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HEALTH EFFECTS OF FISH

WITH SPECIAL ATTENTION ON OTHER THAN CARDIOVASCULAR HEALTH BENEFITS AMONG GENERAL POPULATION

For BENERIS

Benefit-risk assessment for food: an iterative value-of-information approach

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CONTENT

1 Introduction

Beneris (Benefit-risk assessment for food: an iterative value-of-information approach) - project aims to develop and test the functionality of the novel risk-benefit assessment model. Within Beneris-project this novel method is applied for the estimation of overall health effects and risks of fish consumption. For this purpose quantified data on the health benefits of fish is needed.

The cardiovascular health benefits, which are considered as the most important health benefits of fish have been reviewed in a previous Beneris deliverable 16. The present deliverable reviews other quantifiable health benefits of fish and its constituents for general population and within different age groups. It also points out non-quantified areas, which might be of interest for public health in the future. Finally it gives a short overview on potential therapeutic use of omega-3 fatty acids in certain autoimmune diseases.

The health effects of fish consumption have mainly been examined in large cohort studies among general population, whereas effects of omega-3 fatty acids have been studied in clinical trials among patients with various diseases. Moreover, in majority of large scale clinical trials cardiovascular disease outcomes have been of primary interest and other end-points like cancer have only been of secondary interest.

Several meta-analyses on the health benefits of fish, fish oils or omega-3 fatty acids have been published during the recent years. These meta-analyses have covered different areas of health including *total mortality*, *cancer*, *mental health, neurology, fetal development*, *maternal wellbeing, diabetes* and *various autoimmune diseases.*

2 Objective

The aim of the work presented here was to collect quantified data on other than cardiovascular health benefits of fish in a feasible form to be used in the Fish-case study of Beneris (Benefit-risk assessment for food: an iterative value-of-information approach) - project.

3 Methods

The health benefits of fish and omega-3 fatty acids were examined by reviewing the meta-analyses indexed in Medline and Cochrane Database of Systematic Reviews on fish, omega-3 fatty acids, EPA and DHA. Furthermore the search was extended to some systematic reviews to expand the view on topic of interest. In addition when reviewing the effects on cancer the search was extended on meta-analyses on selenium and vitamin D. The work was based on altogether 68 articles, of which 44 were meta-analyses or systematic reviews on fish or its nutrients. In addition 10 original studies were examined to verify the data and deepen the understanding on the applicability of the results of the meta-analyses for the European population.

4 Overview of results and discussion

4.1 Longevity (Reduced all-cause mortality)

Omega-3 fatty acids of fish are most strongly considered to affect cardiovascular deaths and are unlikely to affect appreciably other causes of mortality. Since cardiovascular diseases are leading causes of death worldwide, omega-3 intake and fish consumption may have a significant effect on longevity. Therefore, at population level, the effect of omega-3 intake on all-cause mortality is highly dependent on the proportion of death due to cardiovascular diseases (Mozaffarian and Rimm 2006).

Results of meta-analyses addressing total mortality and fish or omega-3 fatty acids have ranged from no effect (Hooper et al. 2004) to 16-17 % reduction in relative risk (Mozaffarian and Rimm 2006, Yzebe et al. 2004.) or risk ratio of 0.77 compared with control group (Studer et al. 2005). The conclusions of the various meta-analyses are summarised in table 1. Mozaffarian and Rimm (2006) calculated a 17 % reduction in relative risk of all-cause mortality with at least 1-2 servings of fish/ week. This calculation was considered as the most applicable to be used in Beneris-model as the other meta-analyses did not provide clear dose-response information.

The above presented calculation is applicable for adult population in European countries, but there is insufficient data to extend this information for children. Data on the effect of fish consumption in childhood on all-cause mortality later in life is very limited and no meta-analyses or reviews were found on the area. The only applicable cohort study (Ness et al. 2005), which assessed the effect of childhood diet on mortality later in life, did not find a relation between childhood fish consumption and adult all-cause mortality.

Modest consumption of fish (e.g., 1-2 servings/wk), reduces total mortality by 17% (95% confidence interval, 0%-32%; P = .046). (Mozaffarian and Rimm 2006)

4.2 Nutrition

Fish is a significant source of several macronutrients at population level in Europe. According to dietary studies conducted in United Kingdom (The National Diet Nutrition Survey 2003), Sweden (Kostvanor och näringsintag i Sverige 2002), Denmark (Andersen et al. 1996) and Finland (Männistö et al. 2003) fish and sea foods provide 2 - 3 % of total energy, 6-7 % of protein, 4 -8 % of polyunsaturated fatty acids (PUFA) and 14 -18 % of omega-3 fatty acids intake in the daily diet. Fish is naturally low in saturated fat, its protein is of high quality and it does not contain carbohydrates.

As to the micronutrients, 8-14 % of iodine and 15 -23 % of selenium intake is gained from sea foods. Furthermore fish is an important source of vitamin D (23 - 45 % of intake), vitamin E (5 - 8 % of intake), vitamin B_3 (6 - 9 % of intake) and vitamin B_{12} (18 - 23 % of intake).

Foods prepared of fish also contain some nutrients that are not considered as beneficial for health at the current levels of intake in Europe. Fish and other sea foods provide 8-9 % of daily cholesterol intake. With the currently used preparation methods fish and sea foods provide about 8-9 % of daily salt intake in the above mentioned European countries. It must be noted that the method of preparation has a significant effect on the amount of salt derived from sea foods.

The importance of fish for the optimal nutritional status of European population varies from country to other. In all European countries omitting fish and other sea foods from diet reduces the intake of long chain (more than 20 carbon atoms) omega-3 fatty acids to minimal level, as no other commonly used food products contain them at significant level.

In Northern European countries, especially if other stables are not fortified with vitamin D, fish is essential for maintaining the acceptable vitamin D intake levels (Burgaz et al. 2007, Sioen et al. 2007, Männistö et al. 2003). In Swedish study (Burgaz et al. 2007) fatty fish consumption had the most important effect on vitamin D status of elderly women; 2–3 weekly portions of fatty fish increased serum 25(OH)D concentrations by 45%. In countries like Spain (Campillo et al. 2002, Bonet-Manso et al. 2007) with suboptimal levels of iodine intake, avoidance of fish may lower the intake of iodine on very low level. Respectively, inadequate intake of selenium might be of concern if omitting fish from the diet of for example elderly population (Wolters et al. 2006, González et al. 2006). The intake of protein as well as vitamins E, B_3 and B_{12} can be maintained on safe level through eating other food products and therefore fish is not compulsory to maintain optimal nutritional level of these nutrients. Finally, since fish is relatively low in energy compared to various meat products, eating sea foods as main dish may help to establish a diet with optimal or even reduced calorie intake.

Altogether, fish can improve the overall nutritional quality of diet in several ways. However, there are no readily available methods to quantify the health effects of optimal nutritional status. Therefore, the nutritional importance of fish can not be included in the Beneris-model in form of figures.

At population level in Europe fish is an important source of good quality protein, omega-3 fatty acids, vitamin D, selenium and iodine and it also contains other important nutrients in a significant degree. The overall health effects of optimal nutritional status, which fish consumption may help to maintain, can not be quantified in a form that could be used in Beneris-model.

4.3 Maternal well-being

The developing fetus is entirely dependent on maternal essential fatty acid supply and omega-3 fatty acids are accrued from the mother even if maternal omega-3 concentrations are low (Uauy and Dangour 2006). Epidemiological studies suggest that marine diet could have a preventive effect on early delivery and hypertensive disorders of pregnancy (Olsen et al. 1986). Vilar et al. (2003) reviewed nutritional interventions that have been carried out for the prevention or treatment of maternal morbidity and preterm delivery. They found altogether nine randomized controlled clinical trials to examine the effects of fish oil on pre-eclampsia, pregnancy induced hypertension or pre-term delivery. According to Vilar et al. (2003) current evidence does not support the use of fish oils for the prevention of pre-eclampsia or pregnancy induced hypertension, whereas studies on prevention of pre-term delivery appear, although not conclusive, very promising.

More recent Cohrane-review by Makrides et al. (2006) came to same conclusions as Vilar with his co-workers. They found no effect on pre-eclampsia or pregnancy induced hypertension, but women allocated to marine oil did have a lower risk of giving birth before 34 completed weeks' gestation compared with placebo (RR 0.69, 95% CI 0.49 to 0.99; 2 trials including 860 women). Additionally, Makrides et al. (2006) discussed the typical doses of marine oils used in the trials which had ranged from 133 mg/day to 3 g/day, with most commonly used dose of 2.7 g of EPA and DHA per day. Such a dose would be difficult to achieve from food sources. Although the doses appear high compared with what may be achievable through the diet, the marine oil interventions appeared safe.

No harm has been demonstrated to be caused by fish oil supplementation of pregnant women during pregnancy. Studies on fish oil supplementation to prevent pre-term delivery appear, although not conclusive, very promising.

4.4 Development of fetus and infant

During the third trimester of pregnancy there is a progressive enrichment in the concentration of DHA in circulating lipids in the fetus and furthermore a significant increase in DHA content of the brain tissue (Uauy and Dangour 2006). After the delivery essential fatty acids and DHA are secreted to breast milk. Jensen et al. (2000) studied the effects of DHA supplementation (170-260 mg/d) of breast-feeding mothers on the DHA concentration of breast milk and showed that correlations between the DHA contents of maternal plasma and breast milk and of milk and infant plasma phospholipids were significant. The DHA supplementation was started 2 weeks after the delivery and the final measurements were taken 8 weeks postpartum. DHA in maternal plasma phospholipids and DHA contents of breast milk increased with supplementation, whereas they decreased in control group. Respectively DHA in infant plasma phospholipids increased with maternal supplementation by 11-42%, but only by 5% in control group.

According the meta-analysis of Cohen et al. 2005 increasing maternal docosahexaenoic acid (DHA) intake by 100 mg/day increases child IQ by 0.13 points. The calculation was based on results of eight randomized controlled trials comparing cognitive development (general intelligence, verbal ability and motor skills) in controls and in children who had received omega-3 fatty acid supplementation. Of the eight included studies seven examined the effects of infant formula supplementation and one study the effects of maternal dietary supplementation. The results of the studies were extrapolated to maternal intake capable to affect the DHA concentrations in child's plasma or red blood cells. The authors concluded that even though calculated differences in IQ are not clinically detectable, the results can have important impacts when aggregated over a population.

Moreover Simmer and co-workers (2008 a) have reviewed the clinical trials on the effects of long-chain PUFA supplementation on development of infants born at term and concluded that a beneficial effect on information processing is possible but larger studies over longer periods are still required. The review found no major evidence on the effect of long-chain PUFA supplementation on visual development. To support the relative safety of supplementation Simmer stated that long-chain PUFA supplementation has no impact on growth of the infants.

As to the studies reviewed by Simmer et al. (2008 b) on long-chain PUFA supplemented formulas among *preterm-infants* no positive long-term effects on visual or intellectual development have been demonstrated compared to the formulas supplemented with alpha linolenic acid and linoleic acid. Altogether, the methodology varied considerably between studies included to the review, which made it very difficult to summarize the current evidence. Simmer et al. suggested that the future studies should include more immature preterm infants who are more at risk of developmental delay, since the previous studies have included only relatively healthy preterm infants. Since there is no evidence of important clinical benefits at the moment, the rationale for adding long-chain PUFA to formula is based on the rational of mimicking the composition of human milk. Supplementation should be safe as no harm has been demonstrated on growth of preterm infants, when formula is supplemented with balanced amount of omega-3 and omega-6 long-chain fatty acids (Simmer et al. 2008 b).

Omega-3 fatty acids are essential for fetal and infant development in many ways. However IQ was the only variable with readily quantified data. It has been calculated that increasing maternal docosahexaenoic acid (DHA) intake by 100 mg/day increases child IQ by 0.13 points (Cohen et al. 2005).

4.5 Neurology

Accumulating evidence from observational and epidemiological studies suggest an inverse relationship between dietary intake of omega-3 fatty acids and risk of dementia (Lim et al. 2006). According to Lim and co-workers several mechanisms like reduced risk of cardiovascular disease, attenuation of pro-inflammatory components of dementia disease process and neuroprotective properties have been postulated as cause for the protective effect.

Issa et al. (2006) and MacLean et al. (2005) conducted a systematic review on the effects of omega–3 fatty acids on cognitive function in normal aging and dementia. Both found a single Dutch cohort study that assessed the effects of omega–3 fatty acids on cognitive function with normal aging, which found no association for fish or total omega–3 consumption. In four studies (three prospective cohort studies and one RCT) that assessed the effects of omega–3 fatty acids on incidence and treatment of dementia, a trend in favour of omega–3 fatty acids (fish and total omega–3 consumption) toward reducing risk of dementia and improving cognitive function was reported. Issa et al. 2006 concluded that limited evidence suggests a possible association between omega–3 fatty acids and reduced risk of dementia, but available data is insufficient to draw strong conclusions on the effect.

Recently Schaefer et al. 2006 published their observation on the association between fish consumption with the risk of developing dementia. Among the Framingham Heart Study cohort (n= 899 men and women, mean follow-up time 9.1 years) the adjusted RRs in subjects consuming fish more than twice a week compared with those consuming, at most, 2 servings of fish per week were 0.61 (95% CI, 0.28-1.33; *P*=.22) for all-cause dementia and 0.50 (95% CI, 0.20-1.27; *P*=.14) for Alzheimer disease. These results have not yet been included in any of the published meta-analyses or systematic reviews.

Moreover, Lim et al. (2006) intended to conduct a review on the effect of omega-3 fatty acids in the prevention of dementia. As they searched for RCT's they did not find a single study to answer their search question. However they identified two ongoing trials which are expected to provide additional data during year 2008.

Furthermore, MacLean et al. (2005) have reviewed studies on effect of omega-3 fatty acids in other neurological conditions. They found two studies, one cohort and one case-control assessing the effects of omega-3 fatty acids on incidence of multiple sclerosis with inconclusive results. As to the treatment of multiple sclerosis, they found one RCT in which omega-3 fatty acids (fish, ALA, EPA or DHA) had no effect on the progression of the disease, whereas two single-arm open-label trials showed improvement in disability with omega-3 supplementation. The effects of omega-3 fatty acids on incidence of Parkinson's disease were studied in a single cohort study, which found no significant association between dietary intake of omega-3 fatty acids (fish, ALA, EPA, or DHA) and Parkinson's disease. Altogether, studies on omega-3 fatty acids or fish consumption and any other neurological condition than dementia are very limited.

Visual function in elderly

Age-related losses in visual function are major health concerns in many industrialized countries, where age-related macular degeneration (AMD) is a leading cause of blindness. Epidemiologic studies examining the relation of DHA or fish intake with AMD suggest a trend toward a protective relation. Johnson and Schaefer (2006) identified at least two prospective cohorts and one case-control study that found a significantly reduced risk of AMD among subjects with highest omega-3 fatty acid or fish intake. However, no actual meta-analyses have been carried out on fish consumption and AMD. In lack of clinical trials the role of fish consumption and omega-3 fatty acid intake in AMD remains to be solved later.

Observational and epidemiological studies suggest an inverse relationship between dietary intake of omega-3 fatty acids or fish consumption and risk of dementia, but until now there are no clinical trials to confirm these observations.

4.6 Mental health

Omega-3 fatty acids are important structural components of neuronal cell membranes and therefore essential for neuronal function. The brain contains a high concentration of polyunsaturated fatty acids, especially docosahexaenoic acid and aracidonic acid. Omega-3 fatty acid levels tend to be reduced in mental illnesses, but nutritional studies have failed to find a dietary cause for the reduction. (Maidment 2000) During the recent years omega-3 fatty acids have been of great interest as a potential therapeutic agent for the treatment of depression, schizophrenia and Attention deficit/ Hyperactivity disorder (AD/HD).

Depression

Ecological and cross-sectional studies indicate an inverse correlation between high fish intake and prevalence of depression (Peet and Stokes 2005, Appleton et al 2006, Sontrop and Cambell 2006, Maidment 2000). Sontrop and Cambell (2006) reviewed seven double-blind randomised controlled trials assessing the effects of long-chain omega-3 fatty acids on depression and four of these studies found that depression was significantly improved upon treatment with at least 1 g/day of EPA. All of the four studies with positive effects assessed the effect of EPA as adjunctive treatment and therefore the reviewer concluded that it is unclear whether EPA supplementation is effective independently.

Furthermore, Appleton et al. (2006) identified altogether 12 clinical trials investigating the effects of omega-3 fatty acids on depressed mood for their meta-analysis. As part of the meta-analysis they conducted a meta-regression in trials involving populations with major depression and found a difference in the effect size estimates of 0.73 (95% CI: 0.05, 1.41; $P = 0.04$), but there was also considerable heterogeneity ($I^2 = 72\%$, $P < 0.001$) in these studies. Appleton and co-workers concluded that current evidence is difficult to summarise due to considerable heterogeneity and in the future larger trials with adequate power will be needed to detect clinically important benefits.

Respectively, Lin and Su (2007) pooled the results of 10 RCT's (N = 329) and found a significant antidepressant effect of omega-3 fatty acids (ES = 0.61, p = .003). Likewise, omega-3 fatty acids significantly improved depression in patients with clearly defined depression (ES = 0.69, p = .002) and with bipolar disorder (ES = 0.69, p = .0009). The dosage of eicosapentaenoic acid (EPA) did not change the antidepressant efficacy significantly. However, significant heterogeneity among these studies and publication bias were noted. Therefore also Lin and Su concluded that although meta-analysis showed significant antidepressant efficacy of omega-3 fatty acids, it is still premature to validate this finding.

Schizophrenia

Peet and Stokes (2005) reviewed the double-blind, placebo-controlled studies on omega-3 fatty acids in the treatment of schizophrenia. They found altogether six studies of which five examined the effects of EPA as adjunctive treatment and one as the only treatment of schizophrenia. The dosage in studies ranged 1-4 g of EPA /day and all but one study reported some benefit for schizophrenic symptoms. Interestingly, the single study using EPA as the only treatment reported a reduced need for initiation of antipsychotic medication among those that used EPA compared to subject using placebo.

Despite of the promising initial findings recent Cochrane review by Joy et al. (2006) on the effect of polyunsaturated fatty acid supplementation for schizophrenia still highlights the need for large scale long-term studies as current evidence is not conclusive. Therefore there is currently no reason for clinicians to either encourage of discourage the use of polyunsaturated fatty acid. Joy et al. (2007) stated that if schizophrenic persons self like to use PUFA supplements, perhaps omega-3 preparation should be the preferred option.

ADHD

There is only very limited evidence that supplementary fish oil or omega-3fatty acids are of benefit in attention deficit-hyperactivity disorder (ADHD). Peet and Stokes (2005) found two double-blind, placebo controlled studies on effect of DHA supplementation in ADHD and none of these studies found a significant difference between DHA and placebo. Conversely, they noted that when fish oil was used in combination with primrose oil a significant treatment effect was detected in two studies. Furthermore Schachter et al. (2005) reviewed literature on various mental health problems and found four studies on omega-3 fatty acids as primary treatment and three studies as adjunctive treatment of ADHD. According to Schachter et al. (2005) none of the studies on omega-3 as adjunctive treatment and only one of four studies as primary treatment reported better outcomes compared to placebo.

There is some, yet unquantifiable, evidence that the fish consumption may benefit mental health of general population. Fish oil supplementation in dosage above what is gained through typical fish consumption may be of benefit for those with mental health problems. However, more studies will still be needed before mental health effects of fish can be quantified.

4.7 Diabetes

Fish can be beneficial both in the prevention and treatment of diabetes. There is initial evidence that fish or fish oil consumption may reduce the risk of developing diabetes or conversion from insulin resistance to diabetes (Nettleton and Katz 2005). However this evidence is currently insufficient for building a dose-response model and further data is expected to be gained from currently on-going diabetes prevention studies (www.clinicaltrials.gov).

Omega-3 fatty acids of fish are most strongly considered to affect the cardiovascular health of diabetic subjects. At the moment there is insufficient evidence to conclude that fish consumption is of greater cardiovascular health benefit for diabetic than general population. However, due to higher cardiovascular mortality among diabetic subjects compared to general population it has been proposed that diabetic subjects are especially likely to benefit from regular consumption of fish. In lack of more applicable estimates for benefits of fish consumption in diabetes, the dose-response presented by Mozaffarian and Rimm (2006) for general population can be used also for diabetic subjects. Modest consumption of fish (e.g., 1-2 servings/wk), reduces coronary death by 36 % (95 % CI, 20 %-50 %; P<0.001) (Mozaffarian and Rimm 2006). Results from large-scale on-going trials are expected to give more accurate figures for the effect of fish consumption on prevention of cardiovascular events among diabetic subjects (www.clinicaltrials.gov).

Several trials have assessed the effects of fish oil consumption on risk markers of cardiovascular disease in diabetes. Farmer et al. (2007) conducted a meta-analysis of 18 trials including 823 participants followed for a mean of 12 weeks, in which doses of fish oil ranged from 3 to 18 g/day. They did not identify trials with vascular event or mortality endpoints and the main outcomes studied were glycemic control and lipid levels. Meta-analysis of pooled data demonstrated a statistically significant effect of fish oil in lowering triglycerides by 0.56 mmol/l (95% CI -0.71 to -0.40 mmol/l) and raising LDL cholesterol by 0.21 mmol/l (95% CI 0.02 to 0.41 mmol/l). No statistically significant effect was observed for fasting glucose, HbA1c, total or HDL cholesterol. The triglyceride lowering effect and the elevation in LDL cholesterol were most marked in those trials that recruited people with hypertriglyceridemia and used higher doses of fish oil. No other adverse effects of the intervention were reported.

Studies to treat diabetes associated hypertiglyceridemia have examined the effects of 1,8 g of EPA to 21 g of fish oil/ day. These earlier studies with relatively high intake of fish oil suggest that fasting blood glucose levels may increase with borderline significance in NIDDM subjects with fish oil supplementation (Friedberg et al. 1998). Little later also Montori et al. (2000) conducted a systematic review on the effect of fish oil supplementation in the treatment of diabetic patients and show a significant decrease in triglyceride levels but no adverse effect on HbA1c or fasting plasma glucose levels.

According to recent review (Nettleton and Katz 2005) at dosage of 1-2 g/day fish oils have no adverse effect on glucose control.

Modest consumption of fish (e.g., 1-2 servings/wk) may reduce coronary death by 36 % (95 % CI, 20 %-50 %; P<0.001) (Mozzaffarian and Rimm 2006) **among diabetic subjects.** In absence of more precise data for diabetic population the presented figure for general population can be applied as for diabetic population since the original data is obtain from studies that have also included diabetic subjects. **At dosage of 1-2 g/day fish oils have no adverse effect on glucose control** (Nettleton and Katz 2005).

4.8 Cancer

Epidemiology of cancer

Cancer, which a generic term for a group of more than 100 diseases, is a leading cause of death worldwide, causing about 13% of all deaths. The main types of cancer leading to overall cancer mortality are lung, stomach, liver, colon and breast cancers. As to the world wide incidence of cancer, the most frequent cancer types in descending order among men are lung, stomach, liver, colorectal, oesophagus and prostate cancers whereas among women they are breast, lung, stomach, colorectal and cervical cancers. (http://www.who.int/topics/cancer/en/)

Fish, its constituents and incidence of cancer

Fish contains several nutrients and other substances, which may affect the tumor incidence or behavior, cancer mortality and even well-being during cancer treatment. Some of these substances like dioxins and polychlorinated biphenyls (PCBs) are carcinogenic (Steenland et al. 2004). Furthermore, preservation (salt) or preparation (frying, grilling) methods of fish may play an important, exposing role in the etiology of cancer (Key et al. 2004, Steineck et al. 1993). As this review emphasis on the positive health effects of fish, these negative health effects for cancer are not quantified here. However, it should be noted that the effect of a nutrient exposure on cancer development could be totally different (benefit- adverse) depending on the etiological stage of cancer (initiation, promotion and progression).

No large-scale interventions with fish or fish oil on cancer as primary outcome have been conducted. However, some of the large-scale interventions on cardiovascular disease have reported the overall cancer incidence or mortality. Neither cohort studies nor clinical trials indicate that the consumption of omega-3 fatty acids has an effect on cancer incidence or death of cancer (Hooper et al. 2006, MacLean et al. 2006).

While synthesizing the current evidence on the effect of omega-3 fatty acids on cancer risk, McLean and co-workers (2006) also reviewed the evidence for association between fish consumption and the most common types of cancer. They found three studies assessing *lung cancer incidence* relative to fish consumption. In one study fish consumption was associated with a reduced risk of lung cancer, in another study it was associated with an increased risk and the third study found no significant association between fish intake and lung cancer incidence or death from lung cancer. Furthermore, McLean et al. (2006) identified one study that evaluated the effect of fish consumption on the incidence of *stomach cancer*. This single study found no association between fish consumption and stomach cancer. Respectively *breast cancer* incidence relative to fish consumption was reported in four studies, of which one demonstrated an increased risk, one reduced risk and two other found no association between fish consumption and the risk of breast cancer. Finally, *colorectal cancer* incidence relative to fish consumption was examined in five studies. Four of these found no association with fish consumption and the incidence of colorectal cancer, whereas one study demonstrated a reduced risk with highest fish intake. Altogether, according the review of McLean and co-workers (2006) current evidence is contradictory and there is insufficient data to conclude that fish consumption would have an effect on any of the most common types of cancer.

Moreover, a review of Terry et al. (2003) concentrated on the intakes of fish and marine fatty acids and the risks of cancer of the *breast and prostate and of other hormone-related cancers*. Although it has been proposed that marine fatty acids may lower the risk of cancer through sex hormone-mediated processes, Terry et al. (2003) concluded that most of the studies do not show an association between fish consumption or marine fatty acid intake and hormone related cancers.

Bosetti et al. (2001) pooled the results of 13 case-control studies to examine the effect of fish and shellfish consumption on *thyroid cancer*. As iodine excess alters thyroid gland function, it has been proposed that seafood may have an adverse effect on development of thyroid cancer. However, in pooled analysis no effect on thyroid cancer was found in all studies combined. In fact analysis suggested for protective effect (OR 0.65, 95% CI 0.48-0.88) in endemic goiter areas.

In addition to iodine, fish is a rich dietary source of vitamin D and selenium, which both have been of great interest for prevention of cancer. The meta-analysis of Zhuo et al. (2004) suggests that selenium may have some protective effect against lung cancer in populations where average selenium levels are low (summary RR 0.72, 95% CI 0.45–1.16). There is also evidence from case-control and cohort studies that selenium intake may prevent the risk of developing prostate cancer (Etminan et al. 2005). Furthermore, the meta-analysis of Jacobs et al. (2004) concluded that higher serum selenium was associated with reduced risk of colorectal adenoma recurrence (OR 0.66, 95% CI 0.50 - 0.87; P for trend 0.006). However, although promising, the evidence for all three previously mentioned types of cancer is far from conclusive enough for building dose-response relationships.

Recently, prevention of colorectal cancer has been calculated among the various health effects of vitamin D (Bischoff-Ferrari et al. 2006, Gorham et al. 2005). Individuals with 1000 IU/day or higher oral vitamin D ($p<0.0001$) or 33 ng/ml (82nmol/l) or higher serum 25-hydroxyvitamin D ($p<0.01$) had 50 % lower incidence of colorectal cancer compared to reference values (Gorham et al. 2005). However, it must be noted that intake levels of this high can not be established by dietary means only.

Treatment of cancer patients

The effects of eicosapentaenoic acid (EPA), an omega-3 fatty acid from fish oil, have been studied for the treatment of cancer cachexia (Dewey et al. 2007). Cancer cachexia is a weight loss syndrome characterised by disease-induces starvation and wasting. Cachectic patients have shorter survival time compared to other terminally ill patients and severe weight loss has also been associated with reduced quality of life. Recent Cohrane-review (Dewey et al. 2007) assessed the current evidence on the effects of oral fish oil supplementation in the treatment of cancer cachexia. The reviewers found five randomised controlled studies including altogether 587 patients, but there was lack of common endpoints in these various studies. The reviewers concluded that there were insufficient data to establish whether oral EPA was better than placebo. Comparisons of EPA combined with a protein energy supplementation versus a protein energy supplementation (without EPA) in the presence of an appetite stimulant (Megestrol Acetate) provided no evidence that EPA improves symptoms associated with the cachexia syndrome often seen in patients with advanced cancer.

There is insufficient data to conclude that fish consumption would have an effect on any of the most common types of cancer. There is accumulating evidence that omega-3 fatty acids do not have an effect on development of cancer. Fish contains vitamin D and selenium, which may protect from various types of cancer. Simultaneously, fish may contain substances like dioxins and PCB's which are carcinogenic. See figure 1 for references.

4.9 Autoimmune diseases

Animal experiments and clinical intervention studies indicate that omega-3 fatty acids have anti-inflammatory properties and, therefore, might be useful in the management of inflammatory and autoimmune diseases. Long chain omega-3 fatty acids have been shown to decrease the production of inflammatory cytokines and eicosanoids and they may even alter the expression of inflammatory genes. (Simopoulos 2002, Clader 2004).

Findings of several large studies among adults suggest that high fish intake has beneficial effects on lung function whereas the relationship between fish intake and respiratory symptoms or clinical disease is less evident (Smit et al. 1999). While several cross-sectional studies have reported beneficial associations between dietary fish intake, asthma, and atopic disease (Devereux and Seaton 2005), dietary supplementation trials with fish oil have failed to show clinically relevant effects on severity of atopic dermatitis (Van Gool et al. 2004) or improvement in asthma control (Thien et al. 2002).

The potential therapeutic value of fish oil in inflammatory bowel diseases have recently been evaluated in three Cochrane reviews (Turner et al 2007 a, b, De Ley et al. (2007). Turner et al. (2007 a) conducted a meta-analysis on fish oil for maintenance of remission in Crohn’s disease. As they included all four eligible studies, there was a non-statistically significant benefit of omega-3 therapy for maintaining remission. However, the when pooling all four studies they were both clinically and statistically heterogeneous. Pooling three studies which all used enteric coated capsules revealed a statistically significant benefit for maintenance of remission (RR 0.49; 95% CI 0.35 to 0.69) and number needed to treat to prevent relapse in 1 year was 3 (95% CI 2 to 5; I2 = 19%). However, the total number of patients enrolled in these studies was small (n = 166). No significant adverse events were recorded in any of the studies. The authors concluded that omega-3 fatty acids are safe and may be effective for maintenance of remission in CD when used in enteric coated capsules, but further larger RCTs are still warranted.

De Ley et al. (2007) reviewed the evidence on the use of fish oil for induction of remission in ulcerative colitis. They found six clinical trials, but could not pool the data for meta-analysis due to differences in outcomes and methodology among the studies. One small study showed a positive benefit for induction of remission (RR 19.00; 95%CI 1.27 to 284.24), whereas some of the other included studies show some positive benefits for secondary outcomes. As studies were small and of low quality De Ley et al. (2007) concluded that the current data does not allow for a definitive conclusion regarding the efficacy of fish oil. Respectively Turner et al. (2007 b) reviewed the evidence on omega-3 fatty acids (fish oil) for maintenance of remission in ulcerative colitis and found no evidence from the four applicable studies to supports the use of omega-3 fatty acids for maintenance of remission. The pooled analysis showed a similar relapse rate in the omega-3 treated patients and controls (RR 1.02; 95% CI 0.51 to 2.03; P = 0.96).

Population studies suggest that fish consumption may have a preventive effect for rheumatoid arthritis and clinical trials indicate that fish oils may be of therapeutic use among diseased subjects (Simopoulos 2002, Calder 2006). Goldberg and Katz (2007) conducted a meta-analysis of 17 randomized, controlled trials assessing the pain relieving effects of omega-3 fatty acids in patients with rheumatoid arthritis or joint pain secondary to inflammatory bowel disease and dysmenorrhea. Supplementation with omega-3 fatty acids for 3-4 months significantly reduced patient reported joint pain intensity, minutes of morning stiffness, number of painful and/or tender joints and NSAID consumption, whereas significant effects were not detected for physician assessed pain or Ritchie articular index at 3-4 months. The results suggest that omega-3 fatty acids may be useful as adjunctive treatment for joint pain associated with rheumatoid arthritis.

The potential benefits of fish oil or mega-3 fatty acids have also been studied among patients with kidney transplantation (Lim et al. 2007), Ig A nephropathy (Donadio and Grande 2004, Laville and Alamartine 2004), psoriasis (Simopoulos 2002) and cystic fibrosis (McKarney et al. 2007), but there is insufficient evidence to recommend routine use of fish oil supplements in these conditions. Furthermore, the effects of omega-3 fatty acids have been examined on systemic inflammatory response due to surgery, trauma or critical illness (Calder 2004). However there is only little data on hard endpoints like mortality or length of hospital stay. Most of the studies have concentrated on biomarkers of inflammation and it is a complicated task to quantify the clinical significance of the changes in these inflammatory markers. Therefore, the available studies are still of little clinical value and benefits are unquantifiable for the Beneris project.

Altogether, the therapeutic potency of fish oils has been of great interest in various trials. However, the aim of the present review was to collect readily quantified data on health benefits among general population. Therefore the studies among subjects with evident autoimmune disease were not examined very deeply.

The potential preventive effects of fish oil in autoimmune diseases have not been quantified. Future studies may confirm that fish oil supplementation is of therapeutic value in various autoimmune diseases.

5 Conclusion

Several health benefits have of fish consumption have been proposed for general population, but most of these benefits remain unquantifiable. A dose-response relationship can be presented for fish consumption and longevity. Furthermore dose-response has been calculated for maternal docosahexaenoic acid (DHA) intake and child IQ. For the other reviewed health effects for general population including prevention of cancer, diabetes, dementia, neurological disorders and various autoimmune diseases no quantified estimations for the benefit were found.

Table 1. Dose-responses between fish or its constituents and various **health end points** with the applicability of the available dose-response data in different population subgroups.

Reference	Children	Adults (general population)	Adults (secondary prevention of CVD)	Presented dose response
Total mortality and mortality to overall cardiovascular events				
Hooper et al. 2004	-	+	+	In pooled analysis of RCT's, no reduction in the risk of **total mortality** (relative risk 0.98, 95% CI; 0.70, 1.36) was found in those taking additional omega-3 fatty acids (studies with high risk of bias were excluded from the analysis). Respectively, in cohort studies relative risks were 0.65, 95% CI; 0.48, 0.88 for total mortality. It is of importance to notice, that the original data is from studies with omega 3 fatty acids from both vegetable and/ or marine origin. Furthermore studies for primary and secondary prevention were also analyzed together.
Studer et al. 2005	-	+	+	Compared with control groups risk ratios for **overall mortality** were 0.77 for n-3 fatty acids (95% CI, 0.63-0.94). Risk ratios for non-cardiovascular mortality indicated no association when compared with control groups.
Yzebe et al. 2004	-	-	+	Daily intake of omega-3 fatty acids for a mean duration of 37 months decreased **all causes of mortality** by 16% (relative risk 0.84, 95% CI; 0.76, 0.94).
Mozaffarian and Rimm 2006	-	+	+	Modest consumption of fish (eg, 1-2 servings/wk), reduces **total mortality** by 17% (95% confidence interval, 0%-32%; P = .046).
Wang et al. 2006	-	+	+	No dose –responses given but the reviewers concluded that increased consumption of n-3 FAs from fish or fish-oil supplements, but not of alpha-linolenic acid, reduces **all-cause mortality.**

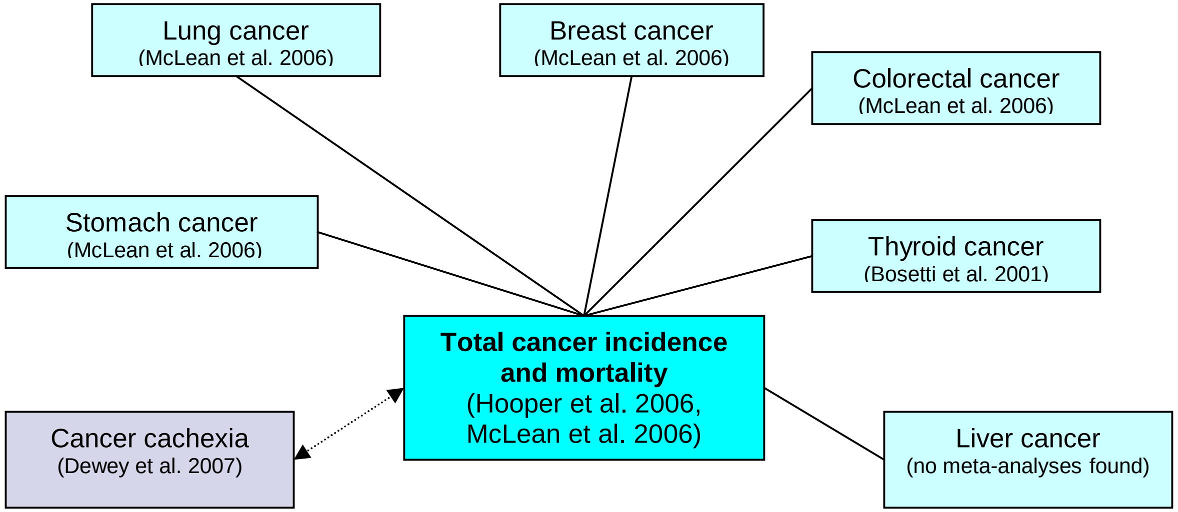

Figure 1. Illustration on the cancer disease outcomes (blue boxes) and potential consequences (violet box) of interest for effects of fish or its constituents. It must be noted that total cancer incidence refers to a group of more than 100 diseases. Dotted arrows represent causal relationships of increased risk. Key references are given in brackets. None of the references contain applicable dose-response data, which would indicate increased or decreased risk for cancer.

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