Nutrigenetics and Prostate Cancer: 2011 and Beyond

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Abstract
Background/Aims: Prostate cancer runs in families and shows a clear dietary involvement. Until recently, the key risk gene(s) have proved elusive. We summarise current understandings of nutrient-gene interactions in prostate cancer risk and progression. Methods: A MEDLINE-based literature search was conducted. Results: Hypothesis-directed candidate gene approaches provide plausible, albeit statistically weak, nutrient-gene interactions. These are based on early understandings of factors likely to impact on carcinogenesis, including both nutrient and genetic effects on androgen biosynthesis and action, xenobiotic metabolism, DNA damage and DNA repair. Non-hypothesis-directed genome-wide association studies provide much stronger evidence for other genes, not hitherto suspected for involvement. Although only a few of these have been formally tested for dietary associations in well-designed epidemiologic studies, the nature of many of the genes suggests that their activity may be regulated by nutrients. These effects may not only be relevant to prostate cancer susceptibility, but also to disease progression. Conclusions: It will be important to move beyond studying single nucleotide polymorphisms, into more complex chromosomal rearrangements and to epigenetic changes. For future progress, large international cohorts will not only need to provide proof of individual nutrient-gene interactions, but also to relate these to more complex nutrient-gene-gene interactions, as parts of pathways. Bioinformatics and biostatistics will be increasingly important tools in nutrigenetic studies beyond 2011.

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Introduction

Prostate cancer has a worldwide incidence of 25.3 per 100,000 [1, 2] and is the second leading cause of death from cancer in males [3, 4]. The incidence of and survival from prostate cancer differs between countries, and among different ethnic groups within a country [5]. Diet and environment have long been recognised as important factors [6–12]. For example, studies on prostate cancer in New Zealand have implicated heterocyclic amines from well-cooked red meats as risk factors [13], and n–3 polyunsaturated fatty acids (PUFAs) and high dietary carotenoid intake, or Mediterranean diet pattern, as protective [14–16]. Other population studies have implicated high caloric or high saturated fat intake and low fibre as risk factors, whereas high intake of folate, cruciferous vegetables such as broccoli and fatty fish such as salmon act as protective factors and reduce the risk of prostate cancer [17, 18].

There have been a number of attempts to define a ‘familial prostate cancer gene’ or genes [19–22], comparable to the BRCA1/2 genes in breast cancer risk [23–25]. The gene which closest approaches the theoretical ‘hereditary prostate cancer’ (HPC1) gene is the ribonuclease L (2′,5′-oligo-isoadenylate synthetase dependent; RNASEL) [20, 26, 27]. While early studies considered candidate genes, by far the majority of recent advances have come from genome-wide association studies (GWAS) that have identified both single nucleotide polymorphisms (SNPs) and copy number variants associated with prostate cancer susceptibility [28, 29]. GWAS implicate a range of genes that had not been tested or even suspected in candidate gene studies, with varying degrees of penetrance [28, 30–40].

Candidate gene studies have also considered potential nutrigenetic approaches to prostate cancer [41–54]. For example, studies on colon cancer had shown interactive effects of well-cooked red meats and heterocyclic amines, and of N-acetyl transferase 2 (NAT2) enzymes which metabolise these. While neither the genetic variants nor the dietary exposure alone reached high statistical significance, carrying a variant in the NAT2 gene led to significantly increased risk in those who ate high amounts of well-cooked red meats [55–57]. Comparable studies in prostate cancer have given variable results [46, 58, 59].

This review will consider nutrigenetic approaches to prostate cancer, acknowledging the inherent challenges in this approach [60, 61]. The first section considers nutrient-gene interactions that were partly predictable from knowledge of how dietary risk factors act to cause cancer [62–64], and how variants in genes determining nutrient metabolism, inflammation, DNA repair or xenobiotic metabolism, for example, were likely to interact (candidate gene studies). The second section summarises possible nutrigenetic effects associated with genes more recently characterised through GWAS [65]. Although nutrient interactions have not been formally tested for most of these, their mechanism of action implies these to be plausible. Finally, we will speculate on where this field needs to move, if we are to put nutrigenetic approaches to prostate cancer into an appropriate perspective.

Hypothesis-Directed Nutrigenetics: Examples of Nutrient-Gene Interactions from Candidate Gene Studies

A range of examples of the genes interacting with diet from candidate gene studies are illustrated in table 1, and some specific examples are detailed below.

Genes Affecting Nutrient Metabolism: Methylenetetrahydrofolate Reductase (MTHFR)

Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme required for DNA synthesis that catalyses the irreversible transformation of 5,10-MTHF into 5-MTHF [66], the major circulatory form of folate. This donates a methyl group for the re-methylation of ho-
mocysteine to methionine [67], which is in turn metabolised to produce S-adenosylmethionine, the main methyl donor for methylation reactions [67]. More generally, folate in the form of 5,10-MTHF is the substrate for MTHFR reactions [68]. It promotes the synthesis of nucleosides and increases the ratio of deoxythymidylate monophosphate to deoxyuridylate monophosphate, thus preventing the mis-incorporation of uracil into DNA [68]. In contrast, folate deficiency leads to the accumulation of deoxyuridylate monophosphate, resulting in uridine mis-incorporation into DNA (as DNA polymerase cannot distinguish between 2'-deoxyuridine 5'-triphosphate and deoxythymidylate triphosphate) [68]. Uridine mis-incorporation may result in double-strand breaks, point mutations and/or chromosome breakage, thus enhancing the risk of carcinogenesis [62]. As a result, an adequate or high intake of folate maintains this nutrient in the form of 5,10-MTHF, which reduces the chance of uracil mis-incorporation and thereby reduces the risk of carcinogenesis [68].

Certain functional SNPs in the MTHFR gene (e.g. rs1801133, also known as C677T or rs1801131, and A1298C) are common in the human population, and substantially alter folate metabolism [69]. Homozygous individuals for the C677T SNP have around 30% of the expected MTHFR enzyme activity, while heterozygous individuals have round 65% activity [70]. The A1298C variant has also been associated with reduced enzyme activity, but to a lesser extent [71]. Both of these common MTHFR polymorphisms have been studied in association with prostate cancer risk. In a meta-analysis, Bai et al. [72] found that carrying the variant C677T allele significantly (p = 0.03) reduced the risk of prostate cancer, with an OR of 0.81 (95% CI 0.68–0.98) overall. A similar trend for this variant was also observed by Safarinejad et al. [67]. In contrast, neither Bai et al. [72] nor Safarinejad et al. [67] found an association between carrying the A1298C variant and prostate cancer risk. These authors suggested that the decreased enzyme activity associated with the 677TT polymorphism was actually beneficial in men who consume adequate amounts of folate. The decreased activity of MTHFR in turn will increase levels of 5,10-MTHF required for the production of thymidylate, which in turn reduces the chance of uracil mis-incorporation and DNA damage [73, 74].

**Table 1. Examples of nutrient-gene interactions from candidate gene studies of prostate cancer**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome region</th>
<th>Alleles</th>
<th>rs No.</th>
<th>Possible nutritional link</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>COX2</td>
<td>1q25.2–q25.3</td>
<td>A/G</td>
<td>5275</td>
<td>increased n–3 fatty acid intake</td>
<td>48, 50, 80, 81, 186</td>
</tr>
<tr>
<td>ERα</td>
<td>1q22–24</td>
<td>A/G</td>
<td>2228480</td>
<td>high phyto-oestrogen intake</td>
<td>11, 54, 84</td>
</tr>
<tr>
<td>ERα</td>
<td>1q22–24</td>
<td>C/G</td>
<td>746432</td>
<td>high phyto-oestrogen intake</td>
<td>11, 54, 84</td>
</tr>
<tr>
<td>ERβ</td>
<td>1q22–24</td>
<td>A/G</td>
<td>2987983</td>
<td>high phyto-oestrogen intake</td>
<td>11, 54, 84</td>
</tr>
<tr>
<td>GSTM1</td>
<td>1p13.3</td>
<td>deletion</td>
<td>N/A</td>
<td>folate</td>
<td>97</td>
</tr>
<tr>
<td>MTHFR</td>
<td>1p36.3</td>
<td>C/T</td>
<td>1801133</td>
<td>cruciferous vegetables intake</td>
<td>66, 68, 69, 72, 187</td>
</tr>
<tr>
<td>XRCC1</td>
<td>19q13.2</td>
<td></td>
<td>25487</td>
<td>lycopene, β-carotene, α-tocopherol</td>
<td>98, 100–102, 106</td>
</tr>
</tbody>
</table>

**Genes Affecting Inflammation: Cyclo-Oxygenase-2 (COX2)**

Inflammation is a risk factor for prostate cancer [75] that is known to be modulated by diet. ω–6 (n–6) PUFAs, such as arachidonic acid, are metabolised into pro-inflammatory eicosanoids [12], while ω–3 (n–3) PUFAs, including eicosapentaenoic acid and docosahexaenoic acid found in oily fish, have anti-inflammatory properties [76, 77]. n–3 PUFA reduce the production of pro-inflammatory prostaglandin derived from arachidonic acid through the cyclo-oxygenase (COX) pathway [78]. One of the key enzymes in this pathway, COX2, is overexpressed in malignant prostate cancer compared with benign prostate cancer in the
same patient [79], and SNPs in this gene have been associated with increased prostate cancer risk [80].

Hedelin et al. [81] considered the relationship between COX-2 variants, and the dietary intake of long-chain n–3 PUFA. Of 5 SNPs they considered, SNP rs5275 was significantly (p < 0.01) associated with reduced risk of prostate cancer in the men who consumed oily fish more than once a week when compared with men who never ate such fish [81]. Fradet et al. [50] found a strong inverse association (p < 0.0001) between increasing intake of n–3 PUFAs and the risk of aggressive prostate cancer. Furthermore, the effect of the variant COX-2 SNP, rs4648310, was greatly enhanced in men consuming low amounts of n–3 PUFA [50]. Reese et al. [48] reviewed the literature to conclude that there is good evidence to believe that oily fish, and particularly long-chain n–3 PUFAs, may have a more pronounced protective effect on biologically aggressive tumours or on their progression, and less on early steps of carcinogenesis.

**Oestrogen Receptor Genes: Oestrogen Receptor β (ERβ)**

Genetic variation in the ERα or ERβ gene may modulate prostate cancer risk. Thellenberg-Karlsson et al. [82] conducted a large population-based study, involving 1,415 prostate cancer patients and 801 controls, in which they found a statistically significant difference in allele frequency between cases and controls for SNP rs2987983 in ERβ [82]. The SNP is located upstream in the promoter region, suggesting an altered ERβ expression [83].

Phyto-oestrogens are plant compounds, found mainly in soya bean and soya products such as miso and tofu, and have structural similarities to mammalian oestrogens, enabling binding to ERβ [54, 84]. Increased phyto-oestrogen consumption, as in the Asian population, has been associated with a reduced risk of prostate cancer, possibly occurring through several different mechanisms [11, 54, 85–90]. Hedelin et al. [54] considered the possible synergistic effects of phyto-oestrogen intake and ERβ polymorphism on prostate cancer risk. They found that men in the highest quartile of phyto-oestrogen consumption had significantly reduced prostate cancer risk, and this was most apparent in men carrying the variant allele of the SNP rs2987983.

**Genes for Xenobiotic Metabolising Enzymes: Glutathione S-Transferase Mu 1 (GSTM1)**

GSTs are phase II detoxification enzymes, which detoxify potential carcinogens as well as reactive oxygen compounds, and are thus important for the protection of DNA from oxidative damage [91]. Gene deletions in GSTM1 result in a complete loss of GSTM1 enzyme activity, and such GSTM1-null genotypes occur at a frequency of somewhere between 40 and 60% in Caucasian populations [92]. Such individuals have been suggested to be at an increased risk of prostate cancer [93].

There is accumulating evidence that consumption of cruciferous vegetables, such as broccoli and cauliflower, may be associated with reduced risk of prostate cancer [9, 10, 94]. Such vegetables contain 4-methylsulphinylbutyl and 3-methylsulphinylpropyl, which are converted by thioglucosidases to sulphoraphane, which exhibits anticancer effects [95]. Once sulphoraphane is absorbed, it is conjugated with glutathione and metabolised via the mercapturic acid pathway and is excreted mainly as N-acetylcysteine conjugates [95, 96].

Gasper et al. [96] found that the GSTM1-null subjects have significantly higher sulphoraphane metabolite plasma concentration and a faster rate of sulphoraphane metabolite excretion during the first 6–24 h after consumption of broccoli compared with GSTM1-positve subjects (p < 0.001). Thus, higher levels of sulphoraphane are typically retained in the body in GSTM1-positive subjects. However, less sulphoraphane was excreted in GSTM1-null subjects following consumption of high-glucosinolate-containing super broccoli [96]. This finding suggests that GSTM-1-null persons may compensate for their loss of sulphoraphane
via excretion if they have a high intake of cruciferous vegetables (or high intake of the bioactive component). A protective effect of GSTM1 was also suggested by Agalliu et al. [93]: the risk of prostate cancer was increased by 54% among middle-aged Caucasian men with GSTM-1-null genotypes. Traka et al. [53] and Joseph et al. [97] also found evidence for potentially protective effects of this genotype, providing a certain level of cruciferous vegetable intake was achieved.

**DNA Repair Genes: X-Ray Repair Cross-Complementing Group 1 (XRCC1)**

DNA lesions induced by reactive oxygen species can be repaired by the base excision repair pathway. It is known that XRCC1 proteins form a complex with DNA polymerase-β, DNA ligase III and poly(ADP-ribose)polymerase that function in the repair of single-strand breaks [98]. The efficiency of repairing DNA may be impaired by genetic variation in one of the base excision repair pathway genes, XRCC1, on chromosome 19 [99, 100]. Functional variants in XRCC1 may lead to an increased risk of unrepaired oxidative DNA damage, and have been shown to have an increased risk of prostate cancer, especially in association with other variants in the APE1 or XPD genes [98, 101, 102].

Lycopene is a fat-soluble carotenoid found at high concentrations in tomatoes and tomato-based products, and appears to be an effective protective dietary factor for prostate cancer [103]. Lycopene acts as an anti-oxidant by scavenging reactive oxygen species to protect from DNA damage [104, 105]. Goodman et al. [106] considered interactions between XRCC1 polymorphisms, lycopene intake and prostate cancer. The study showed that subjects with a common variant (rs25487) showed a very significantly reduced risk of prostate cancer following high lycopene consumption compared to subjects with wild-type genotype [106]. This suggests that XRCC1-null subjects may compensate for the loss of base excision repair by consuming large quantities of lycopene-containing products, thereby reducing their risk of prostate cancer.

**Non-Hypothesis-Directed Nutrigenetics: Examples of Nutrient-Gene Interactions from Linkage Analysis and GWAS**

Some examples of genes associated with prostate cancer from GWAS approaches, and potential dietary interactions, are provided in table 2. A few of these are discussed below.
Ribonuclease L (2',5'-Oligo-Isoadenylate Synthetase Dependent; RNASEL)

Despite clear evidence that prostate cancer risk runs in families, identification of what was originally called the 'hereditary prostate cancer (HPC1)' gene proved much more difficult than in other examples, such as breast cancer [25, 107, 108]. However, in 1996, a genome-wide scan utilising 66 high-risk prostate cancer families provided evidence of linkage to the long arm of chromosome 1 (1q24–25). This work was subsequently confirmed by several other authors working with several different populations, and the relevant chromosomal location fine mapped to reveal that the causal gene was RNASEL, sometimes written as RNase L [109–113]. The gene encodes a ribonuclease that mediates the antiviral and apoptotic activities of interferons. Following activation, RNase L degrades cellular and viral RNA to halt viral replication. A range of different functional SNPs such as rs486907 have been shown to relate to prostate cancer susceptibility in various high-risk families [107, 110, 111, 113, 114].

The nature of the gene does not necessarily give clues to potential dietary actions, and it had not been anticipated that a very strong interaction with trans-FAs would be found. A review on the evidence for the link trans-FA intake and cancer concludes that the best evidence for their involvement in prostate cancer was a large (1,012 subjects) case-control study that showed a strong interaction between risk and trans-FA intake for the RNASEL rs486907 variant genotype (present in about 35% of the population), especially in Caucasian men [115, 116].

Hepatocyte Nuclear Factor 1β (HNF1β)

One of the unexpected associations for prostate cancer is a negative relationship with a high risk of type II diabetes mellitus [117–120], i.e. a high familial risk of one means a low familial risk of the other. While the two diseases have a number of genetic susceptibility genes in common, including obvious candidate genes such as insulin-like growth factor 1 (IGF-1) [121–124], a number of other, initially less predictable genes, have emerged as important.

HNF1β is a homeodomain-containing transcription factor known to regulate the development and function of the pancreas [125]. The HNF1β gene is expressed in pancreatic β cells, and is involved in the regulation of expression of insulin as well as other proteins involved in glucose metabolism [125]. A HNF1β variant is common in individuals with maturity onset diabetes of the young type 5 (MODY) [126]. Winckler et al. [127] showed the SNP rs757210 in the HNF1β gene and Gudmundsson et al. [126] another common variant (rs4430796) to be significantly associated with an increased risk of type II diabetes mellitus. Different SNPs in the same gene have been associated with risk of prostate cancer. Stevens et al. [128] reported that three HNF1β SNPs, rs11649743, rs4430796 and rs7501939, were significantly associated with a reduced risk of prostate cancer. Another GWAS showed a very strong association between variant alleles of rs4430796 and decreased risk of prostate cancer [129]. Similar associations are found in a recent collaborative analysis of data from 19 GWAS, which shows that rs4430796 and rs7501939 are significantly associated with a decreased risk of prostate cancer, but not with any of the other cancers examined.

These findings suggest that certain SNPs in HNF1β may exert a protective effect on the risk of prostate cancer. Although a precise mechanism by which diet interacts with these is not yet clear, a possible mechanism involving the dipeptidyl peptidase-4 (DPP4) gene has been suggested. It is known that HNF1β expression induces DPP4 mRNA [130]. DPP4 is a serine protease which has been implicated in the regulation of immune, inflammatory, nervous and endocrine functions [130], as well as the regulation of serum insulin levels [130]. DPP4-knockout mice had a significantly increased secretion of insulin and a reduction in plasma glucose levels [131]. Since increased insulin levels have been associated with an increased risk of prostate cancer, diabetic patients with HNF1β polymorphisms may have a reduced risk of prostate cancer through increased activity of HNF1β. This would interact
with their high plasma levels of glucose, leading to increased induction of DPP4 mRNA and ultimately inhibition of insulin secretion.

Perhaps more relevant to individuals who carry SNPs in HNF1β is that transcriptional regulation through this gene can affect the uptake and utilisation of certain micronutrients, including magnesium, and vitamins A and C. Polymorphisms in HNF1B have been associated with low serum magnesium levels and renal magnesium wasting. These authors used a luciferase reporter assay to show HNF1B-regulated transcription of FXYD2, which participates in the tubular handling of $\text{Mg}^{2+}$ [132]. Similarly, HNF1β is essential for the transcription of sodium-dependent vitamin C transporter protein 1, thus helping regulate cellular vitamin C levels [133]. Gene expression is also induced by excess exposure to retinoic acid (vitamin A) [134], as well as being regulated by sodium butyrate ([135].

**Juxtaposed with Another Zinc Finger Protein 1 (JAZF1)**

GWAS approaches have associated JAZF1 variants with reduced risk of prostate cancer as well as increased risk of type II diabetes mellitus [136]. In a meta-analysis of GWAS, Zeggini et al. [137] concluded that the rs10486567 variant SNP was associated with a lower risk of prostate cancer in diabetic men as compared to non-diabetic men, suggesting its potential protective effect on prostate cancer in diabetic patients. However, others have found variable results for this same SNP, with Thomas et al. [129] finding that men homozygous for risk allele G at SNP rs10486567 are associated with decreased risk of both nonaggressive and aggressive prostate cancer. In contrast, the meta-analysis by Prokunina-Olsson et al. [138] implied that the variant rs10486567 SNP was very significantly associated with an increased risk of prostate cancer.

Since it is by definition a zinc finger protein, it would be anticipated that the expression of the gene will be partly regulated by cellular levels of this mineral. However, other nutrient interactions occur. JAZF1 is a transcriptional repressor of testicular receptor (TR4), which regulates serum glucose and IGF-1 levels [139]. Phospho-enolpyruvate (PEPCK) is the key gene in gluconeogenesis, and its regulation is important for glucose homeostasis in response to nutritional depletion and/or hormonal alteration [140]. Through other genes in the pathway, the expression of JAZF1 should ultimately lead to decreased plasma glucose levels. The low plasma glucose levels will lead to lower insulin secretion as compared with high glucose levels, which may be protective to prostate cancer, as insulin per se is mitogenic and it has a growth-stimulatory effect on prostate cancer [141]. This hypothesis would be supported by other studies showing a positive association between high serum insulin levels and increased prostate cancer risk [141–143]. It does not, however, explain the fact that an increased risk of prostate cancer in JAZF1 variants has also been suggested [138]. We suggest that whether variants in this pathway increase or decrease risk will depend upon the exact functional alterations in gene activity, and may differ in different populations, depending upon diet and lifestyle factors.

**Homeobox Protein Nkx-3.1 (NKX3.1)**

NKX3.1 is a tumour suppressor gene, which is exclusively expressed in prostate tissue [31, 144]. The gene is haplo-insufficient, implying that a loss of a single allele results in a phenotype similar to homozygous deletion [145]. Thus, down-regulation of the NKX3.1 protein per se appears sufficient to predispose cells to malignancy. GWAS have shown a significantly positive association between NKX3.1 variants rs2928679 and rs1512268 and risk of prostate cancer [28, 33].

It has been shown that increased NKX3.1 expression in PC3 cells is associated with increased levels of IGFBP-3, a down-regulator of IGF-1, which has been implicated in prostate carcinogenesis [146]. A positive association between high levels of circulating IGF-1 and
prostate cancer has been demonstrated by a number of studies [122–124, 147–152]. Muhlbradt et al. [146] showed that IGFBP3 expression was about 10-fold higher in NNX3.1-transfected human prostatic cells as compared with control-transfected cells, and that IGF-1 signalling was diminished in cells expressing the gene [146]. These findings suggest that NNX3.1 mediates inhibition of IGF-1 signalling by increasing the expression of IGFBP-3, again implying that the gene product may interact with plasma glucose.

**Solute Carrier Family 22 Member 3 (SLC22A3)**

A meta-analysis of GWAS showed SLC22A3 rs9364554 to be significantly associated with an increased risk of prostate cancer [33]. The gene encodes for a transport protein, usually localised in the plasma membrane, and is responsible for the cellular uptake and elimination of various cationic substances, as well as for the removal of catecholamine and histamines [153]. Sakata et al. [154] demonstrated that histamine uptake was largely reduced by two other SNPs in the gene (rs8187717 and rs12212246) and moderately reduced for rs8187725 [154].

Histamine is an endogenous transmitter found in most tissues, especially in the granules of mast cells [155]. It acts by stimulating histamine receptors H1, H2 and H3 [156–158]. An experimental study showed that histamine increased intracellular free Ca\(^{2+}\) levels ([Ca\(^{2+}\)]\(_i\)) in PC3 prostate cancer cells [155]. The Ca\(^{2+}\) signal is also contributed by extracellular Ca\(^{2+}\) entry and intracellular Ca\(^{2+}\) release from the endoplasmic reticulum intracellular Ca\(^{2+}\) store [155]. If SLC22A5 variants decrease the activity of the transporter, histamine uptake will also be reduced, thus increasing the cytosolic histamine levels and increasing [Ca\(^{2+}\)]\(_i\) levels in prostate cancer cells. There would also be potential flow-on effects through Wnt/Ca\(^{2+}\) signalling [159–162]. It will be important, in future studies, to test for associations between SNPs in SLC22A5 and calcium intake for both prostate cancer risk and effects on prostate cancer progression.

**Nutrigenetics Beyond 2011: Complex Gene Rearrangements, Gene Pathways and Nutrient-Gene/Nutrient-Epigene Interactions**

Recurrent chromosome translocations are an important class of mutations in prostate cancer. Fusions between TMPRSS2, encoding the transmembrane serine protease isoform 2, and ERG, encoding the v-ets erythroblastosis virus E26 oncogene homolog, are commonly seen in human prostate cancer [163–168]. Such rearrangements associate with further genetic alterations as the cancer develops. Han et al. [169] suggested that PTEN deletion is a secondary event after ERG rearrangements, with the two events contributing to different stages in prostate cancer progression. Sircar et al. [170] also showed that the PTEN genomic deletion was associated with p-Akt and AR signalling in poorer outcome, hormone-refractory prostate cancer, and that the presence of both events may suggest a poor prognosis. Furthermore, King et al. [171] identified the translational start site of a common TMPRSS2-ERG fusion and showed that mice with this fusion gene product developed prostatic invasive neoplasia in the context of PI3-kinase pathway activation. To add to the complexity, Yu et al. [172] described an integrated network of androgen receptor, polycomb, and TMPRSS2-ERG gene fusions in prostate cancer progression. They found that ERG disrupts androgen receptor signalling by inhibiting gene expression and inducing repressive epigenetic programmes through direct activation of the H3K27 methyltransferase EZH2, a polycomb group protein. Rickman et al. [173] also revealed a novel mechanism for enhanced tumour cell aggressiveness resulting from ERG rearrangement in the castration-resistant setting through Trefoil factor 3 (TFF3) gene expression.
While ERG gene fusions are the most common, other events are being discovered with newer technologies. Pflueger et al. [174] used next-generation transcriptome sequencing (RNA-seq) to discover and characterise seven new cancer-specific gene fusions, two involving the ETS genes ETV1 and ERG and four involving non-ETS genes such as CDKN1A (p21), CD9 and IKKB (IKK-β). These genes are known to exhibit key biological roles in cellular homeostasis. More generally, Chinnaiyan and Palanisamy [175] described the range of currently available cytogenetic and non-cytogenetic methods for the characterisation of changes at DNA and RNA levels, and their current understanding of the molecular mechanisms involved in the formation of gene fusions in solid cancer.

The mechanism of these gene rearrangements suggests that diet will impact heavily on this step. Haffner et al. [165] showed that androgen signalling promotes co-recruitment of androgen receptor and topo-isomerase II (TOP2B) to sites of TMPRSS2-ERG genomic breakpoints, triggering recombinogenic TOP2B-mediated double-strand breaks. These events are likely to be modulated by dietary topo-isomerase II inhibitors [176], and dietary components that modulate inflammation [177] and oxidative stress [178–181]. More generally, Ferguson [62] recognised the influence of dietary contaminants such as aflatoxin B1 and benzo[a]pyrene, and pyrolysis products formed during the heating of proteinaceous materials (heterocyclic amines) on cancers, including prostate cancer. Dietary deficiencies and nutrient imbalances may be strong sources of genomic instability and mutagenesis [182, 183]. Recognition of the roles of nutrients in cell signalling processes and control of micro-RNAs suggests major influences on gene expression, in the absence of permanent DNA changes.

In the NuGO nutrigenomics network, van Ommen et al. [184, 185] have recognised that nutrition research involves a wide range of bioactive compounds acting on an extensive network of interacting processes and can profit from the revolution in ‘omic’ technologies. These authors propose the ‘nutritional phenotype database’ (dbNP) as a repository of publicly available data and knowledge to facilitate storage of biologically relevant, pre-processed-omic data, as well as study-descriptive and study participant phenotype data. They also suggest that work on the interactive pathways and multiple interacting factors in micronutrient genomics be stored in a centralised database and would benefit from international collaborative studies [185]. Such initiatives require enormous resources in terms of bioinformatics and biostatistics. These will become increasingly important as research on nutrient-gene and nutrient-gene-gene interactions on prostate cancer move to recognise the new understanding of and technologies for studying prostate cancer.

**Conclusions**

Early studies on nutrient-gene interactions on prostate cancer looked at nutrients and SNPs one at a time. In consequence, data were often far from compelling, and p values of most studies not greatly above significance. GWAS approaches have used hundreds of thousands of SNPs, and have the potential to identify a large number of potentially valid genetic associations with prostate cancer. However, these approaches do not generally integrate environmental factors such as diet. A number of well-powered validation studies will be necessary to elucidate clear mechanisms of how genetic polymorphisms influence the individual’s response to dietary factors in prostate cancer in terms of absorption and metabolism. Current commonly used approaches do not provide information on genomic rearrangements or on epigenetic events, and alternative technologies will be essential to integrate these into the evolving picture. Bioinformatics and biostatistics will also become increasingly important in designing future nutrigenetic studies on prostate cancer.
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References


177 Ferguson LR: Chronic inflammation and mutagenesis. Mutat Res 2010;690:3–11.


