPA, 380mg/d DHA) as 1 capsule daily	Median 7.4 years	Low	UK
Berson 2004 [14, 15]	n3 DHA vs n6 LA	People aged 18-55 with retinitis pigmentosa	221 randomised overall, analysed 105 intervention, 103 control	Supplement (capsule), 1.2g/d DHA plus 1.8g vegetable oil	48 months	Low	USA
Black 1994 [16, 17]	Higher vs lower n6, higher vs lower PUFA (inverted)	**People with non-melanoma skin cancer	66 intervention, 67 control	Dietary advice, reduce total fat to 20%E, including omega 6 and total PUFA	24 months	Moderate or high	USA
DART fat Burr 1989 [18-20]	n6 LA vs mixed fats, also higher vs lower PUFA	Men recovering from MI	1018 Intervention, 1015 control	dietary advice, ↑ PUFA oil & n6 margarines vs usual dietary fats	24 months	Moderate to high	UK
DART fish Burr 1989 [18-20]	n3 EPA+DHA vs mixed fat	Men recovering from MI	1015 intervention, 1018 intervention	Dietary advice, advised to eat ≥2 portions/wk of 200-400g fatty fish, if not possible given MaxEPA capsules, 0.5g EPA/d	24 months	Moderate or high	UK
DART2 - Burr 2003 [1]	n3 EPA+DHA vs nil	Men treated for angina	1571 intervention, 1543 control	dietary advice, advised to eat ≥2 portions/wk of 200-400g fatty fish, if not possible given MaxEPA capsules, 0.5g EPA /d	3-9 years	Moderate or high	UK
DIPP-Tokudome	n3	**Patients previously	104 intervention,	Advice plus supplement, reduce	24 months	Moderate or	Japan

2015	EPA+DHA+ALA vs nil	polypectomised for colorectal tumours	101 control	total fat intake, decrease n-6 PUFAs, increase fishy n-3 PUFAs, increase n-3 PUFAs from perilla oil rich in ALA, and take 8 capsules of fish oil/day (96 mg/d EPA, 360 mg/d DHA)		high	
DO IT - Einvik 2010 [21, 22]	n3 DHA+EPA vs n6 LA	Elderly men with long standing dyslipidaemia or hypertension	282 intervention, 281 control	Supplement (capsule), 2.4g/d of omega 3 (0.84g/d EPA & 0.48g/d DHA)	36 months	Moderate or high	Norway
EPE-A Sanyal 2014 [23]	n3 EPA, low dose vs high dose vs unclear placebo	People with non-alcoholic steatohepatitis or fatty liver disease	86 intervention (high dose), 82 intervention (low dose), 75 control	Supplement (capsule), High dose EPA-E 2.7g/d, low dose 1.8g/d	12 months	Moderate or high	USA
EPIC-1 2008 [24]	n3 EPA+DHA vs mixed fat	Adults with quiescent Crohn's disease (CDAI) score <150	188 intervention, 186 control	Supplement (capsule), 2.2g/d EPA, 0.8g/d DHA	12 months	Moderate or high	Canada, Europe, Israel, USA
EPIC-2 2008 [24]	n3 EPA+DHA vs mixed fat	Adults with Crohn's disease	189 intervention, 190 control	Supplement (capsule), 2.2g/d EPA, 0.8g/d DHA	13 months	Moderate or high	Canada, Europe, Israel, USA
FOSTAR 2016 [25]	n3 EPA+DHA vs low n3 EPA+DHA+ALA	Adults aged 40+ with knee osteoarthritis	101 intervention, 101 control	Supplementary food (enriched orange juice), 4.5g/d EPA+DHA	24 months	Low	Australia
GISSI-HF 2008 [26, 27]	n3 EPA+DHA vs MUFA	Patients with chronic heart failure	3494 intervention, 3481control	Supplement (capsule), 866mg/d EPA, 1039mg/d DHA, Total Omega-3 Fat: 1905 mg/d	45 months	Moderate or high	Italy
GISSI-P 1999 [28]	n3 EPA+DHA vs nil	People with recent MI	5666 intervention, 5658 control	Supplement (capsule), 850-882 mg/d EPA + DHA daily, ratio 1:2	42 months	Moderate or high	Italy
GLAMT 1993 [29]	n6 GLA vs non-fat	People with mild diabetic neuropathy	54 intervention, 57 control	Supplement (capsule), 0.48g/d GLA	12 months	Moderate or high	UK and Finland
HARP- Sacks 1995 [30]	n3 EPA+DHA vs MUFA	Patients with coronary heart disease	41 intervention, 39 control	Supplement (capsule), 6g/d LCn3	24 months	Moderate or high	USA
Higashihara 2010 [31]	n3 EPA vs nil	**Prostate cancer patients with PSA levels <0.2 ng/ml 3 months after prostatectomy	34 intervention, 34 control	Supplement (capsule), 2.4 g/d EPA	24 months	Moderate or high	Japan
Huang 1996 [32]	n3 EPA+DHA vs n6 LA	**People with Dukes A or B adenocarcinoma of colon or rectum or severely dysplastic	17 intervention, 10 control	Supplement (capsules), 4g/d EPA + 2g/d DHA	12 months	Moderate or high	USA

		adenomatoid polyps post-surgery					
JELIS 2007 [33]	n3 EPA vs nil	People with hypercholesterolaemia	9326 intervention, 9319 control	Supplement (capsule), 1.8g/d EPA	60 months	Moderate or high	Japan
Ley 2004 [34, 35]	Higher vs lower PUFA (inverted)	Adults with impaired glucose intolerance or high normal blood glucose	85 intervention, 90 control	Diet advice, aim reduced fat diet (no specific goal stated), which reduced PUFA	12 months	Low (dietary advice trial)	New Zealand
Macsai 2008 [36]	n3 ALA vs MUFA	People with meibomian gland dysfunction	18 ALA intervention, 20 control	Supplement (capsules), 3.3g/d ALA, 1.14g/d LA	12 months	Moderate to high	USA
Mansel 1990 [37-39]	n6 GLA vs non-fat	Women with macroscopic breast cysts	100 intervention, 100 control	Supplement (capsules), estimated at 0.54g/d GLA	12 months	Moderate or high	UK
McIllmurray 1987 [40]	n6 GLA vs "inert placebo"	**People within 1 month of operation to remove Dukes's C colorectal cancer	25 intervention, 24 control	Supplement (capsules), 3.0g/d GLA	40 months	Moderate to high	UK
Mita 2007 [41]	n3 EPA vs nil	Japanese type 2 diabetics	40 intervention, 41 control	Supplement (capsules), 1.8g/d EPA+DHA	24 months	Moderate or high	Japan
MRC 1968 [42-44]	n6 LA vs mixed fats, also higher vs lower PUFA	Men who have survived a MI	199 intervention, 194 control	Diet advice plus oil supplement, reduce dietary fat to 35g/d fat, add 84g/d soya oil	48 months	Moderate or high	UK
NDHS Open 1st 1968 [43, 45]	n6 LA vs mixed fats, also higher vs lower PUFA	Free-living men aged 45-54 years	829 combined intervention groups, 382 control	Diet provided (bought from a trial shop), saturated fats replaced in shop foods by polyunsaturated fats and oils	12 months	Low	USA
OFAMI - Nilsen 2001 [46]	n3 EPA+DHA vs n6 LA	Patients recruited 4-8 days after MI	150 intervention, 150 control	Supplement (capsules), 3.5g/d EPA+DHA	24 months	Moderate or high	Norway
OMEGA 2009 [47, 48]	n3 EPA+DHA vs MUFA	People who have had an acute MI	1940 intervention, 1911 control	supplement (capsules), 460mg/d EPA and 386mg/d DHA	12 months	Low	Germany
ORIGIN 2013 [49-51]	n3 EPA+DHA vs MUFA	People at high risk of CVD with impaired fasting glucose, impaired glucose tolerance or DM	6319 intervention, 6292 control	supplement (capsule), (465mgEPA + 375mgDHA) EPA+DHA 0.84g/d	72 months	Low	40 locations in Europe and the Americas
ORL Tatsuno 2013 [52, 53]	n3 EPA+DHA high dose vs low dose vs n3 EPA	Japanese adults with hypertriglyceridaemia	171 intervention (4g TAK), 165 control (2g TAK)	Supplement (capsules), 1.68g/d EPA+DHA	12 months	Moderate or high	Japan

PREDIMED 2013 [54, 55]	PUFA vs MUFA	People free of CVD but with DM or at least 3 CVD risk factors	2454 Med with nuts, 2543 Med with olive oil	Dietary advice and food supplement, Mediterranean dietary advice (both groups) plus 30g/d mixed nuts	60 months	Moderate to high	Spain
Puri 2005 [56]	n3 EPA vs non-fat	People with Huntington's Disease	67 intervention, 68 control	Supplement (capsule), 1.9g/d EPA+DHA	12 months	Low	UK, USA, Canada, Australia
Raitt 2005 [57]	n3 EPA+DHA vs MUFA	People with implantable cardioverter defibrillators and recent sustained ventricular tachycardia or ventricular fibrillation	100 intervention, 100 control	Supplement (capsules), 0.76g/d EPA, 0.54g/d DHA (EPA+DHA 1.3g/d)	24 months	Moderate or high	USA
Risk & Prevention 2013 [58, 59]	n3 EPA+DHA vs MUFA	Patients with multiple cardiovascular risk factors	6244 intervention, 6269 control	Supplement (capsules), 0.86g/d EPA+DHA	60 months	Moderate or high	Italy
Rossing 1996 [60, 61]	n3 EPA+DHA vs MUFA	Adults with insulin-dependent DM mellitus, diabetic nephropathy & normal BP	18 intervention, 18 control	Supplement (capsule), 2g/d EPA, 2.6g/d DHA, 4.6g/d EPA+DHA	12 months	Moderate or high	Denmark
Sandhu 2016 [62, 63]	n3 EPA+DHA vs nil, +/- raloxifene	*Healthy postmenopausal women with high breast density detected on routine mammogram screening	54 & 53 intervention, 53 & 53 control	Supplement (capsules), 1.86g/d EPA, 1.5 g/d DHA	24 months	Moderate or high	USA
SCIMO - von Schacky 1999 [64-66]	n3 EPA+DHA vs mixed fats	People with angiographically proven coronary artery disease	112 intervention, 111 control	Supplement (capsule), 1.03g/d EPA+DHA	24 months	Low	Germany
seAFOod Hull 2018 [67]	n3 EPA vs MCT	*Bowel cancer screening patients identified as "high risk" at their 1st colonoscopy	356 intervention, 353 control	supplement (capsule), 2g/d EPA	12 months	Low	UK
Simon 1997 [68]	Higher vs lower PUFA (inverted)	*Women with a high risk of breast cancer	98 intervention, 96 control	Dietary advice, reduced fat including PUFA vs usual diet	24 months	Moderate or high	USA
SOFA 2006 [69-72]	n3 EPA+DHA vs n6 LA	People with previous ventricular arrhythmias & implantable cardioverter defibrillators	273 intervention, 273 control	supplement (capsule), 464mg/d EPA + 335mg/d DHA and 162mg/d other n-3 PUFA, EPA+DHA 0.8g/d	12 months	Low	8 countries in Europe
SU.FOL.OM3 Galan 2010 [73-78]	n3 EPA+DHA vs non-fat	People with a history of MI, unstable angina or ischemic stroke	1253 intervention, 1248 control	supplement (capsule), 400mg/d EPA and 200mg/d DHA, EPA+DHA 0.6g/d	48 months	Low	France

THIS DIET 2008 [79]	n3 EPA+DHA vs nil	Recent survivors of first MI	51 intervention, 50 control	Dietary advice, Mediterranean style diet high in n3 (>0.75%E from n3, unclear how much EPA, DHA, ALA)	24 months	Moderate or high	USA
Veterans Admin 1969 [43, 80, 81]	n6 LA vs SFA, also higher vs lower PUFA	Men living at the Veterans Administration Centre	424 intervention, 422 control	diet provided (residential institution), total fat 40%E, 2/3 of SFA replaced by unsaturated fats (from corn, soybean, safflower and cottonseed oils)	Up to 96 months	Moderate or high	USA
VITAL 2018 [82]	n3 EPA & DHA vs MUFA	Multi-ethnic population of > 25,000 apparently healthy adults without cancer or CVD	12933 intervention, 12938 control	Supplement (capsules), 465 mg/d EPA, 375 mg/d DHA (EPA + DHA 840mg/d)	median 5.3 years	Low	USA
WAHA 2016 [83-85]	n3 ALA vs unclear	Middle aged healthy adults	362 intervention, 346 control	Supplement (food), usual diet & walnuts (15%E, ~5g/d ALA) vs usual diet	24 months	Moderate to high	Spain & USA
WINS 2006 [86-88]	Higher vs lower PUFA (inverted)	**Women with localised resected breast cancer	975 intervention, 1462 control	dietary advice, reduced fat intake (with reduced PUFA)	60 months	Low (as diet advice trial)	USA
Summary: 47 trials, 49 comparisons	34 LCn3 3 ALA 8 n6 9 total PUFA	38 Normal cancer risk 3 *Cancer risk factors 6 **Previous cancer	97,548 LCn3 3,179 ALA 4,976 n6 11,573 tot PUFA Total: 108,194		Mean 30.4 months	17 trials at Low summary risk of bias	15 N America 20 Europe 2 Australia/NZ 5 Japan 5 combined

Footnotes

ALA = alpha-linolenic acid, BP = blood pressure, CVD = cardiovascular disease, DHA = docosahexaenoic acid, DM = diabetes mellitus, DPA = docosapentaenoic acid, E = energy intake, EPA = eicosapentaenoic acid or icosapentaenoic acid, LCn3 = long-chain omega-3, MI = myocardial infarction, MUFA = mono-unsaturated fatty acids, n3 = omega 3, PUFA = polyunsaturated fatty acids, SFA = saturated fatty acids, TG = serum triglycerides.

Colour coding: LCn3 uncoloured, ALA blue, n6 yellow, total PUFA red, N6 and PUFA pink.

Supplementary Table 2. High vs low LCn3 (primary outcomes)

Outcome	Sensitivity Analysis (SA) or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2, %	p-value*
All cancer diagnoses	Main	27	113557	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.98, 1.07]	0	-
	SA Fixed effects	27	113557	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.98, 1.07]	0	-
	SA Low summary risk of bias	12	66335	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.96, 1.06]	0	-
	SA compliance	12	34827	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.96, 1.10]	0	-
	SA n>100	25	113440	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.98, 1.07]	0	-
	Duration: 12 to <24 months duration	9	6464	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.91, 1.15]	0	0.96
	Duration: 24 to <48 months duration	10	15144	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.91, 1.21]	0	
	Duration: 48+ months duration	8	91949	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.97, 1.07]	0	
	Dose: ≤400mg/d LCn3	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-	0.93
	Dose: >400 to ≤1400mg/d LCn3	14	91676	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.98, 1.07]	0	
	Dose: >1400 to ≤2400mg/d LCn3	7	20599	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.93, 1.14]	0	
	Dose: >2400mg/d to ≤4400mg/d LCn3	2	738	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.10, 9.52]	0	
	Dose: >4400mg/d LCn3	2	238	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.64, 3.10]	0	
	Dose: dose unclear	2	306	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.75, 1.23]	0	
	LCn3 replacing MUFA	7	70432	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.97, 1.07]	0	0.23
	LCn3 replacing omega-6	3	1317	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.29, 1.17]	0	
	LCn3 replacing SFA	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-	
	LCn3 replacing CHO	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-	
	LCn3 replacing other or unclear	17	41808	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.97, 1.13]	0	
	Intervention: dietary advice	1	101	Risk Ratio (M-H, Random, 95% CI)	2.94 [0.12, 70.56]	-	0.80
	Intervention: supplementary capsules	23	111016	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.98, 1.07]	0	
	Intervention: supplemental foods	1	202	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.59, 3.02]	-	
	Intervention: all foods provided	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-	
	Intervention: combination	2	2238	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.80, 1.50]	61	

	Baseline cancer risk: low - usual population	24	112499	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.98, 1.08]	0	0.81
	Baseline cancer risk: moderate - CA risk factors	2	853	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.43, 1.96]	11	
	Baseline cancer risk: high - previous CA	1	205	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.75, 1.22]	-	
	Mean age <50 years	6	1346	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.29, 3.75]	0	0.95
	Mean age 50 to <65 years	17	80934	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.98, 1.08]	0	
	Mean age 65+ years	4	31277	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.95, 1.09]	0	
	Men & women mixed	24	110748	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.98, 1.07]	0	0.54
	Men only	2	2596	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.35, 2.19]	77	
	Women only	1	213	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 4.08]	-	
Cancer deaths	Main	18	99336	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.90, 1.06]	0	-
	SA fixed effects	18	99336	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.90, 1.05]	0	-
	SA Low summary risk of bias	6	61433	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.86, 1.04]	0	-
	SA compliance	7	34122	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.85, 1.18]	0	-
	SA n>100	16	99194	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.90, 1.06]	0	-
	Duration: 12 to <24 months duration	2	742	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.10, 9.52]	0	0.88
	Duration: 24 to <48 months duration	9	26379	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.85, 1.20]	0	
	Duration: 48+ months duration	7	72215	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.88, 1.05]	0	
	Dose: ≤400mg/d LCn3	1	4837	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.76, 1.53]	-	0.70
	Dose: >400 to ≤1400mg/d LCn3	10	86135	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.89, 1.06]	0	
	Dose: >1400 to ≤2400mg/d LCn3	2	7037	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.73, 1.23]	0	
	Dose: >2400 to ≤4400mg/d LCn3	3	1042	Risk Ratio (M-H, Random, 95% CI)	1.77 [0.29, 10.83]	0	
	Dose: >4400mg/d LCn3	1	80	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.57]	-	
	Dose: unclear	1	205	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.65]	-	
	LCn3 replacing MUFA	7	78284	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.87, 1.04]	0	0.25

	LCn3 replacing omega-6	3	1071	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.28, 1.56]	0	
	LCn3 replacing SFA	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-	
	LCn3 replacing CHO	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-	
	LCn3 replacing other or unclear	8	19981	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.91, 1.41]	0	
	Intervention: dietary advice	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-	0.76
	Intervention: supplementary capsules	14	89147	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.88, 1.05]	0	
	Intervention: supplemental foods	1	4837	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.76, 1.53]	-	
	Intervention: all foods provided	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-	
	Intervention: combination	3	5352	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.67, 1.68]	6	
	Baseline cancer risk: low - usual population	16	99069	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.90, 1.06]	0	0.15
	Baseline cancer risk: moderate - CA risk factors	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-	
	Baseline cancer risk: high - previous CA	2	267	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.02, 1.75]	0	
	Mean age <50	3	950	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.11, 4.33]	0	0.93
	Mean age 50-<65	11	60140	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.88, 1.08]	2	
	Mean age 65+	4	38246	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.84, 1.12]	0	
	Men & women mixed	14	93564	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.89, 1.06]	0	0.92
	Men only	4	5772	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.70, 1.40]	0	
	Women only	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-	
Breast cancer diagnoses	Main	12	44295	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.89, 1.20]	0	-
	SA fixed effects	12	44295	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.89, 1.20]	0	-
	SA Low summary risk of bias	7	26371	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.87, 1.22]	0	-
	SA compliance	6	13908	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.72, 1.30]	1	-
	SA n >100	11	44285	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.88, 1.20]	0	-
	Duration: 12 to <24 months duration	2	107	Risk Ratio (M-H, Random, 95% CI)	2.92 [0.33, 25.76]	0	0.41

	Duration: 24 to <48 months duration	2	313	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.05, 2.94]	0	
	Duration: 48+ months duration	8	43875	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.89, 1.20]	0	
	Dose: ≤400mg/d LCn3	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-	0.60
	Dose: >400 to ≤1400mg/d LCn3	7	31089	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.90, 1.23]	0	
	Dose: >1400 to ≤2400mg/d LCn3	3	13096	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.41, 1.42]	0	
	Dose: >2400 to ≤4400mg/d LCn3	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-	
	Dose: >4400mg/d LCn3	2	110	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.18, 10.01]	0	
	Dose: unclear	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-	
	LCn3 replacing MUFA	5	28095	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.89, 1.23]	0	0.71
	LCn3 replacing omega-6	1	102	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.01, 6.85]	-	
	LCn3 replacing SFA	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-	
	LCn3 replacing CHO	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-	
	LCn3 replacing other or unclear	6	16098	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.63, 1.54]	5	
	Intervention: dietary advice	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-	0.76
	Intervention: supplementary capsules	11	44195	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.89, 1.20]	0	
	Intervention: supplemental foods	1	100	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.04, 10.35]	-	
	Intervention: all foods provided	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-	
	Baseline cancer risk: low - usual population	11	44082	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.89, 1.20]	0	0.28
	Baseline cancer risk: moderate - CA risk factors	1	213	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 4.08]	-	
	Baseline cancer risk: high - previous CA	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-	
	Mean age <50	2	112	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.10, 9.88]	11	0.43
	Mean age 50-<65	8	28710	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.92, 1.38]	0	
	Mean age 65+	2	15473	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.73, 1.16]	0	
	Men & women mixed	11	44082	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.89, 1.20]	0	0.28
	Men only	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-	

	Women only	1	213	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 4.08]	-	
Breast cancer deaths	Main	2	3216	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.09, 8.96]	3	-
	SA fixed effects	2	3216	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.13, 6.26]	3	-
	SA low summary RoB	1	102	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.01, 6.85]	-	-
	SA compliance	1	102	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.01, 6.85]	-	-
	SA n >100	2	3216	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.09, 8.96]	3	-
Prostate cancer diagnoses	Main	7	38525	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.97, 1.24]	0	-
	SA fixed effects	7	38525	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.98, 1.24]	0	-
	SA Low summary risk of bias	6	36492	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.98, 1.25]	0	-
	SA compliance	4	18658	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.99, 1.39]	0	-
	SA n >100	7	38525	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.97, 1.24]	0	-
Prostate cancer deaths	Main	2	5101	Risk Ratio (M-H, Random, 95% CI)	2.82 [0.43, 18.54]	0	-
	SA fixed effects	2	5101	Risk Ratio (M-H, Fixed, 95% CI)	2.97 [0.47, 18.89]	0	-
	SA low summary risk of bias	1	1987	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.18, 22.00]	-	-
	SA compliance	1	1987	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.18, 22.00]	-	-
	SA n >100	2	5101	Risk Ratio (M-H, Random, 95% CI)	2.82 [0.43, 18.54]	0	-
Dichotomous markers of cancer risk	PSA >2ng/ml twice at consecutive measurements	1	62	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.16, 1.40]	-	-
Continuous markers of cancer risk	Breast density LCn3, cm^2	1	175	Mean Difference (IV, Random, 95% CI)	2.06 [-4.68, 8.81]	-	-
	PSA, ng/ml	1	1622	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.25, -0.01]	-	-

* test for subgroup differences, p-value

Supplementary Table 3. High vs low LCn3 (secondary outcomes)

Outcome	Sensitivity Analysis (SA) or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2, %
Quality of life	-	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable	-
Adiposity, Weight or BMI	Weight, kg	3	14913	Mean Difference (IV, Random, 95% CI)	0.42 [-0.87, 1.71]	63
	BMI, kg/m2	4	14268	Mean Difference (IV, Random, 95% CI)	0.06 [-0.08, 0.19]	0
	Waist circumference, cm	1	71	Mean Difference (IV, Random, 95% CI)	-1.40 [-7.94, 5.14]	-
Side effects	Drop outs due to side effects	13	12324	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.98, 1.76]	19
	Abdominal pain or discomfort	5	13655	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.93, 1.47]	9
	Diarrhoea	7	1869	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.90, 1.48]	11
	Nausea	6	1296	Risk Ratio (M-H, Random, 95% CI)	1.75 [1.25, 2.47]	0
	Any gastrointestinal side effect	14	60282	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.89, 1.39]	84
	Bleeding	6	44641	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.70, 1.70]	59
	Skin problems (itching, rashes)	6	36032	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.44, 2.26]	75
	Headache or worsening migraine	3	996	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.48, 1.36]	0
	Psychiatric disorders	2	940	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.32, 1.54]	0
	All side effects combined	9	37656	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.93, 1.15]	85
Drop outs		15	24461	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.88, 1.10]	33

Supplementary Table 4. GRADE table: summary of findings of effects of omega-3 fats (LCn3 and ALA) on cancers

High compared to low omega 3 (LCn3 and ALA) for cancers

Patient or population: adults, Setting: community, Intervention: Higher omega-3 intake, Comparison: lower omega-3 intake

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with low omega 3 (primary outcomes)	Risk with High				
Cancer diagnoses - LCn3	64 per 1,000	65 per 1,000 (63 to 68)	RR 1.02 (0.98 to 1.07)	113557 (27 RCTs)	⨁⨁⨁⨁ HIGH	Increasing LCn3 has little or no effect on risk of diagnosis of any cancer.
Cancer deaths - LCn3	23 per 1,000	23 per 1,000 (21 to 25)	RR 0.97 (0.90 to 1.06)	99336 (18 RCTs)	⨁⨁⨁◯ MODERATE [a]	Increasing LCn3 probably has little or no effect on risk of cancer death.
Breast cancer diagnoses - LCn3	15 per 1,000	15 per 1,000 (13 to 18)	RR 1.03 (0.89 to 1.20)	44295 (12 RCTs)	⨁⨁⨁◯ MODERATE [b,c]	Increasing LCn3 probably has little or no effect on risk of breast cancer diagnosis.
Breast cancer deaths - LCn3	1 per 1,000	1 per 1,000 (0 to 6)	RR 0.91 (0.09 to 8.96)	3216 (2 RCTs)	⨁◯◯◯ VERY LOW [d,e]	The effect of increasing LCn3 on breast cancer deaths is unclear as the evidence is of very low quality.
Prostate cancer diagnoses - LCn3	25 per 1,000	28 per 1,000 (24 to 31)	RR 1.10 (0.97 to 1.24)	38525 (7 RCTs)	⨁⨁◯◯ LOW [f,g]	Increasing LCn3 may increase the risk of prostate cancer.
Prostate cancer deaths - LCn3	0 per 1,000	1 per 1,000 (0 to 7)	RR 2.82 (0.43 to 18.54)	5101 (2 RCTs)	⨁◯◯◯ VERY LOW [e,f]	The effect of increasing LCn3 on prostate cancer death is unclear as the evidence is of very low quality.
Cancer diagnoses - ALA	22 per 1,000	21 per 1,000 (8 to 55)	RR 0.98 (0.38 to 2.55)	752 (2 RCTs)	⨁◯◯◯ VERY LOW [e,h]	The effect of increasing ALA on diagnosis of any cancer is unclear as the evidence was of very low quality.
Cancer deaths - ALA	22 per 1,000	23 per 1,000 (16 to 32)	RR 1.05 (0.74 to 1.49)	5545 (2 RCTs)	⨁⨁⨁◯ MODERATE [c]	Increasing ALA probably has little or no effect on risk of cancer death.
Breast cancer diagnoses - ALA	8 per 1,000	9 per 1,000 (1 to 58)	RR 1.11 (0.17 to 7.40)	513 (2 RCTs)	⨁◯◯◯ VERY LOW [e,h]	The effect of increasing ALA on risk of breast cancer diagnosis is unclear as the evidence is of very low quality.
Breast cancer deaths - ALA	not pooled	not pooled	not pooled	(0 RCTs)	-	We found no evidence to address this issue.
Prostate cancer diagnoses - ALA	10 per 1,000	13 per 1,000 (7 to 23)	RR 1.30 (0.72 to 2.32)	4010 (2 RCTs)	⨁⨁◯◯ LOW [i,j]	Increasing ALA may increase the risk of prostate cancer diagnosis.
Prostate cancer deaths - ALA	not pooled	not pooled	not pooled	(0 RCTs)	-	No evidence found

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio

High compared to low omega 3 (LCn3 and ALA) for cancers

Patient or population: adults, Setting: community, Intervention: Higher omega-3 intake, Comparison: lower omega-3 intake

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with low omega 3 (primary outcomes)	Risk with High				

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Imprecision: 95% CI included a small reduction in risk as well as little or no effect. Downgraded once.
b. Inconsistency: data were consistent across all sensitivity analyses, including limiting analysis to only trials at low summary risk of bias, and consistent with the suggestion of little or no effect for breast density. Not downgraded.
c. Imprecision: 95% CI included both increases and reductions in risk. Downgraded once.
d. Risk of bias: sensitivity analysis retaining only trials at low summary risk of bias altered apparent effect. Downgraded once.
e. Imprecision: 95% CI included both important benefit and important harm. Downgraded twice.
f. Inconsistency: While data on prostate cancer diagnosis and deaths across sensitivity analyses are consistent in suggesting that increasing LCn3 increases prostate cancer risk, including limiting to trials at low summary risk of bias, PSA data suggest that LCn3 reduces PSA (which would tend to protect against prostate cancer). Downgraded once.
g. Imprecision: 95% CI included no effect as well as harm. Downgraded once.
h. Risk of bias: Neither included trial was at low summary risk of bias. Downgraded once.
i. Inconsistency: consistent across all sensitivity analyses, including when limiting only to trials at low summary risk of bias, and consistent with PSA data. Not downgraded.
j. Imprecision: 95% CI included benefits as well as harms. Downgraded twice.

Supplementary Table 5. High vs low ALA (primary outcomes)

Outcome	Sensitivity Analysis (SA) or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2, %
All cancer diagnoses	Main	2	752	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.38, 2.55]	0
	SA Fixed effects	2	752	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.37, 2.46]	0
	SA Low summary risk of bias	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-
	SA compliance	1	708	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.40, 2.98]	-
	SA n>100	1	708	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.40, 2.98]	-
Deaths from any cancer	Main	2	5545	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.74, 1.49]	0
	SA fixed effects	2	5545	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.75, 1.50]	0
	SA low summary risk of bias	1	4837	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.73, 1.48]	-
	SA compliance	2	5545	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.74, 1.49]	0
	SA n>100	2	5545	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.74, 1.49]	0
Breast cancer diagnoses	Main	2	513	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.17, 7.40]	0
	SA fixed effects	2	513	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.18, 6.40]	0
	SA Low summary risk of bias	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-
	SA compliance	1	481	Risk Ratio (M-H, Random, 95% CI)	1.94 [0.18, 21.28]	-
	SA n>100	1	481	Risk Ratio (M-H, Random, 95% CI)	1.94 [0.18, 21.28]	-
Breast cancer deaths	Main	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-
	Main	2	4010	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.72, 2.32]	0

Prostate cancer diagnoses	SA fixed effects	2	4010	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.73, 2.34]	0
	SA Low summary risk of bias	1	3783	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.67, 2.24]	0
	SA compliance	2	4010	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.72, 2.32]	0
	SA n >100	2	4010	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.72, 2.32]	0
Prostate cancer deaths	Main	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-
Dichotomous markers of cancer risk	PSA >4ng/ml	1	1622	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.86, 1.50]	-
Continuous markers of cancer risk	PSA, ng/ml	1	1622	Mean Difference (IV, Random, 95% CI)	0.10 [-0.03, 0.23]	-

Supplementary Table 6. High vs low ALA (secondary outcomes)

Outcome	Sensitivity Analysis (SA) or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2, %
Quality of life	-	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable	-
Adiposity	Weight, kg, ALA	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable	-
	BMI, kg/m2, ALA	1	1260	Mean Difference (IV, Random, 95% CI)	0.15 [-0.03, 0.33]	-
Side effects	Drop outs due to side effects	1	2433	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.47, 1.65]	-
	Any gastrointestinal side effect	1	2433	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.38, 2.28]	-
Dropouts		0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-

Supplementary Table 7. High vs low omega-6 (primary outcomes)

Outcome	Sensitivity Analysis (SA) or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2, %
Cancer diagnoses	Main	6	4272	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.96, 1.53]	0
	dietary advice & supplemental foods	4	3961	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.80, 1.70]	35
	GLA supplement	2	311	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.31, 5.98]	0
	SA fixed effects	6	4272	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.95, 1.51]	0
	SA low summary RoB	1	689	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.99]	-
	SA compliance	4	3961	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.80, 1.70]	35
	SA n >100	6	4272	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.96, 1.53]	0
Cancer deaths	Main	4	3321	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.51, 1.85]	52
	SA fixed effects	4	3321	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.77, 1.64]	52
	SA low summary RoB	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-
	SA compliance	3	3272	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.33, 2.66]	58
	SA n >100	3	3272	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.33, 2.66]	58
Breast cancer diagnoses	Main	1	200	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.14, 6.96]	-
	SA fixed effects	1	200	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.14, 6.96]	-
	SA low summary RoB	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-
	SA compliance	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-
	SA n >100	1	200	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.14, 6.96]	-
Breast cancer deaths	Main	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-

Prostate cancer diagnoses	Main	1	2033	Risk Ratio (M-H, Random, 95% CI)	2.24 [0.69, 7.26]	-
	SA fixed effects	1	2033	Risk Ratio (M-H, Fixed, 95% CI)	2.24 [0.69, 7.26]	-
	SA low summary RoB	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-
	SA compliance	1	2033	Risk Ratio (M-H, Random, 95% CI)	2.24 [0.69, 7.26]	-
	SA n >100	1	2033	Risk Ratio (M-H, Random, 95% CI)	2.24 [0.69, 7.26]	-
Prostate cancer deaths		0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-
Dichotomous markers of cancer risk		0	0	Mean Difference (IV, Random, 95% CI)	Not estimable	-
Continuous markers cancer risk	Breast density	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable	-
	PSA	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable	-

Supplementary Table 8. High vs low omega-6 (secondary outcomes)

Outcome	Sensitivity Analysis (SA) or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2, %
Quality of life		0	0	Mean Difference (IV, Random, 95% CI)	Not estimable	-
Adiposity	Weight, kg	1	177	Mean Difference (IV, Random, 95% CI)	Not estimable	-
	BMI, kg/m^2	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable	-
Side effects		0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-
Drop outs		2	311	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.40, 1.22]	0

Supplementary Table 9. GRADE table: summary of findings of effects of omega-6 fats on cancers

High compared to low omega 6 for cancer outcomes

Patient or population: adults, Setting: community, Intervention: Higher omega-6 intake, Comparison: low omega 6 intake

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with low omega 6 (primary outcomes)	Risk with High				
Cancer diagnoses	56 per 1,000	68 per 1,000 (54 to 86)	RR 1.21 (0.96 to 1.53)	4272 (6 RCTs)	⨁◯◯◯ VERY LOW [a,b]	The effect of increasing omega-6 on cancer diagnosis is unclear as the evidence is of very low quality.
Cancer deaths	26 per 1,000	25 per 1,000 (13 to 48)	RR 0.97 (0.51 to 1.85)	3321 (4 RCTs)	⨁◯◯◯ VERY LOW [c,d,e]	The effect of omega-6 on cancer deaths is unclear as the evidence is of very low quality.
Breast cancer diagnoses	20 per 1,000	20 per 1,000 (3 to 139)	RR 1.00 (0.14 to 6.96)	200 (1 RCT)	⨁◯◯◯ VERY LOW [c,f,g]	The effect of omega-6 on breast cancer diagnoses is unclear as the evidence is of very low quality.
Breast cancer deaths	not pooled	not pooled	not pooled	(0 RCTs)	-	We found no trials for this comparison
Prostate cancer diagnosis	4 per 1,000	9 per 1,000 (3 to 29)	RR 2.24 (0.69 to 7.26)	2033 (1 RCT)	⨁◯◯◯ VERY LOW [c,e,f]	The effect of omega-6 on risk of prostate cancer diagnosis is unclear as the evidence is of very low quality.
Prostate cancer death	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	(0 RCTs)	-	We found no trials assessing this effect.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio; OR: Odds ratio; MD: Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Risk of bias: limiting analysis to trials at low summary risk of bias moves effect from harm to benefit (in the single remaining trial). Downgraded twice.
b. Imprecision: 95% CI includes harm and also no effect. Downgraded once.
c. Risk of bias: None of the included trials were at low summary risk of bias. Downgraded once.
d. Inconsistency: I2 was >50% but less than 60%. Downgraded once.
e. Imprecision: 95% CI includes both benefits and harms. Downgraded once.
f. Indirectness: Only one trial assessed this outcome. Downgraded once.
g. Imprecision: 95% includes both important benefits and harms. Downgraded twice.

Supplementary Table 10. High vs low total PUFA (primary outcomes)

Outcome	Sensitivity Analysis (SA) or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	I^2, %	p-value*
Cancer diagnoses	Main	8	9428	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.99, 1.42]	0	-
	SA fixed effects	8	9428	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.98, 1.41]	0	-
	SA low summary risk of bias	3	3262	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.78, 1.51]	0	-
	SA by compliance	6	4230	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.94, 1.54]	5	-
	SA n >100	8	9428	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.99, 1.42]	0	-
	Duration: 1 to <2 years	2	825	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.06, 2.79]	0	0.54
	Duration: 2 to <4 years	2	2166	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.86, 1.53]	0	
	Duration: 4+ years	4	6437	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.89, 1.69]	27	
	Dose of PUFA: <0.5%E	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-	0.89
	Dose of PUFA: 0.5 to <1.0%E	1	136	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.04, 5.08]	-	
	Dose of PUFA: 1.0 to <2.0%E	1	2437	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.80, 1.56]	-	
	Dose of PUFA: 2.0 to <5.0%E	2	2166	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.86, 1.53]	0	
	Dose of PUFA: ≥5.0%E	3	1928	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.24, 2.64]	52	
	Dose of PUFA: unclear	1	2761	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.57, 3.63]	-	
	PUFA replacing MUFA	1	2761	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.57, 3.63]	-	0.50
	PUFA replacing mixed fats	3	3115	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.35, 1.85]	29	
	PUFA replacing SFA	1	846	Risk Ratio (M-H, Random, 95% CI)	1.49 [1.01, 2.20]	-	
	PUFA replacing CHO	3	2706	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.83, 1.53]	0	
	Low risk - usual population	6	6858	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.93, 1.56]	7	0.80
	Moderate risk - CA risk factors	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-	
	High risk - previous cancer	2	2570	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.84, 1.56]	0	
	Mean age <50 years	1	689	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.99]	-	0.27
	Mean age 50- <65	5	5132	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.89, 1.36]	0	
	Mean age 65+	2	3607	Risk Ratio (M-H, Random, 95% CI)	1.48 [1.04, 2.12]	0	

	Men & women mixed	3	3030	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.71, 2.30]	0	0.92
	Men only	4	3961	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.80, 1.70]	35	
	Women only	1	2437	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.80, 1.56]	-	
Cancer deaths	Main	4	3408	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.48, 2.49]	37	-
	SA fixed effects	4	3408	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.81, 1.99]	37	-
	SA low summary risk of bias	1	136	Risk Ratio (M-H, Random, 95% CI)	1.89 [0.18, 20.31]	-	-
	SA compliance	4	3408	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.48, 2.49]	37	-
	SA n >100	4	3408	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.48, 2.49]	37	-
Breast cancer diagnoses	Main	2	5198	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.71, 1.73]	0	-
	SA fixed effects	2	5198	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.71, 1.73]	0	-
	SA low summary risk of bias	1	2437	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.62, 1.71]	-	-
	SA compliance	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-	-
	SA n >100	2	5198	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.71, 1.73]	0	-
Breast cancer deaths	Main	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-	-
Prostate cancer diagnoses	Main	2	2879	Risk Ratio (M-H, Random, 95% CI)	1.64 [0.80, 3.36]	0	-
	SA fixed effects	2	2879	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [0.82, 3.38]	0	-
	SA low summary risk of bias	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-	-
	SA compliance	2	2879	Risk Ratio (M-H, Random, 95% CI)	1.64 [0.80, 3.36]	0	-
	SA n >100	2	2879	Risk Ratio (M-H, Random, 95% CI)	1.64 [0.80, 3.36]	0	-

Prostate cancer deaths	Main	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-	-
Dichotomous markers of cancer risk		0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-	-
Continuous measures of cancer risk	Breast density	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable	-	-
	PSA	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable	-	-

Supplementary Table 11. High vs low total PUFA (secondary outcomes)

Outcome	**Sensitivity Analysis (SA) or Subgroup**	**Studies**	**Participants**	**Statistical Method**	**Effect Estimate**	**I^2, %**
Quality of life	Main	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable	-
Adiposity	Weight, kg	2	3800	Mean Difference (IV, Random, 95% CI)	0.37 [-0.05, 0.78]	0
	BMI, kg/m^2	1	320	Mean Difference (IV, Random, 95% CI)	0.01 [-0.30, 0.31]	0
	Waist circumference, cm	1	331	Mean Difference (IV, Random, 95% CI)	0.31 [-0.80, 1.43]	0
Side effects	Drop outs due to side effects	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-
	Bleeding	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable	-
Drop outs		0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable	-

Supplementary Table 12. GRADE table: summary of findings of effects of total PUFA on cancers

High compared to low total PUFA for cancers

Patient or population: adults, Setting: community, Intervention: Higher total PUFA, Comparison: low total PUFA

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with low total PUFA (primary outcomes)	Risk with High				
Cancer diagnoses	41 per 1,000	49 per 1,000 (41 to 58)	RR 1.19 (0.99 to 1.42)	9428 (8 RCTs)	⨁⨁◯◯ LOW [a,b,c]	Increasing total PUFA may increase risk of diagnosis of any cancer.
Cancer deaths	19 per 1,000	21 per 1,000 (9 to 47)	RR 1.10 (0.48 to 2.49)	3408 (4 RCTs)	⨁⨁◯◯ LOW [d]	Increasing total PUFA may increase the risk of cancer death.
Breast cancer diagnoses	13 per 1,000	14 per 1,000 (9 to 23)	RR 1.11 (0.71 to 1.73)	5198 (2 RCTs)	⨁◯◯◯ VERY LOW [e,f]	The effect of increasing total PUFA on risk of breast cancer diagnosis is unclear as the evidence is of very low quality.
Breast cancer deaths	not pooled	not pooled	not pooled	(0 RCTs)	-	We found no trials assessing effects of total PUFA on breast cancer death.
Prostate cancer diagnoses	8 per 1,000	14 per 1,000 (7 to 28)	RR 1.64 (0.80 to 3.36)	2879 (2 RCTs)	⨁◯◯◯ VERY LOW [f,g]	The effect of increasing total PUFA on risk of prostate cancer diagnosis is unclear as the evidence is of very low quality.
Prostate cancer deaths	not pooled	not pooled	not pooled	(0 RCTs)	-	We found no trials assessing this outcome.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio; MD: Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Risk of bias: Limiting to the 3 trials at low summary risk of bias moved the RR into "no effect" (RR 1.08). Downgraded once.
b. Imprecision: 95% CI includes no effect as well as harm. Downgraded once.
c. Publication bias: funnel plot suggests that if missing small studies were added into the meta-analysis it would increase RR. Not downgraded.
d. Imprecision: 95% CI includes important benefit as well as harm. Downgraded twice.
e. Risk of bias: Limiting to the single trial at low summary risk of bias moved the RR into "no effect" (RR 1.03). Downgraded once.
f. Imprecision: 95% CI includes important benefits and harms. Downgraded twice.
g. Risk of bias: no included trial was at low summary risk of bias. Downgraded once.

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