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The Sheila Bingham Memorial Lecture
Diet, insulin-like growth factor-1 and cancer risk

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Despite extensive research it has proved difficult to establish the role of diet in the aetiology of common types of cancer. Obesity and alcohol definitely increase the risk for several types of cancer, but the importance of particular foods and nutrients is not clear. Part of the difficulty is our poor understanding of the physiological changes that might mediate the effect of diet on cancer risk. Recent research in prospective studies with biobanks of stored blood samples has shown that the serum concentration of insulin-like growth factor-1 (IGF-1) is positively associated with the risk for both breast cancer in women and prostate cancer in men. It is also known that circulating IGF-1 concentrations can change in response to nutritional changes including energy and protein restriction, and some studies suggest that, even within well-nourished western populations, men and women with relatively high intakes of protein from dairy products have higher blood levels of IGF-1. These observations have led to the hypothesis that high intakes of protein from dairy products might increase the risk for some cancers by increasing the endogenous production of IGF-1. Further evaluation of this hypothesis requires clinical nutritional studies of the effects of diet on IGF-1 metabolism, and large epidemiological studies of cancer risk incorporating reliable measures of diet and serum IGF-1 concentrations.

Cancer: Diet: Insulin-like growth factor-1

Comparisons of cancer rates and dietary patterns in different countries in the 1970s suggested that dietary factors might be associated with the risk for several types of cancer[1], and in 1981 it was estimated that about 30% of cancer mortality in the USA might be attributable to dietary factors[2]. However, despite extensive research over the past thirty years, it has proved difficult to establish the role of diet in the aetiology of common types of cancer[3,4]. Obesity and alcohol definitely increase the risk for several types of cancer, but the importance of particular foods and nutrients is not clear[3]. In 2007, an expert report based on a systematic review of the worldwide data concluded that, apart from obesity and alcohol, the only dietary association for which the evidence was convincing is that red and processed meat are causally related to the development of colorectal cancer; none of the many other foods and nutrients examined in this report were judged to be convincingly associated with risk for any type of cancer[5].

Research in this area is challenging, partly because of the difficulty in measuring long-term diet accurately[6]. Another problem is that there are many hypotheses for foods, nutrients and non-nutrient food components increasing or decreasing the risk for various cancers; the large number of hypotheses is partly a consequence of our poor understanding of the physiological changes that might mediate the effect of diet on cancer risk, and makes it hard to focus nutritional measurements on the right factors.

Biomarkers can help us to understand the processes through which diet may influence the development of disease. For example, intermediate markers of disease, such as serum cholesterol and blood pressure in relation to

Abbreviations: IGF, insulin-like growth factor.

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CVD, make it easier to design studies to assess whether diet affects physiological characteristics that are likely in turn to affect disease risk. Few such intermediate markers have emerged in relation to diet and cancer, but one area of progress has been the relationship of hormones with cancer. For example, there is now substantial evidence that high blood levels of oestrogens increase the risk for breast cancer in postmenopausal women, and that this is the mechanism through which obesity increases risk[7].

In this overview, I discuss the role of the hormone insulin-like growth factor (IGF)-1 in relation to cancer risk, and consider whether IGF-1 might mediate some effects of diet on cancer risk. This is not a systematic review of the topic, but rather a presentation of the epidemiological aspects of this hypothesis in the light of recent results from large prospective studies and pooled analyses.

Insulin-like growth factor-1

IGF-1 is a peptide hormone that stimulates mitosis and inhibits apoptosis in most tissues in the body[8,9]. IGF-1 synthesis is stimulated by growth hormone, and IGF-1 plays a very important role during growth. IGF-1 is mainly produced by the liver, as well as locally in many tissues. IGF-1 circulates in the blood bound to IGF binding protein-3 (bound to IGF-1 in a ternary complex with the acid-labile subunit) and to five other binding proteins. The IGF binding proteins prolong the half-life of IGF-1 in the circulation, so that circulating IGF-1 acts as a reservoir. The binding proteins also modulate the activity of IGF-1 at receptors on the cell surface[8–10].

Insulin-like growth factor-1 and breast cancer risk

Interest in the role of IGF-1 in the development of breast cancer began in the 1980s[11,12]. An early case–control study reported higher plasma concentrations of IGF-1 in women with breast cancer than in controls[13], and in the first prospective study of breast cancer plasma concentrations of IGF-1 were positively associated with breast cancer risk for premenopausal women, but not for postmenopausal women[14]. In a recent collaborative re-analysis of individual participant data from seventeen prospective studies, the Endogenous Hormones and Breast Cancer Collaborative group showed a highly significant positive association between the circulating level of IGF-1 and breast cancer risk[15], with a 28% increase in risk for women with the highest levels of IGF-1 compared to those with the lowest. The association did not differ according to menopausal status and was not affected by further adjustment for IGF binding protein-3. However, the association was confined to oestrogen receptor positive breast cancer, with a 38% increase in risk in women with relatively high circulating levels of IGF-1[15].

Insulin-like growth factor-1 and prostate cancer risk

The first prospective study of circulating IGF-1 and prostate cancer was published in 1998, and showed a large increase in risk in men with high levels of IGF-1[16]. The results of subsequent studies broadly supported this association, and in a recent collaborative re-analysis of individual participant data from twelve prospective studies, the Endogenous Hormones and Prostate Cancer Collaborative group showed a highly significant positive association between the circulating level of IGF-1 and prostate cancer risk[17], with a 38% increase in risk for men with the highest levels of IGF-1 relative to those with the lowest. The association was not affected by further adjustment for IGF binding protein-3 and did not differ according to the stage of disease at diagnosis, but was stronger for low-grade than high-grade disease[17]. This association with IGF-1 is currently the only established hormonal risk factor for prostate cancer, since prospective studies of endogenous sex hormones have not shown any significant association with prostate cancer risk[18].

Insulin-like growth factor-1 and other cancers

There is less epidemiological information on the possible association of IGF-1 with the risks for cancers other than breast and prostate cancer. A meta-analysis of IGF-1 and lung cancer did not show an association[19], whereas a recent meta-analysis of ten prospective studies of IGF-1 and colorectal cancer showed a moderate, statistically significant positive association between circulating IGF-1 and risk for colorectal cancer (7% increase in risk for a one standard deviation increase in IGF-1[20]). More information is needed for other cancers.

Nutritional factors and insulin-like growth factor-1

An adequate supply of both energy and protein is essential for the maintenance of IGF-1 production[21]. In the liver, adequate amino acid availability to the hepatocytes is required for expression of the IGF-1 gene, resulting in synthesis of IGF-1. Protein-energy malnutrition causes a decrease in the synthesis and an increase in the clearance of IGF-1, leading to a decrease in circulating concentrations of IGF-1[21,22].

In addition to the well-established reductions in IGF-1 caused by protein-energy malnutrition, there is also evidence that diet may affect circulating IGF-1 in affluent western populations. Vegans living in the United Kingdom have been reported to have circulating IGF-1 levels about 10% lower than either vegetarians or meat-eaters[23,24], and several large cross-sectional studies in western populations have observed positive correlations between dietary intake of dairy products or dairy protein and circulating IGF-1[25,26]. Furthermore, a meta-analysis of randomised controlled trials showed that circulating IGF-1 was significantly higher in people receiving a short-term milk intervention than in controls[25]. As well as the evidence that circulating IGF-1 is increased by high intakes of dairy protein, other studies have suggested that other types of animal protein, and some minerals such as Zn and Ca, may also be positively associated with IGF-1 in generally well-nourished men[27,28].

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Dietary factors, insulin-like growth factor-1 and cancer risk

The evidence discussed above leads to the hypothesis that dietary factors which affect circulating IGF-1 might affect cancer risk[27–29]. Few studies have rigorously addressed this hypothesis; indeed, although there is evidence that dairy products and perhaps other animal proteins may be important determinants of IGF-1, our understanding of the impact of diet on IGF-1 in western populations is not good enough to be certain of which nutritional factors to focus on. For breast cancer, obesity (in postmenopausal women) and alcohol are well-established diet-related risk factors, but studies of other dietary factors, such as fat, have been inconclusive[30]; large prospective studies of overall consumption of dairy products have not shown positive associations[31,32], but relatively little attention has been given to protein intake. For prostate cancer, a number of observational studies have reported a positive association of dairy foods with risk[33], and one study that focused on protein from dairy products reported a significant positive association[34].

For colorectal cancer, the relationships of diet and IGF-1 with risk may be more complex. Most observational studies have shown that the intake of dairy products is moderately inversely associated with risk[35–37]; similar associations have been seen for Ca and it has been proposed that Ca could explain the reduction in risk associated with dairy products, although in the Women's Health Initiative randomised controlled trial Ca supplements did not reduce the incidence of colorectal cancer[38]. More research is needed on the role of Ca in the aetiology of colorectal cancer, but if it does have some protective effect then this would complicate analyses aiming to evaluate the possible importance of dairy protein and circulating IGF-1. For example, in the Physician's Health Study circulating IGF-1 (expressed as the molar ratio of IGF-1:IGF binding protein-3) was significantly positively associated with both the intake of low-fat milk and the risk of colorectal cancer, but the intake of low-fat milk itself was associated with a non-significant reduction in the risk of colorectal cancer[39]. It is possible that other components of milk could also have some protective effect for other cancers[5], further complicating the interpretation of observational studies.

The evidence currently available suggests that the 'diet, IGF-1, cancer' hypothesis is worth pursuing, but the evidence is not sufficient to conclude whether this pathway really is important. Future analyses should be based on knowledge of dietary determinants of IGF-1, such as the amount and source of protein, and should incorporate relevant dietary factors measured by the most accurate methods available[6], as well as measurements of circulating IGF-1.

The relative risks in association with high IGF-1 reported in observational studies are not large, but the true relative risks are likely to be larger because IGF-1 measured in a single blood sample per individual is subject to substantial random error, thus diluting the true association[40]. The effect of diet on IGF-1 also appears to be only of moderate magnitude, but may be of substantial importance if present over many years.

Conclusions

Observational epidemiological studies have shown that circulating IGF-1 is positively associated with the risk for breast cancer in women and with the risk for prostate cancer in men. Relatively few data are available for other cancers. Observational studies and clinical trials have shown that dietary factors can alter circulating concentrations of IGF-1, with substantial evidence that a high intake of dairy protein is associated with raised circulating IGF-1. Further research is needed to extend the evidence on IGF-1 and cancer risk, to better understand the effect of diet on IGF-1, and to examine whether the dietary factor(s) that affect IGF-1 have any important effect on cancer risk.

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