

## Dietary $\alpha$ -Linolenic Acid Is Associated with Reduced Risk of Fatal Coronary Heart Disease, but Increased Prostate Cancer Risk: A Meta-Analysis<sup>1,2</sup>

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**ABSTRACT** The objective of this meta-analysis was to estimate quantitatively the associations between intake of  $\alpha$ -linolenic acid [ALA, the (n-3) fatty acid in vegetable oils], mortality from heart disease, and the occurrence of prostate cancer in observational studies. We identified 5 prospective cohort studies that reported intake of ALA and mortality from heart disease. We also reviewed data from 3 clinical trials on ALA intake and heart disease. In addition, we identified 9 cohort and case-control studies that reported on the association between ALA intake or blood levels and incidence or prevalence of prostate cancer. We combined risk estimates across studies using a random-effects model. High ALA intake was associated with reduced risk of fatal heart disease in prospective cohort studies (combined relative risk 0.79, 95% CI 0.60–1.04). Three open-label trials also indicated that ALA may protect against heart disease. However, epidemiologic studies also showed an increased risk of prostate cancer in men with a high intake or blood level of ALA (combined relative risk 1.70; 95% CI 1.12–2.58). This meta-analysis shows that consumption of ALA might reduce heart disease mortality. However, the association between high intake of ALA and prostate cancer is of concern and warrants further study. *J. Nutr.* 134: 919–922, 2004.

**KEY WORDS:** • linolenic acid • (n-3) fatty acids • cardiovascular • prostate cancer • meta-analysis

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A high intake of very long-chain (n-3) fatty acids from fish decreases the risk of death from coronary heart disease (1–6). However, much less is known about the effects of  $\alpha$ -linolenic acid [18:3 (n-3); ALA], the parent compound of all (n-3) fatty acids. Dietary ALA occurs mainly in plants and vegetable oils; its intake in affluent countries is 5–10 times higher than that of (n-3) fatty acids from fish. In the Netherlands, the major sources of ALA include margarine (25% of daily intake), meat (11%), bread (10%), and vegetables (8%) (7). In the United States, important sources of ALA are mayonnaise, creamy salad dressings, margarine, butter, beef, pork, lamb, and oil-and-vinegar-based dressings (8). An advantage of ALA over the very long-chain (n-3) fatty acids from fish is that it is easier to incorporate into food products because it does not have the pronounced smell and taste of fish oil. Furthermore, replacing very long-chain (n-3) fatty acids from fish by ALA from vegetable sources would prevent further depletion of the already low stocks of edible fish in the ocean (9). Here, we present quantitative estimates of the associations between ALA intake, mortality from heart disease, and occurrence of prostate cancer in observational studies.

### MATERIALS AND METHODS

**Sources and search criteria.** Studies on the relationship between ALA intake and disease were identified in the MEDLINE databases by using the keywords, linolenic acid and human, and by checking citations in identified publications. For our meta-analysis of the magnitude of the association between dietary intake of ALA and fatal heart disease risk, we selected only prospective cohort studies. We used only prospective studies because these are regarded as having the strongest design of all observational studies, and also because case-control studies do not provide reliable information on diet and fatal heart disease. Because the cases in these studies have died, it is very hard to obtain reliable dietary intake data retrospectively. In addition to the meta-analysis, we reviewed the results of 3 randomized clinical trials investigating effects of ALA intake on heart disease.

For a meta-analysis on the relationship between ALA intake or status and risk of prostate cancer we selected all observational studies that related either ALA intake or ALA concentrations in blood with incidence or prevalence of prostate cancer. In this meta-analysis, we did include case-control studies because prospective studies on a possible association are scarce and a possible association has never been systematically addressed. Furthermore, retrospective assessment of the diet is feasible because prostate cancer is not immediately fatal.

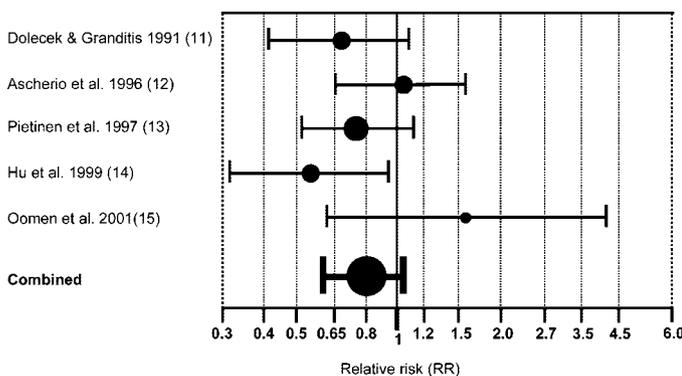
**Meta-analyses.** For inclusion in the meta-analyses, studies had to provide a quantitative estimate of relative risk (RR) and its standard error. We extracted from individual studies the risk estimate that referred to the largest difference in intake. Combined risk estimates were calculated by using the crude estimates of the individual studies (unadjusted RR) and by using the risk estimates that reflected the greatest degree of control for other environmental and dietary risk factors (RR adjusted for confounding factors). Risk estimates were combined using the random-effects model of DerSimonian and Laird (10).

### RESULTS

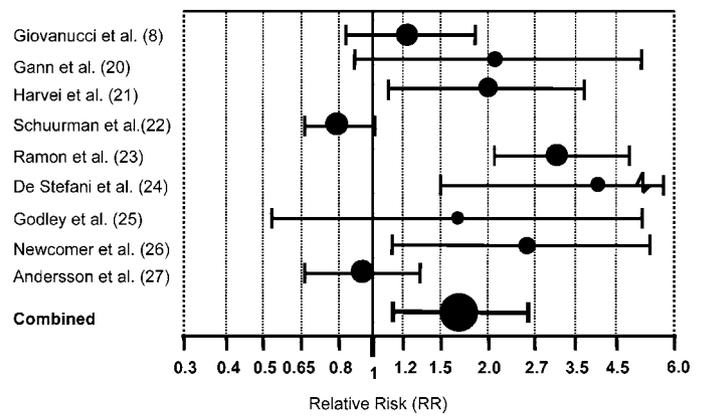
Five prospective epidemiologic studies (11–15) reported intake of ALA in relation to the incidence of fatal heart

disease (Fig. 1). Four of these cohort studies consisted of men (11–13,15) and one of women (14). All cohorts consisted of people who were free of diagnosed cardiovascular disease at baseline. The 12,866 participants of the MRFIT study were between 35 and 57 y old at baseline and were determined to be at high risk of coronary heart disease (11). The 43,757 health professionals were between 40 and 75 y of age at baseline (12). The 21,930 men in the Finnish ATBC study were all smokers and aged between 50 and 69 y (13). The 667 men in the Zutphen study were between 64 and 84 y old at the start of the study (15). The 76,283 female nurses in the Nurses' Health Study were 30–55 y old (14). The combined risk estimates of fatal heart disease for a high vs. low intake of ALA were 0.88 (95% CI: 0.66–1.17) when using unadjusted RR of the individual studies, and 0.79 (95% CI: 0.60–1.04) when using RR adjusted for confounding factors (Fig. 1). The mean ALA intake in the highest categories in the individual studies was 2.0 vs. 0.8 g/d in the lowest categories; thus the RR referred to a mean difference of 1.2 g/d.

Three clinical trials investigated the effect of increasing ALA intake on the incidence of fatal coronary heart disease (3,16,17). In the Lyon Diet Heart Study, 192 patients in the experimental group consumed 1.1 g ALA/d more than the 219 patients in the control group. The experimental group had a significantly lower incidence of fatal coronary heart disease (adjusted RR 0.24; 95% CI 0.07–0.85) than the control group (3). In a trial in India, 120 patients received 20 g/d mustard oil (similar to canola oil) containing 2.9 of ALA daily and 118 patients received placebo treatment, which contained no ALA, for 1 y. All patients had experienced an acute myocardial infarction shortly before they entered the study. Patients using mustard oil had a lower risk of cardiac death (RR 0.60; 95% CI 0.23–1.40) than patients who received placebo treatment (16). In another recent Indian trial, 499 patients in the experimental group were advised to consume an Indo-Mediterranean diet and 501 patients in the control group were advised to consume the step I National Cholesterol Education Program diet. The experimental diet contained on average 1.0 g ALA more than the control diet. Patients in the experimental group experienced significantly fewer total cardiac events (RR 0.48; 0.33–0.71) and sudden deaths (RR 0.33; 0.13–0.86) than those in the control group. In all three trials, the investigators were aware of the treatment. Another shortcoming of the large Indian trial and the Lyon Diet Heart trial is that changes in the diet involved more than ALA intake



**FIGURE 1** Relative risk of fatal heart disease for high vs. low intake of ALA in prospective cohort studies. Values are mean RR and 95% CI. The density of the points represents the weighting factor used for calculating the combined RR.



**FIGURE 2** Relative risk of prostate cancer with high versus low ALA intake or blood concentrations in prospective (8,20–22) and case-control studies (23–27). Values are mean RR and 95% CI. The density of the points represents the weighting factor used for calculating the combined RR.

alone (3,17). Moreover, the small Indian trial lacked power, and the number of cardiac events in this population was extremely high (30% in 1 y), making it difficult to extrapolate from this specific patient population to other populations. Thus, the above three trials did not have the ideal double-blind structure and had other limitations in design. Therefore, they cannot firmly establish a causal relationship between intake of ALA and reduced risk of fatal heart disease. Nevertheless, the findings from these trials are in line with the associations found in the prospective observational studies. Furthermore, animal experiments indicate that ALA may prevent fatal heart disease by inhibiting life-threatening arrhythmias (18,19). Taken together, the prospective studies and the trials provide strong indications for a role of ALA in preventing fatal heart disease; they suggest that increasing intake of ALA by 1.2 g/d decreases the risk of fatal coronary heart disease by at least 20%.

Any favorable effects of ALA should be weighed against possible adverse effects. There have been reports suggesting that subjects with high ALA intake may be at increased risk of prostate cancer. We found a total of 9 observational studies (8,20–27) that investigated the relationship between prostate cancer incidence or prevalence and intake of ALA or blood levels of ALA (Fig. 2). Blood levels of ALA reflect intake of ALA (28). A cohort study from the Netherlands consisting of 58,279 men aged 55–69 y at baseline was the only prospective study showing a slight protective effect of ALA intake on prostate cancer incidence (RR 0.76; 95% CI 0.66–1.04) (22). The U.S. Health Professionals' follow-up study, which involved 51,529 men age 40–75 y at baseline, showed a slightly increased risk with increasing dietary ALA intake (RR 1.25; 95% CI 0.82–1.92) (8). Two nested case-control studies, one from the United States (20) and one from Norway (21) showed an increased risk of prostate cancer for men in the highest quartile of blood ALA. In these four prospective studies (8,20–22), the combined estimate of adjusted RR for prostate cancer incidence was 1.32 (95% CI 0.80–2.18) for men with high vs. low intake or blood levels of ALA. When we combined these data with those from five nonprospective studies (23–27), the risk estimate increased to 1.70 (95% CI 1.12–2.58). It should be noted that the results from these studies were quite heterogeneous (Fig. 2).

## DISCUSSION

The outcome of our meta-analysis of prospective studies taken together with the results of the clinical trials (3,16,17) suggests that an increased intake of ALA can lower the risk of fatal coronary heart disease.

The most likely mechanism by which ALA may prevent fatal heart disease is by reducing cardiac arrhythmia. In the Western world, ~50% of all deaths from cardiovascular disease can be ascribed to sudden cardiac death (29). The majority of sudden deaths are directly caused by acute ventricular arrhythmia (30). In vitro and animal studies have suggested antiarrhythmic effects of ALA (18,19).

The data reviewed here suggest that ALA protects against heart disease, but there are also indications for an increased risk of prostate cancer in men with a high intake of ALA compared with those with a low intake. It is quite uncertain at present whether the effect on prostate cancer is real. Even if it were real, the protective effect on fatal coronary heart disease would probably outweigh these possible negative effects, especially for men with an increased risk of heart disease. In the United States, 6 times more men are diagnosed with coronary heart disease than with prostate cancer, and almost 8 times more men die of coronary heart disease than of prostate cancer (CDC/NCHS, www.cdc.gov). Furthermore, prostate cancer occurs at an older age: >40% of coronary heart disease patients are <65 y old when diagnosed, whereas >50% of prostate cancer patients are >75 y old when diagnosed.

A possible explanation for the heterogeneity in results between the observational studies might be that ALA can come from different dietary sources. This might lead to different types of confounding for different studies. For example, in some countries, such as Uruguay (24), meat and not vegetable oil is the major source of ALA, and the apparently deleterious effect of ALA could therefore be caused by high meat intake instead of high ALA intake. This would lead to an increased risk of prostate cancer in those studies in which meat was the major source of ALA and not in those studies in which vegetable oils were the major source of ALA. In the Netherlands, where the study of Schuurman et al. (22) showed a protective effect of linolenic acid intake on prostate cancer, vegetable oils in margarines are indeed the main source of ALA (7). Unfortunately, only 3 studies of ALA intake and prostate cancer provided additional information about the source of ALA. These studies do not show a clear association with intake of either vegetable oils or meat (8,23,24). In the Health Professionals Follow-Up Study (8), red meat was an important source of ALA, but not the main source. Furthermore, the relation between ALA intake and prostate cancer was still present after adjustment for meat intake in the Health Professionals Follow-Up Study (8) and after adjustment for animal fat in the study of Ramon et al. (23). Moreover, in the study in Uruguay, both ALA from animal sources and ALA from vegetable sources were associated with an increased risk of prostate cancer (24). Thus, it is unlikely that the differences in results between populations are caused by either meat or vegetable oil as the major source of ALA in a particular population. Other reasons for the heterogeneity of the results might include the differences in the design of the studies, differences in the background diets of the populations, random error, and publication bias.

Intake of very-long chain (n-3) PUFA as present in fish is not related to an increased risk of prostate cancer in epidemiologic or animal studies. There are even indications that high intakes of very-long chain (n-3) PUFA from fish may protect against prostate cancer (31). Data from clinical trials and

prospective studies showed that moderate-to-high intake of (n-3) fatty acids from fish reduces the risk of total mortality by at least 20% (1,2,16). Therefore, fish should be the first recommended source of (n-3) fatty acids. However, ALA could provide an alternative for those subjects who are at high risk of cardiovascular disease and who, for various reasons, do not want to consume fish. Another advantage of increased use of ALA instead of (n-3) fatty acids from fish would be the lower burden on the environment. Use of ALA instead of fish fatty acids could help to prevent depletion of the oceans from certain fish species.

ALA consumption might have a substantial effect on heart disease mortality, but the positive association between intake of ALA and prostate cancer is of concern and requires further study. Double-blind, randomized clinical trials are required to provide definitive answers on ALA intake and heart disease. Such trials will lack the power to detect effects of ALA intake on prostate cancer, but studies of prostate-specific antigen may provide a surrogate marker. In the meantime, very long-chain (n-3) fatty acids from fish should remain the recommended source of (n-3) fatty acids in the prevention of heart disease.

**Note added in proof:** In a recent prospective study in male smokers [Männistö, S., Pietinen, P., Virtanen, M. J., Salminen, I., Albanes, D., Giovannucci, E. & Virtamo, J. (2003) Fatty acids and risk of prostate cancer in a nested case-control study in male smokers. *Cancer Epidemiol. Biomarkers Prev.* 12: 1422–1428] the relative risk (RR) for prostate cancer in the fourth versus the first quartile of ALA intake was 1.16 (95% CI 0.64–2.13). Inclusion of this study changes the combined RR for prospective studies from 1.32 to 1.28 (95% CI 0.84–1.94). The combined RR for all studies on ALA and prostate cancer changes from 1.70 to 1.62 (95% CI 1.11–2.37).

## LITERATURE CITED

1. GISSI-Prevenzione Investigators (1999) Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. *Lancet* 354: 447–455.
2. Burr, M. L., Fehily, A. M., Gilbert, J. F., Rogers, S., Holliday, R. M., Sweetnam, P. M., Elwood, P. C. & Deadman, N. M. (1989) Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet* 2: 757–761.
3. de-Lorgeril, M., Renaud, S., Mamelle, N., Salen, P., Martin, J. L., Monjaud, I., Guidollet, J., Touboul, P. & Delaye, J. (1994) Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet* 343: 1454–1459.
4. Kromhout, D., Bosschieter, E. B. & de-Lezanne-Coulander, C. (1985) The inverse relation between fish consumption and 20-year mortality from coronary heart disease. *N. Engl. J. Med.* 312: 1205–1209.
5. Albert, C. M., Hennekens, C. H., O'Donnell, C. J., Ajani, U. A., Carey, V. J., Willett, W. C., Ruskin, J. N. & Manson, J. E. (1998) Fish consumption and risk of sudden cardiac death. *J. Am. Med. Assoc.* 279: 23–28.
6. Hu, F. B., Bronner, L., Willett, W. C., Stampfer, M. J., Rexrode, K. M., Albert, C. M., Hunter, D. & Manson, J. E. (2002) Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. *J. Am. Med. Assoc.* 287: 1815–1821.
7. Voskuil, D. W., Feskens, E. J., Katan, M. B. & Kromhout, D. (1996) Intake and sources of alpha-linolenic acid in Dutch elderly men. *Eur. J. Clin. Nutr.* 50: 784–787.
8. Giovannucci, E., Rimm, E. B., Colditz, G. A., Stampfer, M. J., Ascherio, A., Chute, C. C. & Willett, W. C. (1993) A prospective study of dietary fat and risk of prostate cancer. *J. Natl. Cancer Inst.* 85: 1571–1579.
9. Naylor, R. L., Goldburg, R. J., Primavera, J. H., Kautsky, N., Beveridge, M. C., Clay, J., Folke, C., Lubchenco, J., Mooney, H. & Troell, M. (2000) Effect of aquaculture on world fish supplies. *Nature (Lond.)* 405: 1017–1024.
10. DerSimonian, R. & Laird, N. (1986) Meta-analysis in clinical trials. *Control Clin. Trials* 7: 177–188.
11. Dolecek, T. A. & Granditis, G. (1991) Dietary polyunsaturated fatty acids and mortality in the Multiple Risk Factor Intervention Trial (MRFIT). *World Rev. Nutr. Diet.* 66: 205–216.
12. Ascherio, A., Rimm, E. B., Giovannucci, E. L., Spiegelman, D., Stampfer, M. & Willett, W. C. (1996) Dietary fat and risk of coronary heart disease in men: cohort follow up study in the United States. *Br. Med. J.* 313: 84–90.
13. Pietinen, P., Ascherio, A., Korhonen, P., Hartman, A. M., Willett, W. C., Albanes, D. & Virtamo, J. (1997) Intake of fatty acids and risk of coronary heart

disease in a cohort of Finnish men. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *Am. J. Epidemiol.* 145: 876–887.

14. Hu, F. B., Stampfer, M. J., Manson, J. E., Rimm, E. B., Wolk, A., Colditz, G. A., Hennekens, C. H. & Willett, W. C. (1999) Dietary intake of alpha-linolenic acid and risk of fatal ischemic heart disease among women. *Am. J. Clin. Nutr.* 69: 890–897.

15. Oomen, C. M., Ocke, M. C., Feskens, E. J., Kok, F. J. & Kromhout, D. (2001)  $\alpha$ -Linolenic acid intake is not beneficially associated with 10-y risk of coronary artery disease incidence: the Zutphen Elderly Study. *Am. J. Clin. Nutr.* 74: 457–463.

16. Singh, R. B., Niaz, M. A., Sharma, J. P., Kumar, R., Rastogi, V. & Moshiri, M. (1997) Randomized, double-blind, placebo-controlled trial of fish oil and mustard oil in patients with suspected acute myocardial infarction: the Indian experiment of infarct survival—4. *Cardiovasc. Drugs Ther.* 11: 485–491.

17. Singh, R. B., Dubnov, G., Niaz, M. A., Ghosh, S., Singh, R., Rastogi, S. S., Manor, O., Pella, D. & Berry, E. M. (2002) Effect of an Indo-Mediterranean diet on progression of coronary artery disease in high risk patients (Indo-Mediterranean Diet Heart Study): a randomised single-blind trial. *Lancet* 360: 1455–1461.

18. Leaf, A., Kang, J. X., Xiao, Y. F. & Billman, G. E. (1999) n-3 Fatty acids in the prevention of cardiac arrhythmias. *Lipids* 34 (suppl.): S187–S189.

19. McLennan, P. L. & Dallimore, J. A. (1995) Dietary canola oil modifies myocardial fatty acids and inhibits cardiac arrhythmias in rats. *J. Nutr.* 125: 1003–1009.

20. Gann, P. H., Hennekens, C. H., Sacks, F. M., Grodstein, F., Giovannucci, E. L. & Stampfer, M. J. (1994) Prospective study of plasma fatty acids and risk of prostate cancer. *J. Natl. Cancer Inst.* 86: 281–286.

21. Harvei, S., Bjerve, K. S., Tretli, S., Jellum, E., Røsbjæ, T. E. & Vatten, L. (1997) Prediagnostic level of fatty acids in serum phospholipids: omega-3 and omega-6 fatty acids and the risk of prostate cancer. *Int. J. Cancer* 71: 545–551.

22. Schuurman, A. G., van-den-Brandt, P. A., Dorant, E., Brants, H. A. &

Goldbohm, R. A. (1999) Association of energy and fat intake with prostate carcinoma risk: results from The Netherlands Cohort Study. *Cancer* 86: 1019–1027.

23. Ramon, J. M., Bou, R., Romea, S., Alkiza, M. E., Jacas, M., Ribes, J. & Oromi, J. (2000) Dietary fat intake and prostate cancer risk: a case-control study in Spain. *Cancer Causes Control* 11: 679–685.

24. De-Stefani, E., Deneo-Pellegrini, H., Boffetta, P., Ronco, A. & Mendilaharsu, M. (2000) Alpha-linolenic acid and risk of prostate cancer: a case-control study in Uruguay. *Cancer Epidemiol. Biomark. Prev.* 9: 335–338.

25. Godley, P. A., Campbell, M. K., Miller, C., Gallagher, P., Martinson, F. E., Mohler, J. L. & Sandler, R. S. (1996) Correlation between biomarkers of omega-3 fatty acid consumption and questionnaire data in African American and Caucasian United States males with and without prostatic carcinoma. *Cancer Epidemiol. Biomark. Prev.* 5: 115–119.

26. Newcomer, L. M., King, I. B., Wicklund, K. G. & Stanford, J. L. (2001) The association of fatty acids with prostate cancer risk. *Prostate* 47: 262–268.

27. Andersson, S. O., Wolk, A., Bergstrom, R., Giovannucci, E., Lindgren, C., Baron, J. & Adami, H. O. (1996) Energy, nutrient intake and prostate cancer risk: a population-based case-control study in Sweden. *Int. J. Cancer* 68: 716–722.

28. Bjerve, K. S., Brubakk, A. M., Fougner, K. J., Johnsen, H., Midthjell, K. & Vik, T. (1993) Omega-3 fatty acids: essential fatty acids with important biological effects, and serum phospholipid fatty acids as markers of dietary omega 3-fatty acid intake. *Am. J. Clin. Nutr.* 57: 801S–805S.

29. Zipes, D. P. & Wellens, H. J. (1998) Sudden cardiac death. *Circulation* 98: 2334–2351.

30. Huikuri, H. V., Castellanos, A. & Myerburg, R. J. (2001) Sudden death due to cardiac arrhythmias. *N. Engl. J. Med.* 345: 1473–1482.

31. Augustsson, K., Michaud, D. S., Rimm, E. B., Leitzmann, M. F., Stampfer, M. J., Willett, W. C. & Giovannucci, E. (2003) A prospective study of intake of fish and marine fatty acids and prostate cancer. *Cancer Epidemiol. Biomark. Prev.* 12: 64–67.