Review

Nutrigenetics and Prostate Cancer: 2011 and Beyond

Yinan Yuan^a Lynnette R. Ferguson^{a, b}

^aDiscipline of Nutrition and ^bAuckland Cancer Society Research Centre, Faculty of Medicine and Health Sciences, University of Auckland, Auckland, New Zealand

Key Words

Cancer progression • Cancer risk • Complex chromosome rearrangements • Nutrients • Nutrigenetics • Prostate cancer • Single nucleotide polymorphisms

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.

Copyright © 2011 S. Karger AG, Basel

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-

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

Gene	Chromosome region	Alleles	rs No.	Possible nutritional link	References
<i>COX2</i>	1q25.2–q25.3	A/G	5275	increased n–3 fatty acid intake	48, 50, 80, 81, 186
<i>ERα</i>	14q22–24	A/G	2228480	high phyto-oestrogen intake	11, 54, 84
<i>ERα</i>	14q22–24	C/G	746432	high phyto-oestrogen intake	11, 54, 84
<i>ERβ</i>	14q22–24	A/G	2987983	high phyto-oestrogen intake	11, 54, 84
<i>GSTM1</i>	1p13.3	deletion	N/A	cruciferous vegetables intake	97
<i>MTHFR</i>	1p36.3	C/T	1801133	folate	66, 68, 69, 72, 187
<i>XRCC1</i>	19q13.2	C/T	25487	lycopene, β-carotene, α-tocopherol	98, 100–102, 106

homocysteine 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].

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 ($ER\beta$)

Genetic variation in the $ER\alpha$ or $ER\beta$ gene may modulate prostate cancer risk. Thellénberg-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 $ER\beta$ [82]. The SNP is located upstream in the promoter region, suggesting an altered $ER\beta$ 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 $ER\beta$ [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 $ER\beta$ 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-methylsulphanylbutyl and 3-methylsulphanylpropyl, 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].

Gaspar 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 $GSTM1$ -positive 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 $GSTM1$ -null persons may compensate for their loss of sulphoraphane

Table 2. Examples of potential nutrient-gene interactions from GWAS studies of prostate cancer

Gene	Chromosome region	Alleles	rs No.	Possible nutritional link	References
<i>CTBP2</i>	10q26	T/C	4962416	zinc	40, 188
<i>HNF1β</i>	17q12	C/T	7501939	glucose, magnesium, vitamin A, vitamin C, sodium butyrate	32, 34, 117, 132, 134
<i>HNF1β</i>	17q12	A/G	4430796	glucose, magnesium, vitamin A, vitamin C, sodium butyrate	32, 34, 132, 134, 117
<i>JAZF1</i>	7p15.2–p15.1	A/G	10486567	glucose, zinc	28, 128, 138, 189
<i>MSMB</i>	10q11.2	C/T	10993994	proteins, tannins	35, 37, 190–193
<i>MSMB</i>	10q11.2	A/G	7920517	proteins, tannins	35, 166–169
<i>NKX3.1</i>	8q21	A/G	2928679	glucose	147, 193
<i>NKX3.1</i>	8q21	C/T	1512268	glucose	147, 193
<i>NUDT10/11</i>	Xp11.23	G/A	5945572	magnesium	28, 45, 194
<i>SLC22A3</i>	6q25.3	C/T	9364554	calcium	28, 154, 195

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 *XPB* 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 1 β (HNF1 β)

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.

HNF1 β is a homeodomain-containing transcription factor known to regulate the development and function of the pancreas [125]. The *HNF1 β* 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 *HNF1 β* 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 *HNF1 β* 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 *HNF1 β* 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 *HNF1 β* 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 *HNF1 β* 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 *HNF1 β* polymorphisms may have a reduced risk of prostate cancer through increased activity of *HNF1 β* . 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 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 *NKX3.1*-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 *NKX3.1* 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 ($[\text{Ca}^{2+}]_i$) 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 reticular 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 $[\text{Ca}^{2+}]_i$ 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-Epigenetic 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 IKBKB (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 β (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.

Acknowledgements

Nutrigenomics New Zealand is a collaboration between AgResearch Ltd., Plant and Food Research and the University of Auckland, with funding through the Foundation for Research Science and Technology. L.R.F. also acknowledges funding support from the Auckland Cancer Society and the Cancer Society of New Zealand.

References

- Griffiths K, Prezioso D, Turkes A, Denis LJ: The prevention of prostate cancer. *Recent Results Cancer Res* 2007;175:33–63.
- Nelen V: Epidemiology of prostate cancer. *Recent Results Cancer Res* 2007;175:1–8.
- Penney KL, Pyne S, Schumacher FR, Sinnott JA, Mucci LA, Kraft PL, et al: Genome-wide association study of prostate cancer mortality. *Cancer Epidemiol Biomarkers Prev* 2010;19:2869–2876.
- Hussain S, Gunnell D, Donovan J, McPhail S, Hamdy F, Neal D, et al: Secular trends in prostate cancer mortality, incidence and treatment: England and Wales, 1975–2004. *BJU Int* 2008;101:547–555.
- Sneyd MJ: Ethnic differences in prostate cancer survival in New Zealand: a national study. *Cancer Causes Control* 2008;19:993–999.
- Lophatananon A, Archer J, Easton D, Pocock R, Dearnaley D, Guy M, et al: Dietary fat and early-onset prostate cancer risk. *Br J Nutr* 2010;103:1375–1380.
- Hu J, La Vecchia C, Gibbons L, Negri E, Mery L: Nutrients and risk of prostate cancer. *Nutr Cancer* 2010;62:710–718.
- Szymanski KM, Wheeler DC, Mucci LA: Fish consumption and prostate cancer risk: a review and meta-analysis. *Am J Clin Nutr* 2010;92:1223–1233.
- Kolonel LN, Hankin JH, Whittemore AS, Wu AH, Gallagher RP, Wilkens LR, et al: Vegetables, fruits, legumes and prostate cancer: a multiethnic case-control study. *Cancer Epidemiol Biomarkers Prev* 2000;9:795–804.
- Jain MG, Hislop GT, Howe GR, Ghadirian P: Plant foods, antioxidants, and prostate cancer risk: findings from case-control studies in Canada. *Nutr Cancer* 1999;34:173–184.
- Adlercreutz H: Epidemiology of phytoestrogens. *Baillieres Clin Endocrinol Metab* 1998;12:605–623.
- Rose DP: Dietary fatty acids and prevention of hormone-responsive cancer. *Proc Soc Exp Biol Med* 1997;216:224–233.
- Norrish AE, Ferguson LR, Knize MG, Felton JS, Sharpe SJ, Jackson RT: Heterocyclic amine content of cooked meat and risk of prostate cancer. *J Natl Cancer Inst* 1999;91:2038–2044.
- Norrish AE, Jackson RT, Sharpe SJ, Skeaff CM: Men who consume vegetable oils rich in monounsaturated fat: their dietary patterns and risk of prostate cancer (New Zealand). *Cancer Causes Control* 2000;11:609–615.
- Norrish AE, Jackson RT, Sharpe SJ, Skeaff CM: Prostate cancer and dietary carotenoids. *Am J Epidemiol* 2000;151:119–123.
- Norrish AE, Skeaff CM, Arribas GL, Sharpe SJ, Jackson RT: Prostate cancer risk and consumption of fish oils: a dietary biomarker-based case-control study. *Br J Cancer* 1999;81:1238–1242.
- Divisi D, Di Tommaso S, Salvemini S, Garramone M, Crisci R: Diet and cancer. *Acta Biomed* 2006;77:118–123.
- Gonzalez CA: Nutrition and cancer: the current epidemiological evidence. *Br J Nutr* 2006;96(suppl 1):S42–S45.
- Colloca G, Venturino A: The evolving role of familial history for prostate cancer. *Acta Oncol* 2011;50:14–24.
- Alberti C: Hereditary/familial versus sporadic prostate cancer: few indisputable genetic differences and many similar clinicopathological features. *Eur Rev Med Pharmacol Sci* 2010;14:31–41.
- Hemminki K, Forsti A, Lorenzo Bermejo J: New cancer susceptibility loci: population and familial risks. *Int J Cancer* 2008;123:1726–1729, erratum 2009;124:2250.
- Camp NJ, Farnham JM, Cannon Albright LA: Genomic search for prostate cancer predisposition loci in Utah pedigrees. *Prostate* 2005;65:365–374.
- Black DM, Solomon E: The search for the familial breast/ovarian cancer gene. *Trends Genet* 1993;9:22–26.
- Porter DE, Dixon M, Smyth E, Steel CM: Breast cancer survival in BRCA1 carriers. *Lancet* 1993;341:184–185.
- Hall JM, Lee MK, Newman B, Morrow JE, Anderson LA, Huey B, et al: Linkage of early-onset familial breast cancer to chromosome 17q21. *Science* 1990;250:1684–1689.
- Beuten J, Gelfond JAL, Franke JL, Shook S, Johnson-Pais TL, Thompson IM, et al: Single and multivariate associations of MSR1, ELAC2, and RNASEL with prostate cancer in an ethnic diverse cohort of men. *Cancer Epidemiol Biomarkers Prev* 2010;19:588–599.
- Breyer JP, McReynolds KM, Yaspan BL, Bradley KM, Dupont WD, Smith JR: Genetic variants and prostate cancer risk: candidate replication and exploration of viral restriction genes. *Cancer Epidemiol Biomarkers Prev* 2009;18:2137–2144.
- Liu H, Wang B, Han C: Meta-analysis of genome-wide and replication association studies on prostate cancer. *Prostate* 2011;71:209–224.
- Shelling AN, Ferguson LR: Genetic variation in human disease and a new role for copy number variants. *Mutat Res* 2007;622:33–41.

- 30 Zeegers MP, Khan HS, Schouten LJ, van Dijk BAC, Goldbohm RA, Schalken J, et al: Genetic marker polymorphisms on chromosome 8q24 and prostate cancer in the Dutch population: DG8S737 may not be the causative variant. *Eur J Hum Genet* 2011;19:118–120.
- 31 Akamatsu S, Takata R, Ashikawa K, Hosono N, Kamatani N, Fujioka T, et al: A functional variant in NKX3.1 associated with prostate cancer susceptibility down-regulates NKX3.1 expression. *Hum Mol Genet* 2010;19:4265–4272.
- 32 Harries LW, Perry JRB, McCullagh P, Crundwell M: Alterations in LMTK2, MSMB and HNF1B gene expression are associated with the development of prostate cancer. *BMC Cancer* 2010;10:315.
- 33 Kim S-T, Cheng Y, Hsu F-C, Jin T, Kader AK, Zheng SL, et al: Prostate cancer risk-associated variants reported from genome-wide association studies: meta-analysis and their contribution to genetic variation. *Prostate* 2010;70:1729–1738.
- 34 Elliott KS, Zeggini E, McCarthy MI, Gudmundsson J, Sulem P, Stacey SN, et al: Evaluation of association of HNF1B variants with diverse cancers: collaborative analysis of data from 19 genome-wide association studies. *PLoS One* 2010; 5:e10858.
- 35 Xu B, Wang J, Tong N, Mi Y, Min Z, Tao J, et al: A functional polymorphism in MSMB gene promoter is associated with prostate cancer risk and serum MSMB expression. *Prostate* 2010;70:1146–1152.
- 36 Zheng SL, Hsing AW, Sun J, Chu LW, Yu K, Li G, et al: Association of 17 prostate cancer susceptibility loci with prostate cancer risk in Chinese men. *Prostate* 2010;70:425–432.
- 37 Kote-Jarai Z, Leongamornlert D, Tymrakiewicz M, Field H, Guy M, Al Olama AA, et al: Mutation analysis of the MSMB gene in familial prostate cancer. *Br J Cancer* 2010;102:414–418.
- 38 Xu J, Kibel AS, Hu JJ, Turner AR, Pruett K, Zheng SL, et al: Prostate cancer risk associated loci in African Americans. *Cancer Epidemiol Biomarkers Prev* 2009;18:2145–2149.
- 39 Song H, Koessler T, Ahmed S, Ramus SJ, Kjaer SK, Dicioccio RA, et al: Association study of prostate cancer susceptibility variants with risks of invasive ovarian, breast, and colorectal cancer. *Cancer Res* 2008;68:8837–8842.
- 40 Thomas G, Jacobs KB, Yeager M, Kraft P, Wacholder S, Orr N, et al: Multiple loci identified in a genome-wide association study of prostate cancer. *Nat Genet* 2008;40:310–315.
- 41 Cross D, McCarty C, Reding D: PSI-13: using the PMRP cohort to develop a model for incorporating genetic and environmental factors into prostate cancer screening decisions. *Clin Med Res* 2010;8:192.
- 42 Simopoulos AP: Genetic variants in the metabolism of omega-6 and omega-3 fatty acids: their role in the determination of nutritional requirements and chronic disease risk. *Exp Biol Med (Maywood)* 2010;235:785–795.
- 43 Saini S, Majid S, Dahiya R: Diet, microRNAs and prostate cancer. *Pharm Res* 2010;27:1014–1026.
- 44 Steinbrecher A, Rohrmann S, Timofeeva M, Risch A, Jansen E, Linseisen J: Dietary glucosinolate intake, polymorphisms in selected biotransformation enzymes, and risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* 2010; 19:135–143.
- 45 Tamura K, Makino A, Hullin-Matsuda F, Kobayashi T, Furihata M, Chung S, et al: Novel lipogenic enzyme ELOVL7 is involved in prostate cancer growth through saturated long-chain fatty acid metabolism. *Cancer Res* 2009;69:8133–8140.
- 46 Koutros S, Berndt SI, Sinha R, Ma X, Chatterjee N, Alavanja MCR, et al: Xenobiotic metabolizing gene variants, dietary heterocyclic amine intake, and risk of prostate cancer. *Cancer Res* 2009;69:1877–1884.
- 47 Wang S, Wang F, Shi X, Dai J, Peng Y, Guo X, et al: Association between manganese superoxide dismutase (MnSOD) Val-9Ala polymorphism and cancer risk – a meta-analysis. *Eur J Cancer* 2009;45:2874–2881.
- 48 Reese AC, Fradet V, Witte JS: Omega-3 fatty acids, genetic variants in COX-2 and prostate cancer. *J Nutrigenet Nutrigenomics* 2009;2:149–158.
- 49 Wright ME, Peters U, Gunter MJ, Moore SC, Lawson KA, Yeager M, et al: Association of variants in two vitamin E transport genes with circulating vitamin E concentrations and prostate cancer risk. *Cancer Res* 2009;69:1429–1438.
- 50 Fradet V, Cheng I, Casey G, Witte JS: Dietary omega-3 fatty acids, cyclooxygenase-2 genetic variation, and aggressive prostate cancer risk. *Clin Cancer Res* 2009;15:2559–2566.
- 51 Mikhak B, Hunter DJ, Spiegelman D, Platz EA, Wu K, Erdman JW Jr, et al: Manganese superoxide dismutase (MnSOD) gene polymorphism, interactions with carotenoid levels and prostate cancer risk. *Carcinogenesis* 2008;29: 2335–2340.
- 52 Nelson EC, Rodriguez RL, Dawson K, Galvez AF, Evans CP: The interaction of genetic polymorphisms with lifestyle factors: implications for the dietary prevention of prostate cancer. *Nutr Cancer* 2008;60:301–312.
- 53 Traka M, Gasper AV, Melchini A, Bacon JR, Needs PW, Frost V, et al: Broccoli consumption interacts with GSTM1 to perturb oncogenic signalling pathways in the prostate. *PLoS One* 2008;3:e2568.
- 54 Hedelin M, Balter KA, Chang ET, Belloc R, Klint A, Johansson JE, et al: Dietary intake of phytoestrogens, estrogen receptor-beta polymorphisms and the risk of prostate cancer. *Prostate* 2006;66:1512–1520.
- 55 Lilla C, Verla-Tebit E, Risch A, Jager B, Hoffmeister M, Brenner H, et al: Effect of NAT1 and NAT2 genetic polymorphisms on colorectal cancer risk associated with exposure to tobacco smoke and meat consumption. *Cancer Epidemiol Biomarkers Prev* 2006;15:99–107.
- 56 Ishibe N, Sinha R, Hein DW, Kulldorff M, Strickland P, Fretland AJ, et al: Genetic polymorphisms in heterocyclic amine metabolism and risk of colorectal adenomas. *Pharmacogenetics* 2002;12:145–150.
- 57 Chen J, Stampfer MJ, Hough HL, Garcia-Closas M, Willett WC, Hennekens CH, et al: A prospective study of N-acetyltransferase genotype, red meat intake, and risk of colorectal cancer. *Cancer Res* 1998;58:3307–3311.
- 58 Sharma S, Cao X, Wilkens LR, Yamamoto J, Lum-Jones A, Henderson BE, et al: Well-done meat consumption, NAT1 and NAT2 acetylase genotypes and prostate cancer risk: the multiethnic cohort study. *Cancer Epidemiol Biomarkers Prev* 2010;19:1866–1870.

- 59 Hooker S, Bonilla C, Akereyeni F, Ahaghotu C, Kittles RA: NAT2 and NER genetic variants and sporadic prostate cancer susceptibility in African Americans. *Prostate Cancer Prostatic Dis* 2008;11:349–356.
- 60 Blumberg J, Heaney RP, Huncharek M, Scholl T, Stampfer M, Vieth R, et al: Evidence-based criteria in the nutritional context. *Nutr Rev* 2010;68:478–484.
- 61 Zeisel SH: A grand challenge for nutrigenomics. *Front Genet* 2010;1:1–3.
- 62 Ferguson LR: Dietary influences on mutagenesis – where is this field going? *Environ Mol Mutagen* 2010;51:909–918.
- 63 Ferguson LR: Meat and cancer. *Meat Sci* 2010;84:308–313.
- 64 Ferguson LR: Nutrigenomics approaches to functional foods. *J Am Diet Assoc* 2009;109:452–458.
- 65 Ferguson LR: Genome-wide association studies and diet. *World Rev Nutr Diet* 2010;101:8–14.
- 66 Hazra A, Kraft P, Lazarus R, Chen C, Chanock SJ, Jacques P, et al: Genome-wide significant predictors of metabolites in the one-carbon metabolism pathway. *Hum Mol Genet* 2009;18:4677–4687.
- 67 Safarinejad MR, Shafiei N, Safarinejad S: Relationship between three polymorphisms of methylenetetrahydrofolate reductase (MTHFR C677T, A1298C, and G1793A) gene and risk of prostate cancer: a case-control study. *Prostate* 2010;70:1645–1657.
- 68 Van Guelpen BR, Wiren SM, Bergh AR, Hallmans G, Stattin PE, Hultdin J: Polymorphisms of methylenetetrahydrofolate reductase and the risk of prostate cancer: a nested case-control study. *Eur J Cancer Prev* 2006;15:46–50.
- 69 Solis C, Veenema K, Ivanov AA, Tran S, Li R, Wang W, et al: Folate intake at RDA levels is inadequate for Mexican American men with the methylenetetrahydrofolate reductase 677TT genotype. *J Nutr* 2008;138:67–72.
- 70 Frosst P, Blom HJ, Milos R, Goyette P, Sheppard CA, Matthews RG, et al: A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. *Nat Genet* 1995;10:111–113.
- 71 Weisberg IS, Jacques PF, Selhub J, Bostom AG, Chen Z, Curtis Ellison R, et al: The 1298A→C polymorphism in methylenetetrahydrofolate reductase (MTHFR): in vitro expression and association with homocysteine. *Atherosclerosis* 2001;156:409–415.
- 72 Bai JL, Zheng MH, Xia X, Ter-Minassian M, Chen YP, Chen F: MTHFR C677T polymorphism contributes to prostate cancer risk among Caucasians: a meta-analysis of 3511 cases and 2762 controls. *Eur J Cancer* 2009;45:1443–1449.
- 73 Chen J, Giovannucci E, Kelsey K, Rimm EB, Stampfer MJ, Colditz GA, et al: A methylenetetrahydrofolate reductase polymorphism and the risk of colorectal cancer. *Cancer Res* 1996;56:4862–4864.
- 74 Ma J, Stampfer MJ, Giovannucci E, Artigas C, Hunter DJ, Fuchs C, et al: Methylenetetrahydrofolate reductase polymorphism, dietary interactions, and risk of colorectal cancer. *Cancer Res* 1997;57:1098–1102.
- 75 De Marzo AM, Platz EA, Sutcliffe S, Xu J, Gronberg H, Drake CG, et al: Inflammation in prostate carcinogenesis. *Nat Rev Cancer* 2007;7:256–269.
- 76 Chang B-L, Isaacs SD, Wiley KE, Gillanders EM, Zheng SL, Meyers DA, et al: Genome-wide screen for prostate cancer susceptibility genes in men with clinically significant disease. *Prostate* 2005;64:356–361.
- 77 Larsson SC, Kumlin M, Ingelman-Sundberg M, Wolk A: Dietary long-chain n-3 fatty acids for the prevention of cancer: a review of potential mechanisms. *Am J Clin Nutr* 2004;79:935–945.
- 78 McEntee MF, Whelan J: Dietary polyunsaturated fatty acids and colorectal neoplasia. *Biomed Pharmacother* 2002;56:380–387.
- 79 Kirschenbaum A, Klausner AP, Lee R, Unger P, Yao S, Liu XH, et al: Expression of cyclooxygenase-1 and cyclooxygenase-2 in the human prostate. *Urology* 2000;56:671–676.
- 80 Shahedi K, Lindstrom S, Zheng SL, Wiklund F, Adolfsson J, Sun J, et al: Genetic variation in the COX-2 gene and the association with prostate cancer risk. *Int J Cancer* 2006;119:668–672.
- 81 Hedelin M, Chang ET, Wiklund F, Belloc R, Klint A, Adolfsson J, et al: Association of frequent consumption of fatty fish with prostate cancer risk is modified by COX-2 polymorphism. *Int J Cancer* 2007;120:398–405.
- 82 Thellenberg-Karlsson C, Lindstrom S, Malmer B, Wiklund F, Augustsson-Balter K, Adami HO, et al: Estrogen receptor beta polymorphism is associated with prostate cancer risk. *Clin Cancer Res* 2006;12:1936–1941.
- 83 Li LC, Yeh CC, Nojima D, Dahiya R: Cloning and characterization of human estrogen receptor beta promoter. *Biochem Biophys Res Commun* 2000;275:682–689.
- 84 Ganry O: Phytoestrogens and prostate cancer risk. *Prev Med* 2005;41:1–6.
- 85 Adlercreutz H: Phytoestrogens: epidemiology and a possible role in cancer protection. *Environ Health Perspect* 1995;103(suppl 7):103–112.
- 86 Nagata C, Inaba S, Kawakami N, Kakizoe T, Shimizu H: Inverse association of soy product intake with serum androgen and estrogen concentrations in Japanese men. *Nutr Cancer* 2000;36:14–18.
- 87 Fritz WA, Wang J, Eltoum IE, Lamartiniere CA: Dietary genistein down-regulates androgen and estrogen receptor expression in the rat prostate. *Mol Cell Endocrinol* 2002;186:89–99.
- 88 Bektic J, Berger AP, Pfeil K, Dobler G, Bartsch G, Klocker H: Androgen receptor regulation by physiological concentrations of the isoflavonoid genistein in androgen-dependent LNCaP cells is mediated by estrogen receptor beta. *Eur Urol* 2004;45:245–251, discussion 251.
- 89 Lund TD, Munson DJ, Adlercreutz H, Handa RJ, Lephart ED: Androgen receptor expression in the rat prostate is down-regulated by dietary phytoestrogens. *Reprod Biol Endocrinol* 2004;2:5.
- 90 Barnes S: Role of phytochemicals in prevention and treatment of prostate cancer. *Epidemiol Rev* 2001;23:102–105.
- 91 Hayes JD, Pulford DJ: The glutathione S-transferase supergene family: regulation of GST and the contribution of the isoenzymes to cancer chemoprotection and drug resistance. *Crit Rev Biochem Mol Biol* 1995;30:445–600.
- 92 Rebbeck TR: Molecular epidemiology of the human glutathione S-transferase genotypes GSTM1 and GSTT1 in cancer susceptibility. *Cancer Epidemiol Biomarkers Prev* 1997;6:733–743.

- 93 Agalliu I, Langeberg WJ, Lampe JW, Salinas CA, Stanford JL: Glutathione S-transferase M1, T1, and P1 polymorphisms and prostate cancer risk in middle-aged men. *Prostate* 2006;66:146–156.
- 94 Cohen JH, Kristal AR, Stanford JL: Fruit and vegetable intakes and prostate cancer risk. *J Natl Cancer Inst* 2000;92:61–68.
- 95 Conaway CC, Getahun SM, Liebes LL, Pusateri DJ, Topham DK, Botero-Omary M, et al: Disposition of glucosinolates and sulforaphane in humans after ingestion of steamed and fresh broccoli. *Nutr Cancer* 2000;38:168–178.
- 96 Gasper AV, Al-Janobi A, Smith JA, Bacon JR, Fortun P, Atherton C, et al: Glutathione S-transferase M1 polymorphism and metabolism of sulforaphane from standard and high-glucosinolate broccoli. *Am J Clin Nutr* 2005;82:1283–1291.
- 97 Joseph MA, Moysich KB, Freudenheim JL, Shields PG, Bowman ED, Zhang Y, et al: Cruciferous vegetables, genetic polymorphisms in glutathione S-transferases M1 and T1, and prostate cancer risk. *Nutr Cancer* 2004;50:206–213.
- 98 Savas S, Kim DY, Ahmad MF, Shariff M, Ozcelik H: Identifying functional genetic variants in DNA repair pathway using protein conservation analysis. *Cancer Epidemiol Biomarkers Prev* 2004;13:801–807.
- 99 Goode EL, Ulrich CM, Potter JD: Polymorphisms in DNA repair genes and associations with cancer risk. *Cancer Epidemiol Biomarkers Prev* 2002;11:1513–1530, erratum 2003;12:1119.
- 100 van Gils CH, Bostick RM, Stern MC, Taylor JA: Differences in base excision repair capacity may modulate the effect of dietary antioxidant intake on prostate cancer risk: an example of polymorphisms in the XRCC1 gene. *Cancer Epidemiol Biomarkers Prev* 2002;11:1279–1284.
- 101 Chen L, Ambrosone CB, Lee J, Sellers TA, Pow-Sang J, Park JY: Association between polymorphisms in the DNA repair genes XRCC1 and APE1, and the risk of prostate cancer in white and black Americans. *J Urol* 2006;175:108–112.
- 102 Rybicki BA, Conti DV, Moreira A, Cicek M, Casey G, Witte JS: DNA repair gene XRCC1 and XPD polymorphisms and risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* 2004;13:23–29.
- 103 Lu QY, Hung JC, Heber D, Go VLW, Reuter VE, Cordon-Cardo C, et al: Inverse associations between plasma lycopene and other carotenoids and prostate cancer. *Cancer Epidemiol Biomarkers Prev* 2001;10:749–756.
- 104 Heber D, Lu QY: Overview of mechanisms of action of lycopene. *Exp Biol Med (Maywood)* 2002;227:920–923.
- 105 Pohar KS, Gong MC, Bahnson R, Miller EC, Clinton SK: Tomatoes, lycopene and prostate cancer: a clinician's guide for counseling those at risk for prostate cancer. *World J Urol* 2003;21:9–14.
- 106 Goodman M, Bostick RM, Ward KC, Terry PD, van Gils CH, Taylor JA, et al: Lycopene intake and prostate cancer risk: effect modification by plasma antioxidants and the XRCC1 genotype. *Nutr Cancer* 2006;55:13–20.
- 107 Gronberg H, Isaacs SD, Smith JR, Carpten JD, Bova GS, Freije D, et al: Characteristics of prostate cancer in families potentially linked to the hereditary prostate cancer 1 (HPC1) locus. *JAMA* 1997;278:1251–1255.
- 108 Cooney KA, McCarthy JD, Lange E, Huang L, Miesfeldt S, Montie JE, et al: Prostate cancer susceptibility locus on chromosome 1q: a confirmatory study. *J Natl Cancer Inst* 1997;89:955–959.
- 109 Silverman RH: Implications for RNase L in prostate cancer biology. *Biochemistry* 2003;42:1805–1812.
- 110 Casey G, Neville PJ, Plummer SJ, Xiang Y, Krumroy LM, Klein EA, et al: RNASEL Arg462Gln variant is implicated in up to 13% of prostate cancer cases. *Nat Genet* 2002;32:581–583.
- 111 Rennert H, Bercovich D, Hubert A, Abeliovich D, Rozovsky U, Bar-Shira A, et al: A novel founder mutation in the RNASEL gene, 471delAAAG, is associated with prostate cancer in Ashkenazi Jews. *Am J Hum Genet* 2002;71:981–984.
- 112 Simard J, Dumont M, Soucy P, Labrie F: Perspective: prostate cancer susceptibility genes. *Endocrinology* 2002;143:2029–2040.
- 113 Rokman A, Ikonen T, Seppala EH, Nupponen N, Autio V, Mononen N, et al: Germline alterations of the RNASEL gene, a candidate HPC1 gene at 1q25, in patients and families with prostate cancer. *Am J Hum Genet* 2002;70:1299–1304, erratum 2002;7:215, 2004;75:1158.
- 114 Powell IJ, Carpten J, Dunston G, Kittles R, Bennett J, Hoke G, et al: African-American heredity prostate cancer study: a model for genetic research. *J Natl Med Assoc* 2001;93:120–123.
- 115 Thompson AK, Shaw DI, Minihane AM, Williams CM: Trans-fatty acids and cancer: the evidence reviewed. *Nutr Res Rev* 2008;21:174–188.
- 116 Liu X, Schumacher FR, Plummer SJ, Jorgenson E, Casey G, Witte JS: Trans-fatty acid intake and increased risk of advanced prostate cancer: modification by RNASEL R462Q variant. *Carcinogenesis* 2007;28:1232–1236.
- 117 Pierce BL, Ahsan H: Genetic susceptibility to type 2 diabetes is associated with reduced prostate cancer risk. *Hum Hered* 2010;69:193–201.
- 118 Leitzmann MF, Ahn J, Albanes D, Hsing AW, Schatzkin A, Chang SC, et al: Diabetes mellitus and prostate cancer risk in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *Cancer Causes Control* 2008;19:1267–1276.
- 119 Gong ZH, Neuhauser ML, Goodman PJ, Albanes D, Chi C, Hsing AW, et al: Obesity, diabetes, and risk of prostate cancer: results from the prostate cancer prevention trial. *Cancer Epidemiol Biomarkers Prev* 2006;15:1977–1983.
- 120 Rodriguez C, Patel AV, Mondul AM, Jacobs EJ, Thun MJ, Calle EE: Diabetes and risk of prostate cancer in a prospective cohort of US men. *Am J Epidemiol* 2005;161:147–152.
- 121 Meyer TE, Boerwinkle E, Morrison AC, Volcik KA, Sanderson M, Coker AL, et al: Diabetes genes and prostate cancer in the Atherosclerosis Risk in Communities study. *Cancer Epidemiol Biomarkers Prev* 2010;19:558–565.
- 122 Oliver SE, Gunnell D, Donovan J, Peters TJ, Persad R, Gillatt D, et al: Screen-detected prostate cancer and the insulin-like growth factor axis: results of a population-based case-control study. *Int J Cancer* 2004;108:887–892.
- 123 Li L, Yu H, Schumacher F, Casey G, Witte JS: Relation of serum insulin-like growth factor-I (IGF-I) and IGF binding protein-3 to risk of prostate cancer (United States). *Cancer Causes Control* 2003;14:721–726.
- 124 Chokkalingam AP, Pollak M, Fillmore CM, Gao YT, Stanczyk FZ, Deng J, et al: Insulin-like growth factors and prostate cancer: a population-based case-control study in China. *Cancer Epidemiol Biomarkers Prev* 2001;10:421–427.

- 125 Haldorsen IS, Vesterhus M, Raeder H, Jensen DK, Sovik O, Molven A, et al: Lack of pancreatic body and tail in HNF1B mutation carriers. *Diabetic Med* 2008;25:782–787.
- 126 Gudmundsson J, Sulem P, Steinthorsdottir V, Bergthorsson JT, Thorleifsson G, Manolescu A, et al: Two variants on chromosome 17 confer prostate cancer risk, and the one in TCF2 protects against type 2 diabetes. *Nat Genet* 2007;39:977–983.
- 127 Winckler W, Weedon MN, Graham RR, McCarroll SA, Purcell S, Almgren P, et al: Evaluation of common variants in the six known maturity-onset diabetes of the young (MODY) genes for association with type 2 diabetes. *Diabetes* 2007;56:685–693.
- 128 Stevens VL, Ahn J, Sun J, Jacobs EJ, Moore SC, Pate AV, et al: HNF1B and JAZF1 genes, diabetes, and prostate cancer risk. *Prostate* 2010;70:601–607.
- 129 Thomas G, Jacobs KB, Yeager M, Kraft P, Wacholder S, Orr N, et al: Multiple loci identified in a genome-wide association study of prostate cancer. *Nat Genet* 2008;40:310–315.
- 130 Senkel S, Lucas B, Klein-Hitpass L, Ryffel GU: Identification of target genes of the transcription factor HNF1 β and HNF1 α in a human embryonic kidney cell line. *Biochim Biophys Acta* 2005;1731:179–190.
- 131 Marguet D, Baggio L, Kobayashi T, Bernard AM, Pierres M, Nielsen PF, et al: Enhanced insulin secretion and improved glucose tolerance in mice lacking CD26. *Proc Natl Acad Sci USA* 2000;97:6874–6879.
- 132 Adalat S, Woolf AS, Johnstone KA, Wirsing A, Harries LW, Long DA, et al: HNF1B mutations associate with hypomagnesemia and renal magnesium wasting. *J Am Soc Nephrol* 2009;20:1123–1131.
- 133 Michels AJ, Hagen TM: Hepatocyte nuclear factor 1 is essential for transcription of sodium-dependent vitamin C transporter protein 1. *Am J Physiol Cell Physiol* 2009;297:C1220–C1227.
- 134 Power SC, Cereghini S: Positive regulation of the vHNF1 promoter by the orphan receptors COUP-TF1/Ear3 and COUP-TFII/Arp1. *Mol Cell Biol* 1996;16:778–791.
- 135 Hiesberger T, Shao X, Gourley E, Reimann A, Pontoglio M, Igarashi P: Role of the hepatocyte nuclear factor-1 β (HNF-1 β) C-terminal domain in Pkhd1 (ARPKD) gene transcription and renal cystogenesis. *J Biol Chem* 2005;280:10578–10586.
- 136 Manolio TA: Genomewide association studies and assessment of the risk of disease. *N Engl J Med* 2010;363:166–176.
- 137 Zeggini E, Scott LJ, Saxena R, Voight BF, Marchini JL, Hu T, et al: Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. *Nat Genet* 2008;40:638–645.
- 138 Prokunina-Olsson L, Fu YP, Tang W, Jacobs KB, Hayes RB, Kraft P, et al: Refining the prostate cancer genetic association within the JAZF1 gene on chromosome 7p15.2. *Cancer Epidemiol Biomarkers Prev* 2010;19:1349–1355.
- 139 Liu NC, Lin WJ, Kim E, Collins LL, Lin HY, Yu IC, et al: Loss of TR4 orphan nuclear receptor reduces phosphoenolpyruvate carboxykinase-mediated gluconeogenesis. *Diabetes* 2007;56:2901–2909.
- 140 Olswang Y, Cohen H, Papo O, Cassuto H, Croniger CM, Hakimi P, et al: A mutation in the peroxisome proliferator-activated receptor gamma-binding site in the gene for the cytosolic form of phosphoenolpyruvate carboxykinase reduces adipose tissue size and fat content in mice. *Proc Natl Acad Sci USA* 2002;99:625–630.
- 141 Albanes D, Weinstein SJ, Wright ME, Mannisto S, Limburg PJ, Snyder K, et al: Serum insulin, glucose, indices of insulin resistance, and risk of prostate cancer. *J Natl Cancer Inst* 2009;101:1272–1279.
- 142 Hsing AW, Chua S, Gao YT, Gentzschein E, Chang L, Deng J, et al: Prostate cancer risk and serum levels of insulin and leptin: a population-based study. *J Natl Cancer Inst* 2001;93:783–789.
- 143 Lehrer S, Diamond EJ, Stagger S, Stone NN, Stock RG: Serum insulin level, disease stage, prostate specific antigen (PSA) and Gleason score in prostate cancer. *Br J Cancer* 2002;87:726–728.
- 144 Asatiani E, Huang WX, Wang A, Ortner ER, Cavalli LR, Haddad BR, et al: Deletion, methylation, and expression of the NKX3.1 suppressor gene in primary human prostate cancer. *Cancer Res* 2005;65:1164–1173.
- 145 Bhatia-Gaur R, Donjacour AA, Scialvolino PJ, Kim M, Desai N, Young P, et al: Roles for Nkx3.1 in prostate development and cancer. *Genes Dev* 1999;13:966–977.
- 146 Muhlbradt E, Asatiani E, Ortner E, Wang A, Gelmann EP: NKX3.1 activates expression of insulin-like growth factor binding protein-3 to mediate insulin-like growth factor-I signaling and cell proliferation. *Cancer Res* 2009;69:2615–2622.
- 147 Harman SM, Metter EJ, Blackman MR, Landis PK, Carter HB, Baltimore Longitudinal Study on Aging: Serum levels of insulin-like growth factor I (IGF-I), IGF-II, IGF-binding protein-3, and prostate-specific antigen as predictors of clinical prostate cancer. *J Clin Endocrinol Metab* 2000;85:4258–4265.
- 148 Chan JM, Stampfer MJ, Ma J, Gann P, Gaziano JM, Pollak M, et al: Insulin-like growth factor-I (IGF-I) and IGF binding protein-3 as predictors of advanced-stage prostate cancer. *J Natl Cancer Inst* 2002;94:1099–1106.
- 149 Platz EA, Pollak MN, Leitzmann MF, Stampfer MJ, Willett WC, Giovannucci E: Plasma insulin-like growth factor-1 and binding protein-3 and subsequent risk of prostate cancer in the PSA era. *Cancer Causes Control* 2005;16:255–262.
- 150 Stattin P, Bylund A, Rinaldi S, Biessy C, Dechaud H, Stenman UH, et al: Plasma insulin-like growth factor-I, insulin-like growth factor-binding proteins, and prostate cancer risk: a prospective study. *J Natl Cancer Inst* 2000;92:1910–1917.
- 151 Stattin P, Rinaldi S, Biessy C, Stenman UH, Hallmans G, Kaaks R: High levels of circulating insulin-like growth factor-I increase prostate cancer risk: a prospective study in a population-based nonscreened cohort. *J Clin Oncol* 2004;22:3104–3112.
- 152 Wolk A, Mantzoros CS, Andersson SO, Bergstrom R, Signorello LB, Lagiou P, et al: Insulin-like growth factor 1 and prostate cancer risk: a population-based, case-control study. *J Natl Cancer Inst* 1998;90:911–915.

- 153 Martel F, Azevedo I: An update on the extraneuronal monoamine transporter (EMT): characteristics, distribution and regulation. *Curr Drug Metab* 2003;4:313–318.
- 154 Sakata T, Anzai N, Kimura T, Miura D, Fukutomi T, Takeda M, et al: Functional analysis of human organic cation transporter OCT3 (SLC22A3) polymorphisms. *J Pharmacol Sci* 2010;113:263–266.
- 155 Lee KC, Chang HT, Chou KJ, Tang KY, Wang JL, Lo YK, et al: Mechanism underlying histamine-induced intracellular Ca^{2+} movement in PC3 human prostate cancer cells. *Pharmacol Res* 2001;44:547–552.
- 156 Ohuchi Y, Yanai K, Sakurai E, Fukui H, Yanagisawa T, Watanabe T: Histamine-induced calcium mobilization in single cultured cells expressing histamine H1 receptors: a relationship between its sensitivity and the density of H1 receptors. *Int J Mol Med* 1998;1:355–360.
- 157 Koizumi H, Ohkawara A: H2 histamine receptor-mediated increase in intracellular Ca^{2+} in cultured human keratinocytes. *J Dermatol Sci* 1999;21:127–132.
- 158 Kishi F, Nakaya Y, Ito S: Histamine H2-receptor-mediated nitric oxide release from porcine endothelial cells. *J Cardiovasc Pharmacol* 1998;32:177–182.
- 159 Kuhl M, Sheldahl LC, Malbon CC, Moon RT: Ca^{2+} /calmodulin-dependent protein kinase II is stimulated by Wnt and frizzled homologs and promotes ventral cell fates in *Xenopus*. *J Biol Chem* 2000;275:12701–12711.
- 160 Torres MA, YangSnyder JA, Purcell SM, DeMarais AA, McGrew LL, Moon RT: Activities of the Wnt-1 class of secreted signaling factors are antagonized by the Wnt-5A class and by a dominant negative cadherin in early *Xenopus* development. *J Cell Biol* 1996;133:1123–1137.
- 161 Okamoto KI, Narayanan R, Lee SH, Murata K, Hayashi Y: The role of CaMKII as an F-actin-bundling protein crucial for maintenance of dendritic spine structure. *Proc Natl Acad Sci USA* 2007;104:6418–6423.
- 162 Witze ES, Litman ES, Argast GM, Moon RT, Ahn NG: Wnt5a control of cell polarity and directional movement by polarized redistribution of adhesion receptors. *Science* 2008;320:365–369.
- 163 Brenner JC, Chinnaiyan AM: Translocations in epithelial cancers. *Biochim Biophys Acta* 2009;1796:201–215.
- 164 Demichelis F, Setlur SR, Beroukhi R, Perner S, Korbel JO, Lafargue CJ, et al: Distinct genomic aberrations associated with ERG rearranged prostate cancer. *Genes Chromosomes Cancer* 2009;48:366–380.
- 165 Haffner MC, Aryee MJ, Toubaji A, Esopi DM, Albadine R, Gurel B, et al: Androgen-induced TOP2B-mediated double-strand breaks and prostate cancer gene rearrangements. *Nat Genet* 2010;42:668–675.
- 166 Hofer MD, Kuefer R, Maier C, Herkommer K, Perner S, Demichelis F, et al: Genome-wide linkage analysis of TMPRSS2-ERG fusion in familial prostate cancer. *Cancer Res* 2009;69:640–646.
- 167 Kim JH, Dhanasekaran SM, Mehra R, Tomlins SA, Gu W, Yu J, et al: Integrative analysis of genomic aberrations associated with prostate cancer progression. *Cancer Res* 2007;67:8229–8239.
- 168 Mani R-S, Tomlins SA, Callahan K, Ghosh A, Nyati MK, Varambally S, et al: Induced chromosomal proximity and gene fusions in prostate cancer. *Science* 2009;326:1230.
- 169 Han B, Mehra R, Suleman K, Tomlins SA, Wang L, Singhal N, et al: Characterization of ETS gene aberrations in select histologic variants of prostate carcinoma. *Mod Pathol* 2009;22:1176–1185.
- 170 Sircar K, Yoshimoto M, Monzon FA, Koumakpayi IH, Katz RL, Khanna A, et al: PTEN genomic deletion is associated with p-Akt and AR signalling in poorer outcome, hormone refractory prostate cancer. *J Pathol* 2009;218:505–513.
- 171 King JC, Xu J, Wongvipat J, Hieronymus H, Carver BS, Leung DH, et al: Cooperativity of TMPRSS2-ERG with PI3-kinase pathway activation in prostate oncogenesis. *Nat Genet* 2009;41:524–526.
- 172 Yu J, Yu J, Mani RS, Cao Q, Brenner CJ, Cao X, et al: An integrated network of androgen receptor, polycomb, and TMPRSS2-ERG gene fusions in prostate cancer progression. *Cancer Cell* 2010;18:443–454.
- 173 Rickman DS, Chen Y-B, Banerjee S, Pan Y, Yu J, Vuong T, et al: ERG cooperates with androgen receptor in regulating trefoil factor 3 in prostate cancer disease progression. *Neoplasia* 2010;12:1031–1040.
- 174 Pflueger D, Terry S, Sboner A, Habegger L, Esgueva R, Lin P-C, et al: Discovery of non-ETS gene fusions in human prostate cancer using next-generation RNA sequencing. *Genome Res* 2011;21:56–67.
- 175 Chinnaiyan AM, Palanisamy N: Chromosomal aberrations in solid tumors. *Prog Mol Biol Transl Sci* 2010;95:55–94.
- 176 Ferguson LR: Inhibitors of topoisomerase II enzymes: a unique group of environmental mutagens and carcinogens. *Mutat Res* 1998;400:271–278.
- 177 Ferguson LR: Chronic inflammation and mutagenesis. *Mutat Res* 2010;690:3–11.
- 178 Ferguson LR, Zhu S-T, Harris PJ: Antioxidant and antigenotoxic effects of plant cell wall hydroxycinnamic acids in cultured HT-29 cells. *Mol Nutr Food Res* 2005;49:585–593.
- 179 Karunasinghe N, Ryan J, Tuckey J, Masters J, Jamieson M, Clarke LC, et al: DNA stability and serum selenium levels in a high-risk group for prostate cancer. *Cancer Epidemiol Biomarkers Prev* 2004;13:391–397.
- 180 Philpott M, Ferguson LR, Gould KS, Harris PJ: Anthocyanidin-containing compounds occur in the periderm cell walls of the storage roots of sweet potato (*Ipomoea batatas*). *J Plant Physiol* 2009;166:1112–1117.
- 181 Philpott M, Lim CC, Ferguson LR: Dietary protection against free radicals: a case for multiple testing to establish structure-activity relationships for antioxidant potential of anthocyanic plant species. *Int J Mol Sci* 2009;10:1081–1103.
- 182 Fenech M, Ferguson LR: Vitamins/minerals and genomic stability in humans. *Mutat Res* 2001;475:1–6.
- 183 Ferguson LR: Role of plant polyphenols in genomic stability. *Mutat Res* 2001;475:89–111.
- 184 van Ommen B, Bouwman J, Dragsted LO, Drevon CA, Elliott R, de Groot P, et al: Challenges of molecular nutrition research 6: the nutritional phenotype database to store, share and evaluate nutritional systems biology studies. *Genes Nutr* 2010;5:189–203.

- 185 van Ommen B, El-Sohemy A, Hesketh J, Kaput J, Fenech M, Evelo CT, et al: The Micronutrient Genomics Project: a community-driven knowledge base for micronutrient research. *Genes Nutr* 2010;5:285–296.
- 186 Gillanders EM, Xu J, Chang B-I, Lange EM, Wiklund F, Bailey-Wilson JE, et al: Combined genome-wide scan for prostate cancer susceptibility genes. *J Natl Cancer Inst* 2004;96:1240–1247.
- 187 Collin SM, Metcalfe C, Zuccolo L, Lewis SJ, Chen L, Cox A, et al: Association of folate-pathway gene polymorphisms with the risk of prostate cancer: a population-based nested case-control study, systematic review, and meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2009;18:2528–2539.
- 188 Furusawa T, Moribe H, Kondoh H, Higashi Y: Identification of CtBP1 and CtBP2 as corepressors of zinc finger-homeodomain factor δ EF1. *Mol Cell Biol* 1999;19:8581–8590.
- 189 Johansson A, Marroni F, Hayward C, Franklin CS, Kirichenko AV, Jonasson I, et al: Common variants in the JAZF1 gene associated with height identified by linkage and genome-wide association analysis. *Hum Mol Genet* 2009;18:373–380.
- 190 Chang B-L, Cramer SD, Wiklund F, Isaacs SD, Stevens VL, Sun J, et al: Fine mapping association study and functional analysis implicate a SNP in MSMB at 10q11 as a causal variant for prostate cancer risk. *Hum Mol Genet* 2009;18:1368–1375.
- 191 Whitaker HC, Kote-Jarai Z, Ross-Adams H, Warren AY, Burge J, George A, et al: The rs10993994 risk allele for prostate cancer results in clinically relevant changes in microseminoprotein-beta expression in tissue and urine. *PLoS One* 2010;5:e13363.
- 192 Shimada T: Salivary proteins as a defense against dietary tannins. *J Chem Ecol* 2006;32:1149–1163.
- 193 Eeles RA, Kote-Jarai Z, Al Olama AA, Giles GG, Guy M, Severi G, et al: Identification of seven new prostate cancer susceptibility loci through a genome-wide association study. *Nat Genet* 2009;41:1116–1121.
- 194 Leslie NR, McLennan AG, Safrany ST: Cloning and characterisation of hAps1 and hAps2, human diadenosine polyphosphate-metabolising Nudix hydrolases. *BMC Biochem* 2002;3:20.
- 195 Waters KM, Le Marchand L, Kolonel LN, Monroe KR, Stram DO, Henderson BE, et al: Generalizability of associations from prostate cancer genome-wide association studies in multiple populations. *Cancer Epidemiol Biomarkers Prev* 2009;18:1285–1289.