Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

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Omega-3 fatty acids and prostate cancer

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A case-control study has found that high blood concentrations of omega-3 fatty acids are seen in men with prostate cancer. This study in no way proves causation and the amount of omega-3 fatty acids taken by the men in their diet, or as supplements, is not known. However, it does highlight a possible safety signal, reinforcing the need to consider both the potential risks and benefits of treatment with omega-3 fatty acids. Recent evidence has found no benefit of omega-3 fatty acids for the secondary prevention of cardiovascular disease, and the updated NICE clinical guideline on myocardial infarction: secondary prevention no longer recommends their use.

Overview and current advice

The place in therapy of omega-3 fatty acid supplements is covered in several NICE clinical guidelines. These are summarised in the key therapeutic topic publication on omega-3 fatty acids, which supports the Quality, Innovation, Productivity and Prevention (QIPP) medicines use and procurement work stream.

NICE clinical guidelines on lipid modification (currently being updated; expected publication date July 2014), familial hypercholesterolaemia (FH) and type 2 diabetes (currently being updated; publication date to be confirmed) do not recommend these supplements for the primary prevention of cardiovascular disease. For people with type 2 diabetes and refractory hypertriglyceridaemia, a trial of highly concentrated, licensed omega-3 fish oils can be considered if lifestyle measures and fibrate therapy have failed.

For the secondary prevention of cardiovascular disease, NICE guidance on myocardial infarction (MI): secondary prevention previously recommended consideration of omega-3 fatty acid supplements for people who had experienced an MI within 3 months and were not achieving sufficient consumption in their diet. However, this was based on older evidence in people not receiving current therapies. Newer evidence is now available in people receiving up-to-date treatments (see Commentary). As this showed no benefit of omega-3 fatty acids, the recommendation has been changed. The recently published updated NICE clinical guideline on MI: secondary prevention states:
‘Do not offer or advise people to use the following to prevent another MI:

- omega-3 fatty acid capsules
- omega-3 fatty acid supplemented foods.

If people choose to take omega-3 fatty acid capsules, or eat omega-3 fatty acid supplemented foods, healthcare professionals should be aware that there is no evidence of harm.’

Recently, an observational study has received some media attention as it suggested a possible link between high blood concentrations of omega-3 fatty acids and an increased risk of prostate cancer.

New evidence

This case-control study\(^1\) looked at the association between blood concentrations of omega-3 fatty acids and the risk of prostate cancer among participants in the SELECT trial. SELECT was a placebo-controlled, randomised trial that tested whether selenium and vitamin E, either alone or combined, reduced prostate cancer risk\(^2\). The case-control study included 834 case subjects (men diagnosed with incident, primary prostate cancers, of which 156 were high-grade) matched with 1393 control subjects (men selected randomly at baseline, matched on age and race), of which 1364 had no diagnosis of prostate cancer.

Associations were given for blood concentrations of total long-chain omega-3 fatty acids and individual fatty acids (eicosapentaenoic acid [EPA], docosapentaenoic acid [DPA] and docosahexaenoic acid [DHA]) based on quartiles. These were adjusted for confounders including education, history of diabetes, family history of prostate cancer and treatment assignment in SELECT.

The mean percentages of total long-chain omega-3 fatty acid (EPA + DPA + DHA) blood concentrations were statistically significantly higher in men with ‘total prostate cancer’ (4.66, 95% confidence interval [CI] 4.56 to 4.75, \(p=0.002\)), low-grade prostate cancer (4.66, 95% CI 4.56 to 4.77, \(p=0.002\)) and high-grade prostate cancer (4.71, 95% CI 4.51 to 4.91, \(p=0.03\)) compared with men with no prostate cancer (4.48, 95% CI 4.41 to 4.55).

Higher total long-chain omega-3 fatty acid blood concentrations were associated with increased risks of total, low-grade and high-grade prostate cancers. Compared with men whose blood concentrations were in the lowest quartile, men in the highest quartile had a 43% increased risk of total prostate cancer (hazard ratio [HR] 1.43; 95% CI 1.09 to 1.88), a 44% increased risk of low-grade prostate cancer (HR 1.44; 95% CI 1.08 to 1.93) and a 71% increased risk of high-grade prostate cancer (HR 1.71; 95% CI 1.00 to 2.94).

Commentary provided by NICE Medicines and Prescribing Centre

The authors of this case-control study discuss their findings in the context of other observational studies, some of which also support an association between higher omega-3 fatty acid blood concentrations and an increased risk of prostate cancer. However, all such observational studies have limitations and they can only suggest an association not prove causation. Although efforts were made to adjust for confounding factors, including family history of prostate cancer, some confounding may remain. The study did not look at men’s diets, so it is not known how much oily fish they ate or whether they were taking omega-3
fatty acid capsules or supplemented foods. Other potential reasons for variations in omega-3 fatty acid levels, such as metabolic factors, were also not considered.

Omega-3 fatty acids are widely thought to have beneficial, not harmful, effects and the results of this study were not expected. However, as highlighted in the QIPP key therapeutic topic, the cardiovascular benefits of fatty acid supplementation have now been questioned. Two meta-analyses and the ORIGIN study found that omega-3 fatty acid supplements did not reduce the risk of cardiovascular events or all-cause mortality.

The update of the NICE clinical guideline on MI: secondary prevention included 6 randomised controlled trials of omega-3 fatty acids. In reviewing this evidence, the Guideline Development Group decided that the evidence was not strong enough to recommend the use of omega-3 fatty acid capsules for secondary prevention following an MI. They felt that the benefit of current treatments on a cardiac event is likely to over-ride any potential small gains that omega-3 fatty capsules may provide. Therefore, the recommendation was changed to no longer recommend omega-3 fatty acids for secondary prevention.

The updated guideline states that there is no evidence of harm with omega-3 fatty acids, but the risk of prostate cancer specifically was not reviewed, and the cohort study discussed here was published after the literature search cut-off date for the update. It is unclear why high levels of omega-3 fatty acids are seen in men with prostate cancer and more research in this area would be needed to investigate this further. However, this possible safety signal together with recent evidence showing no cardiovascular benefits of omega-3 fatty acids needs to be taken into account if these supplements are being considered.

In the year to September 2012, approximately 645,000 items of omega-3 fatty acid compounds (such as Omacor and Maxepa) were prescribed in primary care in England, at a cost of about £15.4 million. Based on prescribing data from April to August 2013, the prescribing of these products has now reduced to approximately 535,000 items at a cost of £13.5 million, annually. However, the variation between localities is still marked. In the 5 months to August 2013, the lowest prescribing CCG prescribed 68 items of omega-3 fatty acid compounds at a cost of £2159. This compared with 7935 items and £147,134 in the highest prescribing CCG (data provided by NHS Prescription Services, NHS Business Services Authority, November 2013).

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**References**

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