Role of omega-3 and vitamin b6 in cancer prevention

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Abstract:

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Cancer is a leading cause of death worldwide and according to the World Health Organization(WHO accounted for 8. 2 million deaths in 2012(1). The complex and dynamic nature of cancer is evident, however 30% of cancers could be prevented by modifying factors such as diet, not smoking, physical activity and moderate use of alcohol(2). Scientific evidence suggests that nutritional supplementation of some nutrients can affect the risk of different cancers. For the purposive of this essay I will perform a critical analysis of the role of omega-3 and vitamin B6 in cancer prevention by reviewing the current evidence, proposed mechanisms and investigating the future directions of omega-3 and vitamin B6 use in cancer prevention.

Omega-3(n-3) and omega-6(n-6) polyunsaturated fatty acids(PUFAs) are essential fatty acids that cannot be made by the human body and therefore must be obtained from the diet. The use of n-3 PUFAs in a number of chronic diseases such as coronary artery disease, psoriasis, irritable bowel syndrome and rheumatoid arteritis has been associated with health benefits. Increasing evidence from animal and in vitro studies indicate that n-3 PUFAs, especially eicosapentaenoic acid (EPA) and docosahexaenoic(DHA) acid play a role in inhibiting cancer progression(3). However epidemiological data on the

association between n-3 PUFA intake and cancer risk appears to be somewhat less consistent.

High fat intake, typically seen in western diets is associated with an increased risk for cancer development. N-3 PUFAs are an exception as studies have found that n-3 PUFAs have protective functions in prostate, pancreatic, breast and colon cancer. Western diets typically contain a high n-6 to n-3 ratio which has been found is positively associated with prostate cancer development. A study carried out in Jamaican men who had a high ratio of dietary n-6 to n-3 ratio, found that n-6 PUFAs was positively correlated with prostate carcinogenesis while n-3 PUFAs inhibited cancer growth(4). In agreement with this study a case control study of 79 prostate cancer cases and 187 controls, found a high ratio of n-6 to n-3 PUFAs increased the overall risk of prostate cancer in white men and possibly increase the risk of a high grade prostate cancer in all men(5).

Population based studies have found that the use of n-3 PUFAs are protective against cancer development. A population based prospective cohort study of 90, 296 subjects found that a diet rich in n-3 fish or n-3 PUFA appeared to protect against the development of hepatocellular carcinoma (6). In agreement with this study a population-based prospective study in Japan found an inverse relationship between n-3 PUFA intake and the risk of cancer in the proximal site of the large bowel(7). However not all studies have found beneficial effects of the use of n-3 PUFAs in cancer prevention. A French study comprising of over 56, 000 women, who were followed for eight years found no associated between n-3 PUFA and breast cancer risk(8).

Numerous mechanisms have been proposed for the beneficial effects of n-3 PUFAs in cancer prevention. PUFAs are capable of influencing the fatty acid composition of glycerophospholipids in cell membranes. N-3 PUFAs can replace n-6 PUFAs in glycerophospholipids(9) and a high n-3 to n-6 ratio has been found to affect cell membrane signalling. Lipid rafts are important signalling domains within the cell membrane which contain receptors such as epidermal growth factor receptor(10). As DHA has a poor affinity for cholesterol in lipid rafts it can supress raft associated signal transduction(10). This is important as in many cancers signalling pathways can be over activated. It has also been suggested that n-3 PUFAs may induce apoptosis and reduce proliferation in human cancer cells by decreasing signalling through AKT/NFkB and by modulating the PI3k/AKT/p38 MAPK pathway(11).

N-3 PUFAs are involved in the suppression of arachadonic acid (4n-6) derived eicosanoids, which are involved in cellular growth, cell differentiation and have proinflammatory effects (12). Arachadonic derived eicosanoids such as PGE2, have been positively linked to cancer (13), unlike EPA eicosanoids which have anticancer effects(14). As mentioned above incorporation of n-3 PUFAs into the phospholipid membrane replaces n-6 arachadonic acid precursors, decreasing arachadonic derived eicosanoids and increasing EPA eicosanoids. N-3 PUFAs have also been found to supress cyclooxygenase-2 (15), which has anti-tumour affects as COX-2 down regulates apoptotic pathways(16). This is in contrast to n-6 PUFAs which have been found to upregulate COX-2(17). It is also interesting to note that in breast, colon and prostate cancer COX-2 is overexpressed (18, 19). Taking this into account it

is likely that suppression of COX-2 by n-3 PUFAs may be a preventative measure in these cancers.

In conclusion there is evidence for the beneficial effects of n-3 PUFAs in cancer prevention, however due to inconsistencies in epidemiological data it is too early to recommend the use of n-3 PUFAs for cancer prevention. Possible explanations to explain these inconsistencies may be that population-based studies rely heavily on data from self-reported dietary PUFA intake. This form of data collection may poorly correlate with accurate PUFA intake. Another possible explanation is that the amount of n-3 PUFA administered in studies, may not be of a sufficient quantity to have a protective functions in cancer prevention. Further studies are needed to be carried out to account for the current variation in published studies before recommending n-3 PUFAs for cancer prevention.

According to the latest report from the National Cancer Registry: Colorectal cancer (CRC) is the second most common cancer in both men and women in Ireland (20). Environmental factors such as diet have been identified as playing a role in the risk of CRC development. Preventability estimates from the World Cancer Research Fund show that 47% of cases of CRC in the UK can be prevented by modifying factors such as eating and drinking healthily, being physically active and maintaining a healthy weight(21). According to the National Health and Nutrition Examination Survey 2003-2004 24% of people (who did not take supplements containing vitamin B6) have suboptimal active B6 plasma concentrations (<20nmol/L)(22).

Vitamin B6 is a water soluble vitamin, which in its active form: pyridoxal 5'-phostphate (PIP) is involved in more than 100 coenzyme reactions, including lipid, carbohydrate and protein metabolism(23). Vitamin B6 may play a role in CRC prevention through its role in one carbon related DNA synthesis and methylation(24). Vitamin B6 has also been shown to reduce the formation of nitric oxide(25), inhibit angiogenesis(26) and reduce oxidative stress(27), creating an unfavourable environment for tumour development.

Despite the mechanistic evidence supporting for the role of vitamin B6 in CRC cancer prevention, epidemiological evidence has been inconsistent. A meta-analysis of 9 studies carried out between 2002-2009 on Vitamin B6 intake in relation to CRC risk, found inconsistent results with both an inverse and positive association(28). The same meta-analysis included four nestled case-control studies investigating serum PLP on CRC risk. All four studies found an inverse relationship between PLP levels and CRC risk, with an overall reduced risk of CRC for every 100-pmol/mL increase in serum PLP(28). In the 9 studies of vitamin B6 intake and CRC risk it seems that highest vs lowest category of vitamin B6 intake was most important. When the study's results were pooled together, a 21% significant reduction in CRC risk was found when comparing high vs low vitamin B6 intake in studies with a wider range of exposure (> 1. 5-mg difference)(28).

A different study prospectively followed up 26, 440 women and 44, 410 men to assess whether a higher vitamin B6 intake in the remote past(12-16years prior to diagnosis) was more strongly associated with a lower risk of developing CRC than an intake in the recent past (4 years prior to diagnosis) (23). The results of this study did not support a strong role of vitamin B6

intake in preventing CRC development. However most of the participants were relatively well nourished, with only 5-10% of people having a vitamin B6 intake below the recommended daily allowance(23). This limited the study as it is not the most accurate measures of determining the potential effects on suboptimal vitamin B6 on CRC risk.

The Japan Public Health Centre-based Prospective study investigated the association of dietary folate, vitamin B6, vitamin B12 and methionine on CRC risk(29). The study included 81, 184 participants (38, 107 men and 43, 077 women) who were followed from 1995-98 to the end of 2002. A significantly inverse relationship between vitamin B6 intake and CRC was found in men. Men in the highest quartile of vitamin B6 intake had a 35% decreased risk of CRC compared with men in the lowest quartile. No association was found in vitamin B6 intake and CRC in women. Interestingly a higher intake of vitamin B6 appeared to be beneficial in men with higher alcohol intake. The study found that the risk of CRC associated with alcohol intake was significantly higher in those who had a low vitamin B6 intake, however this risk was found to decrease in those who had a higher vitamin B6 intake(29).

In conclusion there is evidence to suggest that vitamin B6 may play a role in CRC prevention, however it appears that plasma PLP appears to be more strongly linked to a reduced risk in CRC. Studies investigating the effect of vitamin B6 intake on CRC risk appear to be inconsistent. In contrast studies on PLP have found higher plasma PLP CRC risk by 30-50%(23). It is also important to note that studies have found that individuals with higher activity levels, higher dietary intakes of folate and calcium and individuals who do not smoke have higher vitamin B6 levels and a decreased risk of

CRC(23). In these individuals it is difficult to determine if it is these healthier behaviours or the increased B6 levels that decreases CRC risk. It is also difficult to assess the impact of dietary vitamin B6 on its own on CRC risk, as most foods containing vitamin B6 contain various other nutrients such as folate and vitamin D. Further studies are needed to be carried out to explain the current

inconsistencies in the use of vitamin B6 and CRC risk before vitamin B6 can be recommended as a preventive measure.

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