Blood level omega-3 Fatty acids as risk determinant molecular biomarker for prostate cancer
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CRD summary
This review found that elevated levels of docosapentaenoic acid were associated with a decreased risk of prostate cancer but elevated levels of fish oils were associated with an increased risk of high-grade prostate tumours. The authors appear to have over-interpreted the results of their multiple analyses and these conclusions should not be considered to be reliable.

Authors' objectives
To investigate the association between blood levels of omega-3 fatty acids and risk of prostate cancer.

Searching
MEDLINE, EMBASE, Science Direct, ProQuest and The Cochrane Library were searched to July 2012 without language restrictions. Search terms were presented. References from included studies and relevant reviews and textbooks were searched. Relevant experts were contacted to identify other published or unpublished studies.

Study selection
Eligible studies were those that measured blood levels of omega-3 fatty acids (with or without their derivatives) where prostate cancer was the outcome. Both prospective and retrospective case-control studies were eligible. Studies had to report the association between fatty acids and prostate cancer. Studies of tissue levels of fatty acids were excluded. Total prostate cancer occurrence, advanced prostate cancer and high-grade tumours were all considered.

Participant ages ranged from about 40 to 86. Prospective studies identified cancer cases from registries; retrospective studies used histopathology. Four types of fatty acid were considered: alpha-linolenic acid (ALA), docosahexaenoic acid (DHA), docosapentaenoic acid (DPA) and eicosapentaenoic acid (EPA). Fatty acid levels were mostly determined either by measuring serum fatty acids or erythrocyte membrane fatty acids. All studies adjusted their analysis for age; most adjusted for a range of other factors.

Two reviewers independently selected studies for inclusion. Disagreements were resolved by a third reviewer.

Assessment of study quality
Quality was assessed on criteria relevant to observational studies as recommended by the NHS and graded on an 11-point scale. Quality was also assessed using the Newcastle-Ottawa quality assessment scale.

Two reviewers independently performed the assessment. Disagreements were resolved by consensus.

Data extraction
Data were extracted in terms of the odds ratio (OR) or relative risk their 95% confidence intervals (CI) for the association between fatty acids and prostate cancer by comparing risks in the highest blood level of fatty acids to the lowest reference level. Where studies adjusted for potential confounding factors these adjusted results were used.

Authors were contacted if the desired data were not presented in the publication.

One reviewer extracted data which were checked by a second.

Methods of synthesis
Pooled odd ratios with 95% CI were generated using a random-effects meta-analysis. Separate analyses were conducted for different types of fatty acid. Heterogeneity was assessed using Cochran's Q and I². Results from prospective and retrospective studies were compared using subgroup analysis. A sensitivity analysis removed each study one at a time. Publication bias was assessed using funnel plots and Begg's and Egger's tests.
Results of the review

Twelve studies were included: six nested case-control and six case-control. There were slightly over 10,000 participants (range 127 to 3,461) including 4,516 cancer cases. Follow-up in the nested studies ranged from four to 19 years. All studies were judged to be of good quality (scored between eight and 10 out of 11 according to the NHS criteria).

For associations between total prostate cancer and the four specific types of fatty acid only DPA showed a statistically significant association and this favoured higher levels of DPA (OR 0.76, 95% CI 0.60 to 0.96; six studies; $I^2=0\%$). Neither long-chain acids (DHA, DPA and EPA) nor fish oils (DHA and EPA) were significantly associated with total prostate cancer. There was no significant association when all four types of fatty acid were included (OR 1.0, 95% CI 0.90 to 1.11; $I^2=26\%$).

There was no significant association between omega-3 and advanced prostate cancer.

An association between fish oils (DHA and EPA) and high-grade prostate cancer favoured lower levels of fish oil (OR 1.38, 95% CI 1.05 to 1.82; $I^2=18\%$) but there was no significant association for any individual fatty acid or for all fatty acids combined.

Subgroup analyses showed no obvious differences between case-control and nested case-control studies. There was no evidence of publication bias.

Authors' conclusions

Elevated levels of DPA were associated with a decreased risk of prostate cancer. Elevated levels of EPA and DHA in combination were associated with an increased risk of high-grade prostate tumours. Cautious interpretation of these results was needed.

CRD commentary

This was generally a well-conducted review with an appropriate review question and inclusion criteria. A broad search was performed and included unpublished material and publications not written in English. Efforts were made to reduce reviewer error and bias. Study quality was assessed and judged to be good but all included studies were observational case-control studies. These are prone to various biases and despite adjustment for confounding factors, a risk of confounding due to other unidentified factors remains.

The analysis compared only the highest and lowest fatty acid levels and ignored intermediate levels; this may overstate any association between fatty acids and cancer. All studies were conducted in Western populations and findings may not apply to other populations. A large number of meta-analyses were performed and this increased the risk of apparently statistically significant findings arising by chance. The authors did not account for this and consequently appear to have over-interpreted some of the results.

The overall results on the association of all fatty acids combined with prostate cancer may be reliable. The numerous smaller subgroup analyses and the authors’ conclusions based on them should not be considered to be reliable.

Implications of the review for practice and research

Practice: The authors made no recommendations for medical or public health practice.

Research: The authors suggested that further research was needed in multi-ethnic and Eastern populations and that the contribution of environmental toxins to prostate cancer needed more research.

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