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INVITED COMMENTARY

Diet, obesity and cancer

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Abstract
Introduction and aims Obesity and the rising incidence of certain cancers are the manifest expressions of problems with diet and lifestyle. A number of complex and closely inter-related factors mediate the association between environment and cancer development. This review seeks to summarise the current evidence pertaining to dietary factors and cancer incidence and progression.
Methods Relevant literature was identified by search of the Pubmed database using the terms: diet, cancer, carcinogenesis, tumourigenesis. References from relevant articles were searched. Selection of articles was based on peer review, journal and relevance. Where possible, meta-analyses of randomised controlled trials (RCTs) or large RCTs were cited preferentially.
Results Variations in cancer trends between geographic regions and in migration studies point to the key role of environmental differences in cancer incidence. Mechanisms of tumorigenesis, including inflammation, angiogenesis, may be influenced by specific dietary constituents including glucosinolates, organosulphur compounds, genistein, curcumin, catechins, resveratrol and lycopene.
Conclusion Despite epidemiological evidence suggesting a link between dietary factors and cancer development, confounding factors such as obesity, physical activity and the sheer variety of bioactive compounds in a normal diet pose a great challenge to the study of mechanisms linking diet and cancer. A greater understanding of the interplay between dietary constituents and cancer development should un-cover new targets for the prevention and treatment of cancer.

Keywords Diet · Obesity · Cancer · Visceral adiposity · Curcumin · Angiogenesis · Inflammation · Phytochemicals · Catechins · Genistein · Lycopene

Introduction

Obesity is the visible expression in our society of a problem that has serious implications for public health. We are long aware of the link between obesity and type II diabetes mellitus and cardiovascular disease [1], but in the last decade the epidemiological evidence linking obesity, and by extension our diet and lifestyle, with the rising incidence and mortality of many cancers has become firmly established [2, 3]. At this time, approximately 60% of the Irish adult population are overweight or obese, with about 25% obese [4], and the dramatic rise in the incidence of obesity and diabetes in the paediatric and juvenile population in Ireland and its implications for cancer and other health risks is a cause for concern. There is a consensus among numerous international bodies, including the American Institute for Cancer Research (AICR), the World Cancer Research Fund (WCRF), the World Health Organisation (WHO), and the Centre for Disease Control (CDC) that diet and obesity account for approximately 30% of deaths from cancer in the developed world [5, 6]. The association is most significant for cancers that have increased incidence in the West in parallel with the increased prevalence of obesity over 25 years, and this includes adenocarcinoma of the oesophagus, uterine

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cancer, postmenopausal breast cancer, pancreatic and liver cancer, and renal cancer, with a positive but less marked association with some types of lung cancer, colon cancer, and prostate cancer. The AICR/WCRF estimate of cancer preventability through good food, nutrition, exercise and tackling obesity is that approximately one quarter of all cancers could be prevented through these approaches [5].

The obesity problem in the West first took shape in the United States in the decades following World War II. It is linked to industrialisation, urban drifts and sedentary work and lifestyle, protection of food reserves, food processing, and approaches to animal feeding and farming. In the US, vast maize reserves were protected as a priority by the Federal Government, and the health risks associated with the American diet were rarely questioned. This "obesogenic" environment, imported into Ireland over the last 10–15 years, includes an over-reliance on high energy, low nutrient food and drinks, excessive sugar, too much poor quality fats, in particular saturated and trans-fats, and an excess of animal proteins rather than plant foods, all aligned with insufficient exercise. With marketing forces backed by huge budgets pitted against a public receptive to tasty, quick fixes, and large portions, the outcome was inevitable; particularly, in societies where even the so-called well educated have no grounding in food and health through their educational system.

In addition to the need to tackle the problem of bad diet and obesity in our society, an intriguing dimension relates to exploring specific foods that may have health promoting and cancer preventing properties. The philosophy that many foods in nature, valued for health and medicinal purposes over thousands of years in Greek, Roman, Egyptian, Chinese and Indian civilisations, and the Ayurvedic tradition of plant medicine, may have survived for a reason, has intuitive appeal. Current epidemiological and scientific research is uncovering interesting properties of some traditional foods and drinks, and we can begin to consider "good" food in the context of real health benefits, particularly at a time when the consequences of "bad" food is so evident in our society. The greatest potential of research in this area is anticipated to be in cancer prevention rather than treatment, and the major scientific journal *Nature* recently editorialised that "chemoprevention by edible phytochemicals (i.e. plant-derived) is now considered to be an inexpensive, readily applicable, acceptable and accessible approach to cancer control and management" [7].

To understand the links between diet, obesity and cancer, and the promise of specific foods, the key constructs in cancer must be understood. In this review, these pathways will be discussed in brief, followed by a discussion on some specific foods, and emerging research in Ireland related to obesity and cancer.

Cancer constructs

For a tumour to become malignant, it must attract new blood vessels. This concept, called angiogenesis, was first described by a Harvard paediatric surgeon Folkman [8], and drugs that target the central switch of angiogenesis, vascular endothelial growth factor (VEGF), have been in clinical use in cancer over the last 5 years [9]. Autopsy studies on patients dying without cancer that was evident in life reveal that microscopic cancer is very common, perhaps a one-third of all 50-year-old women have breast cancer, and a one-third of all men have prostate cancer cells, and as many as four-fifths of adults have cancer cells in the thyroid gland [10]. Folkman expounded that the balance between pro- and anti-angiogenesis factors allowing neoangiogenesis to occur may be key regulatory factor [11]. If dietary constituents are able to interact with and down-regulate pro-angiogenic transcription factors they could influence the angiogenic switch at primary and metastatic sites, and have potential value in chemoprevention [12]. Some good scientific research has shown that green tea, curcumin and flavanoids, for example, can inhibit angiogenesis through action on VEGF, basic fibroblast growth factor (bFGF) and matrix metalloproteinases (MMPs) [13].

The second construct is the seed and soil hypothesis, with cancer cells the "seed" and the organ in which they develop providing the "soil" or stroma. The surgeon Stephen Paget mused on this topic over a hundred years in relation to why breast cancer may metastasise more commonly to bone than to other sites [14]. It is now understood that cancer cells and more commonly stromal cells may elaborate survival factors, including those that permit angiogenesis and resist programmed cell death (apoptosis). In this schema, certain foods and fat in tissues as a result of obesity can impact on the soil as much as the seed.

The third fundamental point is that inflammation may be directly associated with cancer in about 20% of cases, sometimes through infection (*Helicobacter*, Herpes, Hepatitis), or chemical (tobacco, acid reflux), or chronic inflammatory (ulcerative colitis) stimuli. Anti-inflammatory drugs such as aspirin have been shown to have some anti-cancer properties, and similarly there may be anti-inflammatory properties in some foods that may hold promise. Obesity is now understood to be a pro-inflammatory state in many, with raised levels of circulating inflammatory markers and widespread changes to protein transcription [15]. The clinical expression of obesity and inflammation may be the metabolic syndrome, which incorporates measurements of waist circumference, raised fasting glucose, low high-density lipoprotein, raised triglycerides and hypertension, to define those with clinical manifestations of obesity [16, 17]. At the molecular level,

NFκB is a key transcriptional factor in inflammation and tumour development, it is responsible for regulation of key genes involved in the development and progression of cancer cells including COX-2, cyclin D1, MYC, p53, p21, Bcl-XL, matrix metalloproteinases and VEGF [18]. It is of interest that some dietary foods, in particular curcumin, can have potent anti-inflammatory properties through targeting NFκB and related pathways such as COX2 [7].

Specific foods

It should be acknowledged that there are real difficulties in applying good dietary and nutrition research in humans. Most doctors are accustomed to having evidence-based recommendations established through randomised clinical trials, particularly for new drugs. However, there are a number of potential confounding variables in terms of physical activity, obesity status and dietary composition which make analysis of dietary interventions challenging. Research on diet and specific foods and cancer is acquired through largely laboratory-based experimental studies, as well as epidemiological study and some interventional trials. Much is learned about cellular mechanisms from in vitro studies, and from in vivo experimental tumour models, particularly in mice. In humans, population epidemiological correlation studies may tell us that we eat more fat in the West than East, and have more breast cancer, but there are so many other variables that the conclusion cannot simply be that fat causes cancer. Case–control studies compare groups who have developed cancer, and age and sex-matched non-cancer controls, and evaluate dietary patterns. Prospective observational cohort studies follow large populations for many years, with information on dietary patterns, and analyse differences between those that develop cancer with the remainder. Intervention studies assign experimental group to either major dietary changes such as less fat, or more fruit and vegetables, or a specific product, such as soya or green tea, and follow both cohorts long-term to look at cancer events. Finally, agencies such as the Cochrane Collaboration may perform a systematic review of available epidemiological studies, assessed for quality, and report their analysis of the available evidence.

There is a consistency in epidemiological studies that support the view that diets high in animal protein, and in fat, promote cancer risk, and that diets high in fruit and vegetables and plant foods reduce risk [5]. In animal models, it is well established that tumour take and growth is markedly influence by calorie and protein intake [19]. For a number of foods and drinks, there is less specific epidemiological data available, but some interesting science is as follows.

Curcumin

Turmeric, the brilliant yellow powder obtained by crushing the dried stalk of the *Curcuma longa* plant, had an honoured place in Ayurvedic Medicine which was central to Chinese, Tibetan and Islamic traditions, and persisted most widely to this day in India [20]. It had many uses, particularly for its perceived anti-inflammatory properties. The average intake of turmeric in India is about 2 g/day [21], and interestingly the incidence of Western cancers such as prostate, colon, breast and lung cancer in India is only 4–12% of the incidence seen in Ireland [22]. The active compound in turmeric is curcumin, a substance that has demonstrated chemopreventive properties in several different cancer types including breast, prostate, lung, oesophageal, colorectal and gastric cancers [23]. In vitro studies have demonstrated that curcumin can inhibit the activation of several transcription factors including nuclear factor-κB (NF-κB), COX-2, activated protein-1 (AP-1), signal transducer and activator of transcription (STAT) proteins, peroxisome proliferator-activated receptor-γ (PPAR-γ) and β-catenin. These transcription factors regulate the expression of genes that contribute to tumourigenesis, inflammation, cell survival, cell proliferation, invasion, and angiogenesis [24]. A recent study from the Cork Cancer Research Centre showed protective effects against oesophageal cancer cells in vitro. A detailed analysis of the anti-tumour effects of curcumin can be found in reviews by Goel et al. [25] and López-Lázaro [23].

Curcumin has been studied as a chemopreventive agent in phase 1 clinical trials in patients with premalignant lesions although the small numbers of patients studied that no firm conclusions can be drawn from these studies [26]. Other phase 1 clinical trials in colorectal cancer and pancreatic cancer patients have demonstrated that curcumin can reduce serum tumour markers, DNA damage and leads to stabilisation of disease [27].

Green tea

For the past 5,000 years tea has been made from young shoots of the *Camellia sinensis* bush [28]. Drinking tea was a noble pursuit in Chinese Dynasties and has been used in Chinese medicine for centuries [29]. Green tea contains high concentrations of catechins, whereas black tea, altered by oxidation, has a low catechin concentration [30]. Of the catechins, (−)-epigallocatechin-3-gallate (EGCG) is the most abundant, accounting for greater than 40% of the total polyphenolic mixture [31]. EGCG possesses promising anticancer potential and its anti-angiogenesis properties have been shown in experimental studies of neovascularisation. It also has antioxidant, antimutagenic and chemopreventive properties [30]. Research using experimental

animal models has supported the role of green tea in protection against various cancers including breast, colon, lung, oral, oesophageal, gastric and prostate cancer [5]. Some early interventional trials report promising initial results in chemoprevention [32–34] and population-based epidemiology reports green tea consumption to be inversely associated with risk of breast, ovarian and prostate cancer [5]. The Cochrane systematic review, however, recently reported, identified 51 studies, 47 Asian, and concluded that the clinical data are contradictory and inconclusive.

Cruciferous vegetables

Hippocrates (460–377 BC) described cabbage, the prototype cruciferous, as "the vegetable of a thousand virtues". Cruciferous vegetables include not only cabbage but also broccoli, turnip, cauliflower, radish, watercress, kale, kohlrabi, and Brussel sprouts. Mustard plant, watercress and radishes are also cruciferous. These vegetables are the main players in the benefits ascribed to high vegetable (and fruit) diets. They contain glucosinolates which release compounds known as isothiocyanates and indoles on digestion. The value is maximised if they are cooked as little as possible, in a minimum of liquid, and steaming and stir-frying may allow better preservation of key ingredients, and they should be chewed well.

This chemical has been shown to reduce breast cancer growth in experimental animals [35]. The only cohort study investigating cruciferous vegetable intake and upper aerodigestive cancers (mouth, pharynx or larynx) incidence report increased risk with high cauliflower intake and decreased risk with high cabbage intake [36]. Neither of the risk estimates was statistically significant. There is considerable variability in case–control studies addressing this issue in terms of design and outcome allowing no firm conclusions to be drawn [5]. Four case control studies reported statistically significant decreases in risk with increased intake [5].

Garlic and onions

Garlic in antiquity was considered as much a medicine as a food, particularly in Central Asia, the Middle East, Egypt and China. Garlic, as well as onion, leeks, shallots, and chives, are part of the Allium family of foods with a high content of sulphur-containing phytochemical compounds in the bulb [37]. In cancer prevention the most interesting properties may be prevention of stomach cancer, which is commonly associated with nitrosamines which result from the breakdown by stomach bacteria of nitrites common in food additives and preservatives. Organosulphur compounds in allium vegetables may inhibit the formation of nitrosamines and increase the activity of the detoxifying enzyme glutathione [38]. They may also possess antibiotic properties which reduce recolonisation of the stomach by the known carcinogen *Helicobacter pylori* [39]. Further evidence in support of the anti-cancer benefits of allium vegetables can be derived from population-based epidemiological studies. Two cohort studies and 20 of 27 case control studies found decreased gastric cancer incidence in those with high versus low intake [5]. The estimated risk reduction was 0.55 (95% confidence interval: 0.35–0.87) per 100 g/day. Both laboratory and population studies suggest some benefits in oesophageal [40], colorectal [41, 42] and prostate cancers [43].

Soy

Soya beans and related foods, once a sacred food in China, are now a staple particularly in Japan, China and Indonesia. Intake of soy products is estimated to be 30–35 versus 5–10 g/day in Western populations [5]. The chemical component are the isoflavones, of which genistein is the most interesting, and the content is most abundant in soya flour and dry roasted or boiled soya beans, and less so in miso and tofu, and with very small concentrations in soya sauce or oil.

Genistein is termed a phyto-oestrogen as it shares some structural homology with oestrogen and can thus act as a competitive antagonist at the oestrogen receptor. Genistein is an inhibitor of tyrosine kinase EGFR phosphorylation and can modulate gene expression of key inflammatory pathways: Akt, NFkB, MMPs and BAX/Bcl-2 signalling pathways [44]. In vitro it has been shown to influence cell growth [45, 46], cell cycle progression [47] and apoptosis [48] as well as angiogenesis [49, 50]. Isoflavones have been shown to prevent induction of gastric cancer in rats by increasing apoptosis, decreasing proliferation and angiogenesis [51].

There is a large amount of heterogeneity in epidemiological studies regarding cancer incidence and soy intake, which impedes the ability to analyse their results by meta-analysis. There is a small risk reduction observed in breast cancer and gastric cancer incidence between those with high and low soy intake; however, no studies have shown any difference in prostate cancer occurrence [5]. The National Cancer Institute in the United States is currently sponsoring a number of clinical trials to investigate the use of genistein as a chemoprevention and a therapeutic agent. A recent study soy food intake and breast cancer revealed that soy food protein significantly reduced mortality and recurrence of breast cancer independent of oestrogen receptor status and tamoxifen use.

Fruits

The phytochemicals in berries are the most interesting, in particular ellagic acid which is found principally in raspberries and strawberries [52]. Its anticancer properties have been demonstrated in vivo and in vitro and include enhancing defence against DNA damage, blocking angiogenesis through effects on VEGF and stimulation of apoptosis [53–56].

Citrus fruits, such as lemons, oranges, grapefruit, and mandarins, were cultivated over 3,000 years ago in Indian and China [57]. Everyone knows that they contain vitamin C, but they also contain compounds known as monoterpenes [58]. D-Limonene, the most abundant monoterpene and a major constituent of peel oil from citrus fruits, has demonstrated chemopreventive and chemotherapeutic properties against tumour cells [59, 60]. In rodent models, monoterpenes have been shown to prevent tumour initiation and progression of breast, skin, liver, lung and forestomach [61–63]. The effects appear to be direct on cancer cells, as well as aiding detoxification of carcinogenic substances [64].

Tomatoes

Tomatoes, a primary source of vitamins and minerals in the Western Diet, did not enter into common use until the mid-nineteenth century. Tomatoes are the main dietary source of lycopene, a member of the carotenoid family of natural pigments that contribute to the yellow, orange and red pigments in fruits and vegetables and which cannot be synthesised by the body [65]. It is an anti-oxidant which has been shown in in vitro and animal models to inhibit tumour proliferation, invasion and apoptosis in cancers of the prostate, liver, colon, bladder and breast. There are some supporting epidemiological studies in hormone-dependent cancers such as prostate and breast [66]. Lycopene supplementation reduces prostate-specific antigen levels and slows disease progression; however, there have not been any interventional studies examining its use as a chemopreventive agent [67, 68].

Red wine and grapes

Louis Pasteur considered wine to be "the healthiest and most hygienic beverage". In recent times, the lower rate of deaths from heart disease in the French compared with Americans focused some attention on the possible health benefits, and there is a general consensus now that red wine in moderation can have beneficial effects [69].

The polyphenol resveratrol is of greatest interest. It is synthesised in the skin of grapes, thus red wine, which retains grape skin during fermentation, represents a concentrated source of resveratrol [70]. It inhibits cell signalling events associated with tumour initiation, promotion, and progression, as well as anti-inflammatory COX inhibition and angiogenesis [71]. In laboratory conditions and in experimental animals it has shown properties against breast, prostate and oesophageal cancer [71]. Interventional trials are currently underway [71].

Perspective

The link between obesity and cancer is only recently realised. In contrast to the linear association between tobacco and lung cancer, the linkage with diet and obesity and cancer is still not completely understood, but probably relates in some way to the promotion of inflammation which underlies many problems, more common in the West, including diabetes, cardiovascular disease, neurodegenerative conditions, and autoimmune disease. For comparison, if the British Doctors Study of 1954 showed that 97% of all lung cancer relates to tobacco [72], the estimate of population attributable factors to diet and obesity for oesophageal adenocarcinoma, which tops the list of obesity-associated cancers, is 40% [2].

Obesity and the rising incidence of certain cancers are the manifest expressions of problems with diet and lifestyle. Obesity needs to be tackled in our society, the requirement for public health and hospital services has been well flagged. A parallel strategy to encouraging weight control and exercise is to support good food initiatives, it is probable but not proven that there are significant anti-cancer properties in food. This experiment has already taken place in nature, we should take an interest in what constitutes good food as it applies to health and disease. With increasing cancer, particularly in the West, with a parallel increase in obesity, the research community should begin to apply good science to the evaluation of foods and their ingredients as cancer preventive and treatment approaches.

In addition to food research, the exact mechanisms linking obesity to cancer need to be elucidated. It is probably through promoting inflammation, and researchers at Trinity College Dublin and University College Dublin have shown that central fat, particularly omental, is rich in activated immune cells, particularly macrophages and T cells, and these may drive inflammation and may theoretically promote tumour development [73, 74]. Obesity may also impact on growth factors, in particular insulin-like growth factor 1, and leptin, as well as the hormonal milieu, and these may also contribute to the association with certain cancers, in particular hormone-dependent tumours [75–78].

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