Overview of genes, diet and cancer

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Abstract Quantitative epidemiological analysis suggests that about one third of the variation in cancer risk can be attributed to variation in dietary exposure but it has proved difficult, using conventional epidemiological approaches, to identify which dietary components, in what amounts and over what time-scales are protective or potentially hazardous. Work in this area has been hampered by the lack of robust surrogate endpoints. However, the rapidly accumulating knowledge of the biological basis of cancer and the application of post-genomic technologies are helping the development of novel biomarkers of cancer risk. Genomic damage resulting in aberrant gene expression is the fundamental cause of all cancers. Such damage includes mutations, aberrant epigenetic marking, chromosomal damage and telomere shortening. Since both external agents and normal cell functions, such as mitosis, subject the genome to frequent and diverse insults, the human cell has evolved a battery of defence mechanisms which (a) attempt to minimize such damage (including inhibition of oxidative reactions by free radical scavenging and the detoxification of potential mutagens), (b) repair the damage or (c) remove severely damaged cells by shunting them into apoptosis. When such defences fail and a tumour becomes established, further genomic damage and further alterations in gene expression enable the tumour to grow, to cope with anoxia, to develop a novel blood supply (angiogenesis), to escape from the confines of its initiation

site and to establish colonies elsewhere in the body (metastasis). All of these processes are potentially modifiable by food components and by nutritional status. In addition, interactions between dietary (and other environmental and lifestyle) factors and genetic make-up [seen principally in the assembly of single nucleotide polymorphisms (SNPs) which is unique to each individual] contributes to interindividual differences in cancer risk.

Keywords Cancer · Gene expression · Diet · Biomarkers · Epigenetics

Diet and cancer epidemiology

Since the extensive quantitative analyses of Doll and Peto [1] more than two decades ago, it has been clear that dietary factors explain about one third of the variation in cancer risk with smoking being responsible for a further third. More recent comprehensive reviews of the evidence base undertaken by the American Institute of Cancer Research/World Cancer Research Fund [2] and by the Department of Health in the UK [3] confirm the importance of diet as a modifier of cancer risk. The revelation that lifestyle factors are major determinants of cancer risk forms the basis for the assertion that 75–80% of cancer cases under age 65 years are potentially preventable [1]. Some of the best evidence for relationships between dietary exposure and cancer risk comes from large prospective cohort studies. The European Prospective Investigation into Cancer and Nutrition (EPIC) which has recruited over half a million people in ten European countries to investigate the relationships between diet, metabolic and genetic factors, and cancer [4] demonstrates the benefits of scale, diversity in both dietary intake and disease experience and

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robustness of dietary assessment. For example, Norat et al. [5] showed that colorectal cancer risk was positively associated with intake of red and processed meat yet inversely associated with fish consumption. This analysis included adjustments for a range of potential confounding factors including work-related physical activity, anthropometric indices and intakes of dietary fibre and folate. The EPIC archive of more than nine million biological samples (primarily blood fractions) is a major strength which will facilitate analysis of interactions between diet (and other lifestyle factors) and genotype which are likely to be a core component of understanding of personalised disease risk.

Whilst observational studies such as those carried out by EPIC can provide strong evidence of associations, intervention studies are required to prove causality [6]. To date there have been rather few human nutritional intervention studies with cancer as the endpoint and the outcomes of these studies have not been encouraging [6]. Unlike the case for cardiovascular disease or diabetes where there are well-established intermediate endpoints e.g. abnormal blood lipids concentrations or impaired glucose tolerance respectively, there are few recognised surrogate markers for cancer studies. One of the most widely used is the colorectal adenomatous polyp which is believed to be on the pathway from normal mucosa, through aberrant crypt foci and, later, adenoma to carcinoma. A Randomised Controlled Trial has shown that supplements of 1.2 g Ca/day produced a significant ($P = 0.03$) but modest reduction in the risk of colo-rectal adenoma recurrence [7]. In contrast, there was no evidence that a high-fibre cereal supplement had any effect on adenoma recurrence [8]. This has led some to question the reliability of polyps as surrogate endpoints and has stimulated the search for more robust biomarkers which could be used in future intervention studies.

Although quantitative epidemiological analysis suggests that about one third of the variation in cancer risk can be attributed to variation in dietary exposure it has proved difficult, using conventional epidemiological approaches, to identify which dietary components, in what amounts and over what time-scales are protective or potentially hazardous. Work in this area has been hampered by the lack of robust surrogate endpoints (which have proved to be very valuable in other fields such as the prevention of cardiovascular disease). However, the rapidly accumulating knowledge of the biological basis of cancer and the application of post-genomic technologies are helping the development of novel biomarkers of cancer risk. Such biomarkers will need to be validated against a relevant disease endpoint as an essential prerequisite to attempts to demonstrate that that specific food components or dietary patterns modify these emerging biomarkers of risk.

Overview of cancer biology

Genomic damage resulting in aberrant gene expression is the fundamental cause of all cancers. Such damage includes mutations, aberrant epigenetic marking, chromosomal damage and telomere shortening [9]. During cancer development, a number of tumour suppressor genes are silenced (by both mutations and by epigenetic mechanisms) and oncogenes are inappropriately expressed. Whilst much of the research focus has been on damage to nuclear DNA, more recent evidence suggests that damage to the mitochondrial genome may also play a role in tumorigenesis [10]. For most cancers, time is among the strongest aetiological factors [11] an observation which provides support for the hypothesis that the accumulation of genomic damage is fundamental to carcinogenesis i.e. during ageing there is deterioration in genomic maintenance [12]. There is now also evidence of the accumulation of mitochondrial mutations with age even in apparently normal tissue [13]. Since loss of function of tumour suppressor genes and gain of function of oncogenes is fundamental to tumorigenesis, factors which alter the normal expression of such genes will play an aetiological role. In this context, understanding of the role of altered epigenetic marking of the genome in cancer biology is advancing rapidly [14, 15]. Unlike gene silencing by mutations, silencing as a consequence of promoter hypermethylation is potentially reversible by both drugs and dietary factors [16].

Since both external agents and normal cell functions, such as mitosis, subject the genome to frequent and diverse insults, the human cell has evolved a battery of defence mechanisms which (a) attempt to minimize such damage (including inhibition of oxidative reactions by free radical scavenging and the detoxification of potential mutagens), (b) repair the damage or (c) remove severely damaged cells by shunting them into apoptosis. When such defences fail and a tumour becomes established, further genomic damage and further alterations in gene expression enable the tumour to grow, to cope with anoxia, to develop a novel blood supply (angiogenesis), to escape from the confines of its initiation site and to establish colonies elsewhere in the body (metastasis). All of these processes are potentially modifiable by food components and by nutritional status.

Diets rich in plant foods, especially fruits and vegetables, are associated with reduced cancer risk and evidence is accumulating about the specific mechanisms responsible for the anti-neoplastic action of such phytochemicals [17]. Although it has been known for many years, that some nutrients and phytochemicals may reduce DNA damage by acting as anti-oxidants (at least in vitro) there is exciting new evidence that such compounds may also help reduce cancer risk by enhancing DNA repair [18]. As yet, there are

few reports of studies carried out in human volunteers but the intervention study by Collins and colleagues [19] indicated what might be possible. Healthy volunteers who consumed 1-fiwifruits/day, in addition to their usual diet, showed less evidence of oxidative damage to DNA in lymphocytes but also showed enhanced capacity for Base Excision Repair [19] one of the five mechanisms for sensing and repairing DNA damage in mammals [12].

Genotype–diet interactions

Inheritance of damaged copies of a small number of individual genes (germline mutations) is responsible for the inherited and familial cancer syndromes such as familial breast cancer (caused by mutations in *BRCA1* and *BRCA2*) and familial adenomatous polyposis (caused by mutations in the tumour suppressor gene *APC*) but these account for, at most, 10–12% of cancer cases [20]. For the large majority of cancers (so-called sporadic cases) there is little evidence that individual gene defects are responsible for disease initiation but it is probable that multiple genetic variants (low-penetrance polygenic variants) modify susceptibility [21]. These variants include single nucleotide polymorphisms (SNPs) which are found often in genes encoding metabolising enzymes [21]. However, after the initial excitement accompanying the discovery of such associations between genotype and cancer risk, it has become apparent that few associations are robust in the sense that they can be replicated in different studies. For example, a review of 50 studies which investigated relationships between common SNPs in 13 genes and risk of bowel cancer, significant associations were found in 16 studies but only 3 were reported in more than 1 study [22]. Part of this difficulty in replicating findings about the influence of SNPs on cancer risk may be due to environmental factors. Interactions between dietary (and other environmental and lifestyle) factors and genetic make-up (seen principally in the assembly of SNPs which is unique to each individual and which confer greater or less susceptibility) contributes to inter-individual differences in cancer risk. For example, the apparent protection against bowel cancer afforded by carriage of the TT version of the C677T polymorphism in the gene *MTHFR*, is evident only in those with low intakes of folate and who consume low (or no) alcohol (reviewed in [23]). Those who consumed higher amounts of well-cooked meats and who carried a particular version of a SNP in the gene encoding *N*-acetyltransferase (which conferred a faster acetylation phenotype) appeared to be at higher risk of large bowel neoplasia in some [24, 25], but not all, studies [26]. Whilst examples of genotype–diet interactions with implications for cancer development are accumulating, the large

majority arise from observational studies. Whilst well designed and conducted observational studies can provide strong evidence for associations, unequivocal evidence of causality requires intervention studies. Appropriate intervention studies should use prospective genotyping of volunteers. Whilst such studies are conceptually, and practically, relatively straight-forward when only a single gene is considered, it is probable that SNPs in several genes will influence responses to each dietary intervention. Designing and carrying out intervention studies which address potential interactions between dietary factors and SNPs in multiple genes provide much greater conceptual and practical challenges [27].

Implications for personalised nutrition

The recognition that an individual's genetic make-up interacts with environmental factors to determine cancer risk offers the potential for tailoring advice and provision of personalised services and products based on knowledge of individual genotype and appropriate lifestyle information designed to aid prevention. However, the evidence base for such genetically targeted advice and products is fragmentary. A much more robust body of evidence, including that from genetically targeted intervention studies, will be needed before we can justify application in public health [27].

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