Eicosapentaenoic acid and/or aspirin for preventing colorectal adenomas during colonoscopic surveillance in the NHS Bowel Cancer Screening Programme: the seAFOod RCT

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Scientific summary

The seAFOod RCT

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Scientific summary

Background

Chemoprevention (the use of drugs or nutritional agents) is one strategy for the prevention of colorectal cancer (CRC), the development of which occurs predominantly via a benign colorectal lesion termed an adenoma (also known as a polyp). The molecular pathogenesis of the early stages of colorectal carcinogenesis is complex, and is reflected by two main histological types of precursor lesion [(1) conventional (i.e. tubular, tubulo-villous, villous) adenoma and (2) serrated adenoma (now termed polyp, recognising that no dysplasia is present in most serrated lesions)], which map onto different molecular characteristics, such as chromosomal instability or deoxyribonucleic acid (DNA) hypermethylation, and are both believed to progress to CRC.

The omega-3 (ω-3) polyunsaturated fatty acid (PUFA) eicosapentaenoic acid (EPA) and aspirin are candidate CRC chemoprevention agents: both have proof of concept in humans, aligned with an excellent safety and toxicity profile. Therefore, a randomised, Phase III, polyp-prevention trial was performed to investigate the chemoprevention efficacy of both agents in individuals at risk of 'sporadic' colorectal adenoma recurrence within a colonoscopy screening and surveillance programme.

Different 'nutraceutical' formulations of EPA exist, including EPA in the free fatty acid (FFA) form, as a triglyceride (TG) conjugate, or as ethyl ester. All three forms of EPA have anti-CRC activity in pre-clinical studies. A direct comparison between EPA bioavailability and tolerability of different formulations in a randomised trial has not been reported previously.

Objectives

Primary objective

The primary objective was to determine whether or not EPA prevents colorectal adenomas, either alone or in combination with aspirin.

The following primary hypotheses were tested:

- 2 g of EPA-FFA or 2780 g of EPA-TG (equivalent to a 2-g FFA dose) daily is more effective than placebo for reduction in colorectal adenoma recurrence.
- 300 mg of aspirin daily is more effective than placebo for reduction in colorectal adenoma recurrence.

Secondary objectives

The secondary objectives were to assess the tolerability and safety of EPA, as the FFA or as the TG, alone and in combination with aspirin.

Methods

Trial design

This was a randomised, blinded, placebo-controlled 2 × 2 factorial trial, which was integrated into the screening and surveillance phases of the NHS Bowel Cancer Screening Programme (BCSP) so that participation did not alter routine clinical practice.

Eligibility

Recruitment was restricted to BCSP patients aged 55–73 years who were identified as 'high risk' [five or more small (< 10 mm in size) colorectal adenomas or three or more colorectal adenomas, with at least one being ≥ 10 mm, based on endoscopic findings and confirmed later by the histopathology report] at a complete screening colonoscopy. This included patients who were identified as 'high risk' at colonoscopy after faecal occult blood test (FOBt) screening, or who were deemed 'high risk' after a bowel scope flexible sigmoidoscopy (FS) and subsequent screening colonoscopy.

Interventions

- Four gastro-resistant capsules of 99% EPA-FFA or five soft gelatin capsules of 90% EPA-TG (both equivalent to 2 g of FFA daily), or identical placebos (both containing capric and capryllic acid medium-chain TGs). The capsule investigational medicinal product (IMP) switch was necessitated by cessation of supply of EPA-FFA and its placebo during the trial. Each participant received either the FFA or the TG formulation (or respective placebo), but not both.
- One enteric-coated aspirin tablet (300 mg) or identical placebo.

Both IMPs were provided from randomisation until the day before surveillance colonoscopy, 12 months after the screening procedure.

Randomisation and blinding

After written informed consent was obtained, the participant was randomised according to a 2 × 2 factorial design (*Table a*).

Internet-based treatment assignment was determined by a computer-generated pseudorandom code using random permuted blocks of randomly varying size (4–12). Trial participants were allocated with equal probability to each treatment group. Stratification was by BCSP site. The sequence of treatment allocations was concealed until recruitment, data collection and all other trial-related assessments had been completed. Allocation was not divulged to researchers or participants.

The seAFOod trial biobank

Blood [for red blood cells (RBCs), plasma and leucocytes (DNA)], urine and rectal mucosa samples were obtained at baseline and at 6 and 12 months (rectal mucosa samples were obtained at 12 months only). One or more biological samples were received from 95% of participants, with 73% providing a full sample set.

Outcomes

Primary outcome

The primary outcome was the number of participants with one or more colorectal adenomas detected at the first BCSP surveillance colonoscopy 12 months after the screening examination [the adenoma detection rate (ADRa)].

TABLE a The Systematic Evaluation of Aspirin and Fish Oil (seAFOod) trial 2 × 2 factorial design

• 2 g of EPA-FFA, or equivalent FFA dose of EPA-TG • 300 mg of aspirin	• 2 g of EPA-FFA, or equivalent FFA dose of EPA-TG • Placebo aspirin
• Placebo EPA • 300 mg of aspirin	• Placebo EPA • Placebo aspirin

Secondary outcomes

The secondary outcomes were as follows:

- Total number of colorectal adenomas per participant at BCSP surveillance colonoscopy [total mean adenomas per participant (MAP)].
- Detection of one or more 'advanced' (i.e. ≥ 10 mm in diameter, high-grade dysplasia or villous histology) colorectal adenomas at the 12-month BCSP surveillance colonoscopy (advanced ADRa).
- Number of 'advanced' colorectal adenomas per participant at the 12-month BCSP surveillance colonoscopy (advanced MAP).
- Detection of one or more conventional adenomas (conventional adenoma end points were defined after database lock) at the first BCSP surveillance colonoscopy (conventional ADRa).
- Number of conventional adenomas (conventional adenoma end points were defined after database lock) per participant at the first BCSP surveillance colonoscopy (conventional MAP).
- Detection of one or more serrated adenomas at the first BCSP surveillance colonoscopy (serrated ADRa).
- Number of serrated adenomas per participant at the first BCSP surveillance colonoscopy (serrated MAP).
- The region of the colorectum (right colon: any part of the colon proximal to the splenic flexure; left colon: the rectum and the colon at/distal to the splenic flexure) in which adenomas are detected at the first BCSP surveillance colonoscopy.
- Reclassification from 'high risk' to 'intermediate risk' after the first BCSP surveillance colonoscopy (BCSP risk stratification at the first surveillance colonoscopy states that any individual who does not continue to fulfil 'high-risk' criteria is classified as 'intermediate risk' for further colonoscopic surveillance at 3 years).
- Detection of CRC prior to, or at, the first BCSP surveillance colonoscopy.
- Dietary fish and other seafood intake at baseline and at the end of the trial.
- Red blood cell EPA and rectal EPA levels at baseline and at 6 months (RBC only) and 12 months from randomisation.
- Absolute RBC fatty acid [docosahexaenoic acid (DHA), arachidonic acid (AA), EPA-to-AA ratio] levels and difference from baseline at 6 and 12 months.
- Rectal mucosal fatty acid (DHA, AA, EPA-to-AA ratio) levels at surveillance colonoscopy.
- Adverse events, including clinically significant bleeding episodes [haemorrhagic stroke or gastrointestinal (GI) bleeding requiring hospital admission or investigation].

Exploratory outcomes

- Colorectal adenoma size.
- Association between change of RBC EPA level at 12 months and individual number of total colorectal adenomas.
- Association between rectal and RBC EPA levels at 12 months.

Sample size

It was planned to randomise 853 individuals to detect an 18% relative reduction in ADRa in each two-group comparison, assuming a 10% drop-out rate.

Statistical methods

The primary analysis was performed on an intention-to-treat basis, without imputation of missing data. The primary end point was analysed 'at the margins', as there was no evidence of an interaction between EPA and aspirin. The log relative risk was estimated using a mixed-effects log-binomial regression model, with site included as a random effect. Both interventions were fitted simultaneously and the analysis was adjusted for repeat colorectal endoscopic procedure within 3 months. Other outcomes were analysed using appropriate regression models depending on outcome type.

Results

Recruitment

A total of 3911 'high-risk' individuals were screened for eligibility, of whom 709 (18%) were randomised. Of those individuals not randomised ($n = 3202$), 2179 (68%) met one or more exclusion criteria [regular aspirin/non-steroidal anti-inflammatory drug use, $n = 594$ (19%); need for more than one repeat endoscopy, $n = 328$ (10%); bleeding diathesis or anticoagulant/antiplatelet therapy, $n = 313$ (10%)]. The other 1023 individuals either did not wish to participate or were not randomised for unknown reasons.

Randomisation

A total of 177 participants were randomised to receive EPA + aspirin, 179 were randomised to receive EPA + placebo aspirin, 177 were randomised to receive placebo EPA + aspirin and 176 were randomised to receive placebo EPA + placebo aspirin. Two participants withdrew immediately after randomisation. A total of 422 (60%) participants were randomised to active or placebo EPA-FFA and 287 (40%) participants were randomised to active or placebo EPA-TG. Of those randomised, 641 (90%) participants underwent surveillance colonoscopy; endoscopic data were available for 640 of these participants.

Baseline characteristics

Baseline characteristics were well balanced across all four treatment groups with respect to demographic data, medical history, prevalent GI symptoms and total and oily fish intake, as well as baseline colorectal adenoma characteristics. The mean age was 65 years; the male-to-female ratio was 4 : 1. Thirty-eight per cent of participants were obese. Approximately half of the participants were on regularly prescribed drugs at trial entry, which was balanced (including metformin and statin use) between the treatment groups. Compliance with trial medication was uniformly excellent (> 95%). The median time between randomisation and the 12-month surveillance colonoscopy was between 344 and 348 days in the four treatment groups.

Red blood cell and rectal mucosal polyunsaturated fatty acid levels

Individuals in the active EPA groups had higher RBC EPA levels than placebo EPA users at both time points after the start of the intervention. RBC EPA levels were similar between participants who received either active EPA-FFA or EPA-TG at 6 and 12 months. The increase in RBC EPA level from baseline to the 6- and 12-month time points for all participants was similar across the two EPA formulations. Rectal mucosal EPA levels at the end of the intervention period were higher in those who received EPA-TG than in those who received EPA-FFA, but with substantial overlap between the two groups and no difference in the rectal mucosal EPA-to-AA ratio. As there was no clear difference in RBC or rectal mucosal EPA incorporation between those allocated EPA-FFA and those allocated EPA-TG, it was deemed appropriate to combine the primary and secondary outcome data from those who received either of the capsule investigational medicinal products.

Primary outcome (adenoma detection rate)

In the EPA + aspirin group, 98 out of 161 (61%) participants had at least one colorectal adenoma at surveillance colonoscopy; in the EPA + placebo aspirin group, 97 out of 153 (63%) had at least one colorectal adenoma at surveillance colonoscopy. The ADRa was 61% (100/163) in the placebo EPA + aspirin group and 61% (100/163) in the placebo EPA + placebo aspirin group. When summarised at factorial margins, the ADRa was similar across interventions, with an ADRa of 62% for those who received active EPA versus 61% for those who did not receive EPA, and an ADRa of 61% for aspirin users versus 62% for those who did not receive aspirin (62%). The risk difference for EPA versus no EPA was –0.9% [95% confidence interval (CI) –8.8% to 6.9%] and for aspirin versus no aspirin was –0.6% (95% CI –8.4% to 7.2%). There was no interaction between EPA and aspirin for the ADRa ($p = 0.85$). Sensitivity analyses were supportive of the primary analysis.

Secondary colorectal adenoma outcomes

Aspirin use was associated with a reduction in the total MAP [incidence rate ratio (IRR) 0.78, 95% CI 0.68 to 0.90], with preventative efficacy against conventional (IRR 0.82, 95% CI 0.71 to 0.94), serrated (IRR 0.46, 95% CI 0.25 to 0.87) and right-sided (IRR 0.73, 95% CI 0.61 to 0.88) lesions, but not left-sided (IRR 0.85, 95% CI 0.69 to 1.06) adenomas. There was evidence of chemopreventive efficacy of EPA on conventional (IRR 0.86, 95% CI 0.74 to 0.99) and left-sided (0.75, 95% CI 0.60 to 0.94) adenomas, but not on the total MAP (IRR 0.91, 95% CI 0.79 to 1.05) or on the total number of serrated (IRR 1.44, 95% CI 0.79 to 2.60) or right-sided (IRR 1.02, 95% CI 0.85 to 1.22]) adenomas. Overall, colorectal adenoma number was reduced in the EPA + aspirin group (166 adenomas) compared with the other groups (238 in the EPA + placebo group, 209 in the placebo + aspirin group and 231 in the placebo + placebo group), with 794 (94%) of the recurrent lesions being conventional colorectal adenomas.

Safety and tolerability of eicosapentaenoic acid and aspirin

Dietary fish intake did not change during the trial. There were no safety concerns about either EPA or aspirin. A similar proportion of participants reported at least one adverse event (AE) or adverse drug reaction in all treatment groups (45% in the EPA + aspirin group, 46% in the EPA + placebo group, 39% in the placebo + aspirin group and 44% in the placebo + placebo group). The most commonly reported AEs were GI symptoms, with an excess of mild to moderate GI AEs (i.e. diarrhoea, nausea, abdominal pain) in the EPA + placebo aspirin group. There was no difference in tolerability between EPA-FFA and EPA-TG users. Six significant GI bleeding events were distributed across the treatment groups. No CRCs were detected.

Conclusions

The Systematic Evaluation of Aspirin and Fish Oil (seAFOod) polyp-prevention trial has found no evidence of an effect of either EPA or aspirin on the primary end point of the proportion of individuals with one or more colorectal adenomas at the 12-month surveillance colonoscopy (the ADRa) in patients deemed 'high risk' in the English BCSP.

However, secondary analyses of the effects of EPA and aspirin on colorectal adenoma number provided evidence of chemopreventive activity of both agents. Aspirin was effective at reducing the total number of colorectal adenomas per participant, but the reduction in the total MAP associated with EPA treatment was not statistically significant. Other secondary analyses suggested that there are colorectal adenoma subtype- and site-selective effects of EPA and aspirin. Participants randomised to EPA had a reduced number (MAP) and ADRa of conventional dysplastic colorectal adenomas in the left colon and rectum compared with those randomised to placebo. Participants randomised to aspirin had a reduced number of adenomas in the right colon, particularly for serrated adenomas, and also reduced risk of conventional colorectal adenomas. Although multiple analyses were undertaken with potential for spuriously significant results, reduction in colorectal adenoma number by aspirin is consistent with published polyp-prevention trial data and the 'right sidedness' of the aspirin effect is in keeping with observational data on CRC risk and mortality. Moreover, the 'left sidedness' of EPA is consistent with efficacy in the familial adenomatous polyposis (FAP) trial of EPA-FFA against conventional rectal adenomas (West NJ, Clark SK, Phillips RK, Hutchinson JM, Leicester RJ, Belluzzi A, Hull MA. Eicosapentaenoic acid reduces rectal polyp number and size in familial adenomatous polyposis. *Gut* 2010;**59**:918–25).

Historically, the ADRa has been used as the primary end point in polyp-prevention trials. However, its use may be confounded by its widespread use as a quality assurance measure of colonoscopist performance. By contrast, colorectal adenoma number has always been used as an end point in Phase II FAP trials. Improved colonoscopy lesion reporting in routine practice now allows MAP to be considered as a more sensitive primary end point in 'sporadic' Phase III trials, with the clinical meaningfulness of an approximate 20% reduction in MAP being supported by the CRC risk reduction from aspirin demonstrated in long-term observational studies.

Safety and tolerability of both EPA and aspirin were excellent. Mild GI symptoms are recognised with ω-3 PUFA use. The excess of GI AEs in the EPA-alone group compared with combined treatment with aspirin should be investigated further. This is the first demonstration that two dose-equivalent formulations of EPA have similar bioavailability and tolerability during long-term (12-month) dosing.

The seAFOod trial should create a paradigm shift in CRC chemoprevention research, whereby:

- Colorectal adenoma number will be introduced and further validated as a primary end point in polyp-prevention trials.
- A stratified approach will be employed for use of the colorectal adenoma as an end point, based on histological type and location.

A key objective should be to identify a predictive biomarker(s) for the type and site of colorectal adenoma recurrence, allowing a precision-medicine approach to the provision of optimal chemoprevention at an individual level. The observation that combination EPA and aspirin treatment was associated with the largest reduction in colorectal adenoma number requires investigation in an appropriately powered study.

The trial biobank will be used to support mechanistic studies into the adenoma selectivity of EPA and aspirin, as well as to explore use of ω-3 PUFA levels as a predictor of conventional colorectal adenoma risk.

Trial registration

This trial is registered as ISRCTN05926847.

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