Published in final edited form as:
Curr Nutr Rep. 2012 March 1; 1(1): 37–43. doi:10.1007/s13668-011-0007-6.

Nutrigenomics and Cancer Prevention

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Abstract

Mounting evidence continues to point to dietary habits as a modifier of cancer risk and tumor behavior; although it is clear that considerable variability occurs across studies. While genetic public health messages can be developed, the use of mean values may result in underexposure to some essential and nonessential food components, yet precipitate overexposure to nutrients. Undeniably, inconsistencies in the literature may reflect variation in timing of exposures to specific dietary constituents, interactions with the food matrix, processing technologies, or the genomic variation among individuals, which can influence absorption, metabolism, and/or the molecular target. Inter-individual variability in genetics, epigenetics, transcriptomics, proteomics, metabolomics, or microbiomics can influence the magnitude and direction of response to bioactive food components, as briefly reviewed in this article. Unquestionably, understanding nutrigenomics holds promise to reveal those who will benefit most from dietary interventions plus identify any who might be placed at risk due to overexposures.

Keywords

Nutrigenomics; Epigenetics; Proteomics; Metabolomics; Transcriptomics; Microbiomics; Cancer; Cancer prevention; Diet; Bioactive food components

Introduction

The genetic revolution is providing new insights into a number of health issues, including the role of diet in cancer prevention. Since the completion of the Human Genome Project in 2003, remarkable advances have been made in understanding the human genome's

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Disclosure No potential conflicts of interest relevant to this article were reported.

contribution to health and disease. Knowledge about single genes has led to improved diagnosis and treatment of single-gene disorders and better understanding of the interactions between the entire genome and nongenomic factors, paving the way for “genomic medicine,” in which new diagnostic and therapeutic approaches to common multifactorial conditions are emerging [1••]. A new era of individualized disease prevention based on testing for genetic susceptibilities and safer, more effective use of drugs based on pharmacogenomic testing is anticipated. Genomic research is also predicted to generate innovative therapies that are targeted more precisely to the molecular mechanisms of disease [2]. Nutrigenomics—how nutrients modulate gene and protein expression and ultimately influence cellular metabolism—is the combination of molecular nutrition and genomics.

The evidence is abundant that dietary habits can significantly influence cancer risk. Experimental evidence using a variety of models substantiates the importance of multiple components in the diet that modify one or more cancer-related processes. However, epidemiologic and clinical intervention studies have been inconsistent, making it difficult to draw firm conclusions about which adjustments in eating behaviors are needed to lessen the cancer burden. An example of the variability in study outcome is dietary soy intake and breast cancer risk. Preclinical data have shown soy to have anticancer properties. Many epidemiologic studies have yielded inconsistent results [3, 4, 5•]. Meta-analyses suggest that soy isoflavone intake may be associated with reduced breast cancer risk in Asian populations and may be more protective in premenopausal women [3, 4, 5•]. The variability with regard to soy and other bioactive food components and cancer prevention may reflect the individuality in response.

Timing of exposure may contribute to the variability. The critical period for dietary soy exposure may be during childhood and adolescence [6, 7]. If soy intake information is obtained in adulthood or old age, when cancer is diagnosed, the association between soy intake and cancer might be missed. Furthermore, the variability in study outcome may be related to quantity, composition of the bioactive food component, and interactions between phytoestrogens and other bioactive components in the food matrix, which could enhance or reduce the ultimate health effect. Westernized soy products are different from those consumed in the traditional Asian diet. Most Asian soy products use whole soybeans with or without fermentation. Soy products or second-generation soy foods in the United States are mostly based on soy protein at different levels of purification or extraction with different nutrient compounds. It is likely that processing of soy foods modulates the profile of isoflavones and modifies their bioavailability. Adding to the difficulty in assessing soy and associated health risks, only a few studies use whole soy, while most of the soy research has focused on genistein. Therefore, it is not clear whether effects are related to genistein alone or genistein in another form, such as isoflavone mix, soy protein isolate, or soybeans [8].

Finally, genetics may modify the response. Genistein has been reported to upregulate several tumor suppressor genes and downregulate oncogenes [8]. Other biological insults may modify the response, including excessive energy intake, environmental contaminants, viruses, and/or bacteria. Nutrigenomics may help us understand the variation in response. Nutrigenomics investigates the effects of dietary components on the structure, function, and regulation of coding and noncoding DNA segments of all genes present in the genome of a

given species. Nutrigenomics can influence the response to diet at multiple points, including food preference, food tolerance, transport, metabolism, and effect in target tissue [9].

Genetics

Public health messages have focused on optimizing health for populations. It is becoming clear that not all individuals respond identically to treatment, whether treatment is through diet, lifestyle change, or drug therapy. Genetic differences may account for populations' differences in the risk of developing disease (eg, cancer). Single nucleotide polymorphisms (SNPs) make up about 90% of all human genetic variation; humans have about 5 to 8 million SNPs. SNPs may be important in explaining some of the variation in response to food components. Although not all SNPs directly influence the quality and/or quantity of the gene product, the links among SNPs, food components, and phenotypes might assist in predicting who may benefit from diet intervention.

It has long been recognized that humans have an individual responsiveness to the foods they consume. Phenotypic variation can be as subtle as taste preference. In a study that examined the heritability of food preferences, investigators examined preferences for four food groups in a sample of monozygotic and dizygotic twin pairs. Significant heritability estimates were found for the four food groups, modest for dessert foods, moderate for vegetables and fruits, and high for liking protein foods. Monozygotic correlations were higher than dizygotic correlations [10], suggesting that taste preferences are heritable.

Specific genes may influence not only food preference, but how much of a food is consumed. Glucose sensing in the brain has been proposed to be involved in regulating food intake. Glucose transporter type 2 (GLUT2) is coded by the *SLC2a2* gene and thought to be primarily involved in glucose homeostasis. GLUT2-null mice fail to control their intake in response to glucose [11]. In individuals with an SNP in the *GLUT2* gene, there is a higher daily intake of sugars, irrespective of fat, protein, or alcohol intake [12].

The vitamin D receptor (VDR) mediates the biological actions of 1,25-dihydroxyvitamin D3, the physiologically active form of vitamin D, by regulating a variety of target genes involved in cell proliferation and differentiation. Several VDR polymorphisms may affect the response to various dietary components and disease risk. One particular VDR polymorphism is *Fok1;* individuals who carry the Ff or ff genotype have a greater risk of developing colorectal cancer. Among individuals with low calcium or low fat intake, the risk of colorectal cancer increases in a gene–dose-dependent manner such that individuals possessing the ff genotype display an approximately 2.5-fold increased risk [13]. Additionally, the *Fok1* polymorphism of the VDR directly affects bone mineral accretion during pubertal growth through an effect on calcium absorption [14]. Although the biological basis by which the *Fok1* polymorphism might influence cancer risk is uncertain, there do seem to be vulnerable individuals with inadequate calcium consumption who may have a 2.5 times higher risk of developing colon cancer, which is considerably greater than one would surmise from population studies. Although the association of calcium intake with decreased colorectal cancer risk has been substantiated in clinical and epidemiologic studies, results have varied, with an overall modest protective effect. According to the World Cancer

Research Fund global report on diet, physical activity, and cancer prevention, there was a 0.78 summary effect of calcium supplementation and decreased colorectal cancer [15]. It is possible that the association is really a reflection of a large response in a subpopulation.

Haplotypes may be useful in understanding the distribution of risk alleles in human populations and tailoring prevention strategies to those at increased risk. Two large case-control studies investigated the association of VDR haplotypes [16]. Although the *CDX2* polymorphism was not associated with colon or rectal cancer, the bLFA haplotype (*Bsm*1 b, or B, poly [A]L, *Fok* F, and *CDX2A* polymorphisms) was associated with an increased risk of colon cancer. Interestingly, the frequency of the A allele of the *CDX2* polymorphism varied markedly across populations, occurring in 19% of non-Hispanic whites, 21% of Hispanics, 76% of African Americans, and 47% of Asians. Haplotype analysis of different domains of the VDR might elucidate the role of calcium in cancer prevention, specifically helping to identify those who may benefit or be at risk due to dietary modification.

Another example in which preclinical evidence is suggestive of protection, yet epidemiologic evidence is inconsistent is the role of lycopene and reduced prostate cancer risk. The *XRCC1* (Arg399Gln) polymorphism may influence the response to lycopene [17]. In a case-control study of prostate cancer, *XRCC1* genotypes were detected. Among men with the Arg/ Arg genotype at codon 399, ORs for prostate cancer risk associated with medium and high lycopene intake were 0.59 (95% CI, 0.23–1.50) and 0.21 (95% CI, 0.06–0.71), respectively. Men with the Arg/Arg genotype who consumed above-median lycopene, combined with above-median levels of α-tocopherol and β-carotene were further protected (OR, 0.11 [95% CI, 0.02–0.65]). These findings suggest that the association between lycopene and prostate cancer may be modified by the *XRCC1* genotype and other antioxidants [17].

The simultaneous examination of multiple SNPs may offer advantages in ascertaining the biological response to food components; multiple genes are likely involved in determining physiologic processes and their ultimate influence on an individual’s phenotype. In a study of red meat intake and colon cancer risk, Kury et al. [18] explored the joint effects of several factors. Through an association study based on 1,023 cases and 1,121 controls, they examined the influence of environmental factors co-analyzed with combinations of six polymorphisms located in cytochrome P450 genes [18]. Whereas separate analyses of the SNPs showed no effect on colorectal cancer risk, three allelic variant combinations were found to be associated with a significant increase in colorectal cancer risk in interaction with excessive red meat consumption, thereby exacerbating the intrinsic procarcinogenic effect of this dietary factor [18].

Copy number may also be a significant determinant of whether dietary intervention results in a biological response and phenotypic outcome. Copy number variation, including deletion or amplification of chromosomal regions, is the most prevalent structural variation in the human genome, accounting for about 20% of individual variation. Increases in copy number are often associated with increases in enzyme activity, and deletions are associated with decreases in enzyme activity. Copy number variation has been reported for α-amylase, several cytochrome P450 genes, and Her2/Neu [19–21]. Copy number variation in

enzymatic activity may contribute to some of the differential response to food components across individuals.

Epigenetics

Epidemiologic evidence suggests that early-life environmental exposures are related to disease risk; it has been hypothesized that epigenetic dysregulation may be involved [20]. Epigenetics refers to heritable changes not encoded in the DNA sequence itself but that play an important role in the control of gene expression. Mechanisms include DNA methylation, histone modifications, gene silencing by microRNA, and chromosome stability. Promising evidence in humans suggests that diet and environmental factors directly influence epigenetic mechanisms. Dietary polyphenols from green tea, turmeric, soybeans, broccoli, and other sources may influence epigenetic processes (Table 1) [22].

A classic example of early-life exposures causing epigenetic changes occurred in individuals who were prenatally exposed to famine during the Dutch Hunger Winter in 1944–1945. Six decades later, they had less DNA methylation of the imprinted *IGF2* gene compared with their unexposed, same-sex siblings. The association was specific for periconceptional exposure, suggesting that the critical period for establishing and maintaining epigenetic marks is early development [23].

Dietary variables have been found to be significantly associated with methylation status. In the Lovelace Smokers cohort of current and former smokers, Stidley and colleagues [24] evaluated whether diet and multivitamin use influenced the prevalence of gene promoter methylation in cells exfoliated from the aerodigestive tract. Participants were assessed for promoter methylation of eight genes commonly silenced in lung cancer. Methylation was categorized as low (fewer than two genes methylated) or high (two or more genes methylated). Significant protection against methylation was found for leafy green vegetables and folate and with current use of multivitamins [24].

Restoring proper methylation may represent a fundamental process by which some nutrients function to influence gene expression patterns. Epigallocatechin-3-gallate from green tea can reactivate methylation-silenced genes by inhibiting the enzymatic activity of DNA methyltransferase 1 [25]. Further, the Annurca polyphenol extract from the Annurca apple reversed methylation and reactivation of the DNA repair mismatch gene *hMLH1* in in vitro models of colorectal cancer [26].

Histone modification may cause the silencing and unsilencing of genes [27–29]. In addition to histone occupancy or the overall recruitment and release of histones, interactions of reversible histone modifications govern gene expression, including histone acetylation, methylation, phosphorylation, ubiquitination, and biotinylation. Modification of histone deacetylase (HDAC) may be instrumental for changing tumor behavior [27, 28]. Sulforaphane, found in cruciferous vegetables, acts as a potent inducer of phase 2 detoxification enzymes, and also acts as a HDAC inhibitor. In humans, a single ingestion of broccoli sprouts inhibited HDAC activity within minutes that persisted for a significant amount of time but within 24 h returned to baseline values. How HDAC inhibitors will be affected by other food components known to modify epigenetics is unclear. Furthermore, the

effect that these HDAC inhibitors will have on chronic disease risk and cancer remains to be clarified [30].

Transcriptomics

Transcriptomics is the study of the complete set of RNA transcripts produced by the genome, including mRNA, rRNA, tRNA, and other noncoding RNA, and which link the genome, proteome, and the cellular phenotype [31]. Environmental factors such as diet can influence the transcriptome. In particular, mRNA transcripts may prove to be useful biomarkers for disease risk detection. Because whole blood mRNA shares more than 80% of the transcriptome with major tissues, it may be a good surrogate tissue for predicting events in a target tissue and may potentially lead to earlier and more accurate prediction of disease diagnosis and progression [32].

Transcriptomic studies are providing clues about molecular targets for specific food components. For example, DNA microarrays containing about 9,000 genes were used to determine the changes in colonocyte gene expression in carcinogen-injected rats. The animals were fed diets differing only in the type of fat—corn oil n-6 polyunsaturated fatty acids (PUFAs), fish oil n-3 PUFAs, or olive oil n-9 monounsaturated fatty acids. Changes were seen in the molecular portrait of gene expression profiles in the colonic epithelium at both the initiation (DNA adduct formation) and promotional (aberrant crypt foci) stages of tumor development, and only in the animals consuming the omega-3 PUFAs [33]. Other animal studies are beginning to identify specific sites of action of food components [34]. For example, the gene expression patterns from wild-type and nuclear factor E2 p45-related factor 2 (Nrf2)-deficient mice fed sulforaphane were used to identify novel downstream effects of sulforaphane in the Nrf2 pathway, including upregulation of several genes, such as glutathione-S-transferase [35].

Transcriptomic profiling allows for simultaneous monitoring of the expression of thousands of genes. It provides only a single snapshot, so the physiologic significance should be kept in perspective. Although mRNA microarray technologies are often used in population studies to help characterize individuals and their response to agents [36, 37], they are seldom used in nutrition studies. Transcriptomic technologies were used to find that relatively short-term exposures of a high-carbohydrate or high-protein breakfast meal were sufficient to cause significant changes in the human transcriptome [38].

Cancer prediction using embryonic stem cell gene signatures may be an area of growing importance [39, 40]. Several dietary components, including PUFAs, have been found to influence stem cells [41–43]. The response between healthy and cancer stem cells may ultimately lead to a better understanding of using bioactive food components for cancer prevention.

Proteomics

Proteomics describes how our genome expresses itself as a response to diet [44]; proteomics is the systematic evaluation of changes in the protein constituency of a cell to characterize disease processes through protein pathways that interconnect the extracellular

microenvironment with the control of gene transcription [31]. Proteomic technologies simultaneously examine numerous proteins and detect subtle shifts of proteins in cells, tissues, and bodily fluids. Nutritional proteomics can identify and quantify bioactive proteins and peptides and address questions of nutritional bioefficacy [44]. The proteome is dynamic and varies according to cell type and functional state of the cell; hence, it provides useful feedback about which biological specimens are likely to respond to bioactive food components. In fact, because gene expression patterns are not well-correlated with protein expression patterns, proteomics is likely to determine individuals who may or may not respond to a food component. The nutritional science community is utilizing proteomics as a tool to identify biomarkers of health, disease, treatment, and prevention [45–47].

Proteomic technologies, such as matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry, are used to gather information on individual protein masses from a complex mixture with high throughput. In a controlled dietary intervention study, Mitchell et al. [48] tested a method for identifying serum biomarkers using MALDI-TOF and statistical analysis. During separate feeding periods, participants ate a basal diet devoid of fruits and vegetables and a basal diet supplemented with cruciferous vegetables. Bioinformatics methods identified two significant peaks that could classify participants based on diet (basal vs cruciferous) with 76% accuracy [49]. This type of technology has the potential to be a biomarker tool assisting in the identification of those individuals who may be at disease risk.

Various proteins are modified by the flavonoid quercetin, which is abundant in onions, tea, and apples. Proteomic analysis of quercetin-treated human colon cancer cells revealed altered levels of a variety of proteins involved in growth, differentiation, and apoptosis of colon cancer cells. Their identification as molecular targets of quercetin may explain the anticancer activities of this flavonoid [50].

Metabolomics

The metabolome refers to the complete set of metabolite and low molecular weight intermediates in a given context. The metabolome varies according to the physiology or developmental or pathological state of a cell, tissue, organ, or organism [51]. Because changes in metabolites may be detected more quickly after an exposure than changes in RNA or proteins, researchers may use metabolomic technologies to detect earlier changes in the cancer process following dietary changes [52]. Furthermore, a metabolic fingerprint may be a more physiologically relevant measure of a cell’s state, as metabolites are often the end product of multiple end points with different isoforms arising from various genes [53].

Metabolomic methods have been used to profile cells at various stages in carcinogenesis based on shifts in glucose metabolism [54]. Bioactive food components can modify these metabolic profiles at various steps in glucose metabolism [55]. Metabolomics can also be used to determine mechanisms of action and/or bioavailability of bioactive food components. For example, Solanky et al. [56] measured urinary metabolites in premenopausal women who consumed soy in the form of textured vegetable protein containing conjugated isoflavone glucosides or miso containing unconjugated isoflavones.

Urinary metabolites from women consuming miso had more changes in metabolites than those who consumed textured vegetable protein, suggesting that the composition of the isoflavones is important in determining any biological effects [56].

Microbiomics

Microbiomics is the study of the quality, quantity, and activity of the more than 100 trillion microorganisms in the human gut [57]. Microbiota, depending on composition, can metabolize dietary components to new bioactive compounds that increase the risk of certain cancers, such as hydrogen sulfide and secondary bile acids, or that negatively influence cancer proceses, such as the daidzein metabolite equol or ellagic acid metabolites urolithins [58–60]. Just as the microbiome can modify responses to diet, diet can modify the microbiome. Probiotics, or foods such as yogurts or other processed functional foods, contain live bacteria, usually lactobacilli, streptococci, or bifidobacteria, and can colonize the gastrointestinal tract for short periods of time. Although they have not been found to permanently colonize the gut, they can influence immunity or produce bioactive metabolites. Prebiotics do not contain live bacteria but rather compounds that are beneficial to the microflora. Synbiotics include combinations of probiotics and prebiotics with the goal of improving the survival and activity of the probiotic [57, 61].

Conclusions

Life is a series of intertwined biological signals. During the initiation and progression of cancer, several of these signals are modified to promote uncontrolled cellular growth. It is becoming increasingly apparent that some of the components in foods can have a marked influence on the risk of developing the initial and sustained changes in hallmark cancer signals. The ability of foods and associated constituents to influence the processes is linked to genetic variations that can influence the biological response in terms of the amounts reaching the molecular target(s) (ie, absorption, metabolism, and excretion) and also regulate the constitutive amount of the molecular target(s) requiring modification. Findings to date demonstrate that nutrigenomics and the downstream events (proteomics and metabolomics) and associated “-omics,” such as microbiomics, can have a significant impact on the relationship between dietary exposures and cancer risk/tumor behavior. However, the complexity of defining this interrelationship cannot be overemphasized because the thousands of food components and their common biological characteristics make it exceedingly difficult to unravel which constituent(s) is/are most critical for reducing cancer risk. The future likely will involve defining subgroups of individuals who benefit most from exaggerated intakes of selected foods or their component(s). As not all individuals will be expected to experience the same benefits, guidelines likely will need to be tailored based on selected genetic/epigenetic/transcriptomic variants. This approach also should be appropriate for those individuals who are at increased risk of cancer risk due to exaggerated intakes. Given the alarming increase in cancer worldwide along with other noncommunicable diseases, the impact of incorporating a personalized approach for using diet to curb risk holds enormous potential to improve quality of life, expand productivity, and reduce health care cost.

References

Paper of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1••. Feero WG, Guttmacher AE, Collins FS. Genomic medicine—an updated primer. N Engl J Med. 2010; 362:2001–2011. This review thoroughly discusses recent advances in genomics. [PubMed: 20505179]

2. Burke W, Khoury MJ, Stewart A, Zimmern RL. The path from genome-based research to population health: development of an international public health genomics network. Genet Med. 2006; 8:451–8. [PubMed: 16845279]

3. Wu AH, Yu MC, Tseng CC, Pike MC. Epidemiology of soy exposures and breast cancer risk. Br J Cancer. 2008; 98:9–14. [PubMed: 18182974]

4. Trock BJ, Hilakivi-Clarke L, Clarke R. Meta-analysis of soy intake and breast cancer risk. J Natl Cancer Inst. 2006; 98:459–71. [PubMed: 16595782]

5•. Dong JY, Qin LQ. Soy isoflavones consumption and risk of breast cancer incidence or recurrence: a meta-analysis of prospective studies. Breast Cancer Res Treat. 2011; 125:315–323. This meta-analysis highlights the role that timing of exposure can play in studies on food components and cancer risk. [PubMed: 21113655]

6. Wu AH, Wan P, Hankin J, et al. Adolescent and adult soy intake and risk of breast cancer in Asian-Americans. Carcinogenesis. 2002; 23:1491–6. [PubMed: 12189192]

7. Shu XO, Jin F, Dai Q, et al. Soyfood intake during adolescence and subsequent risk of breast cancer among Chinese women. Cancer Epidemiol Biomarkers Prev. 2001; 10:483–8. [PubMed: 11352858]

8. Hilakivi-Clarke L, Andrade JE, Helferich W. Is soy consumption good or bad for the breast? J Nutr. 2010; 140:2326S–34S. [PubMed: 20980638]

9. Lampe, JW.; Potter, JD. In Gene-Environment Interactions: Fundamentals of Ecogenetics. Hoboken: John Wiley & Sons, Inc; 2006. Genetic variation, diet, and disease susceptibility.

10. Breen FM, Plomin R, Wardle J. Heritability of food preferences in young children. Physiol Behav. 2006; 88:443–7. [PubMed: 16750228]

11. Bady I, Marty N, Dallaporta M, et al. Evidence from glut2-null mice that glucose is a critical physiological regulator of feeding. Diabetes. 2006; 55:988–95. [PubMed: 16567520]

12. Eny KM, Wolever TM, Fontaine-Bisson B, El-Sohemy A. Genetic variant in the glucose transporter type 2 is associated with higher intakes of sugars in two distinct populations. Physiol Genomics. 2008; 33:355–60. [PubMed: 18349384]

13. Wong HL, Seow A, Arakawa K, et al. Vitamin D receptor start codon polymorphism and colorectal cancer risk: effect modification by dietary calcium and fat in Singapore Chinese. Carcinogenesis. 2003; 24:1091–5. [PubMed: 12807755]

14. Abrams SA, Griffin IJ, Hawthorne KM, et al. Vitamin D receptor Fok1 polymorphisms affect calcium absorption, kinetics, and bone mineralization rates during puberty. J Bone Miner Res. 2005; 20:945–53. [PubMed: 15883634]

15. Food, N. Activity P. and the Prevention of Cancer: A Global Perspective. Washington, DC: AICR; 2007.

16. Slattery ML, Herrick J, Wolff RK, et al. CDX2 VDR polymorphism and colorectal cancer. Cancer Epidemiol Biomarkers Prev. 2007; 16:2752–5. [PubMed: 18086783]

17. Goodman M, Bostick RM, Ward KC, et al. Lycopene intake and prostate cancer risk: effect modification by plasma antioxidants and the XRCC1 genotype. Nutr Cancer. 2006; 55:13–20. [PubMed: 16965236]

18. Kury S, Buecher B, Robiou-du-Pont S, et al. Combinations of cytochrome P450 gene polymorphisms enhancing the risk for sporadic colorectal cancer related to red meat consumption. Cancer Epidemiol Biomarkers Prev. 2007; 16:1460–7. [PubMed: 17627011]

19. Ingelman-Sundberg M, Sim SC, Gomez A, Rodriguez-Antona C. Influence of cytochrome P450 polymorphisms on drug therapies: pharmacogenetic, pharmacoepigenetic and clinical aspects. Pharmacol Ther. 2007; 116:496–526. [PubMed: 18001838]
20. Perry GH, Dominy NJ, Claw KG, et al. Diet and the evolution of human amylase gene copy number variation. Nat Genet. 2007; 39:1256–60. [PubMed: 17828263]
21. Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science. 1987; 235:177–82. [PubMed: 3798106]
22. Link A, Balaguer F, Goel A. Cancer chemoprevention by dietary polyphenols: promising role for epigenetics. Biochem Pharmacol. 2010; 80:1771–92. [PubMed: 20599773]
23. Heijmans BT, Tobi EW, Stein AD, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proc Natl Acad Sci U S A. 2008; 105:17046–9. [PubMed: 18955703]
24. Stidley CA, Picchi MA, Leng S, et al. Multivitamins, folate, and green vegetables protect against gene promoter methylation in the aerodigestive tract of smokers. Cancer Res. 2010; 70:568–74. [PubMed: 20068159]
25. Fang MZ, Wang Y, Ai N, et al. Tea polyphenol (−)-epigallocatechin-3-gallate inhibits DNA methyltransferase and reactivates methylation-silenced genes in cancer cell lines. Cancer Res. 2003; 63:7563–70. [PubMed: 14633667]
26. Fini L, Selgrad M, Fogliano V, et al. Annurca apple polyphenols have potent demethylating activity and can reactivate silenced tumor suppressor genes in colorectal cancer cells. J Nutr. 2007; 137:2622–8. [PubMed: 18029474]
27. Glozak MA, Seto E. Histone deacetylases and cancer. Oncogene. 2007; 26:5420–32. [PubMed: 17694083]
28. Myzak MC, Dashwood RH. Histone deacetylases as targets for dietary cancer preventive agents: lessons learned with butyrate, diallyl disulfide, and sulforaphane. Curr Drug Targets. 2006; 7:443–52. [PubMed: 16611031]
29. Holloway AF, Oakford PC. Targeting epigenetic modifiers in cancer. Curr Med Chem. 2007; 14:2540–7. [PubMed: 17979706]
30. Dashwood RH, Ho E. Dietary histone deacetylase inhibitors: from cells to mice to man. Semin Cancer Biol. 2007; 17:363–9. [PubMed: 17555985]
31. Petricoin EF, Liotta LA. Clinical applications of proteomics. J Nutr. 2003; 133:2476S–84S. [PubMed: 12840227]
32. Liew CC, Ma J, Tang HC, et al. The peripheral blood transcriptome dynamically reflects system wide biology: a potential diagnostic tool. J Lab Clin Med. 2006; 147:126–32. [PubMed: 16503242]
33. Davidson LA, Nguyen DV, Hokanson RM, et al. Chemopreventive n-3 polyunsaturated fatty acids reprogram genetic signatures during colon cancer initiation and progression in the rat. Cancer Res. 2004; 64:6797–804. [PubMed: 15374999]
34. Sunde RA. mRNA transcripts as molecular biomarkers in medicine and nutrition. J Nutr Biochem. 2010; 21:665–70. [PubMed: 20303730]
35. Cheung KL, Kong AN. Molecular targets of dietary phenethyl isothiocyanate and sulforaphane for cancer chemoprevention. AAPS J. 2010; 12:87–97. [PubMed: 20013083]
36. Al Tamimi DM, Shawarby MA, Ahmed A, et al. Protein expression profile and prevalence pattern of the molecular classes of breast cancer—a Saudi population based study. BMC Cancer. 2010; 10:223. [PubMed: 20492711]
37. Ornish D, Magbanua MJ, Weidner G, et al. Changes in prostate gene expression in men undergoing an intensive nutrition and lifestyle intervention. Proc Natl Acad Sci U S A. 2008; 105:8369–74. [PubMed: 18559852]
38. van Erk MJ, Blom WA, van Ommen B, Hendriks HF. High-protein and high-carbohydrate breakfasts differentially change the transcriptome of human blood cells. Am J Clin Nutr. 2006; 84:1233–41. [PubMed: 17093179]
39. Zhu J, Ding J, Ding F. Tumor stem cell, or its niche, which plays a primary role in tumorigenesis? World J Gastrointest Oncol. 2010; 2:218–21. [PubMed: 21160620]

40. Ben-Porath I, Thomson MW, Carey VJ, et al. An embryonic stem cell-like gene expression signature in poorly differentiated aggressive human tumors. Nat Genet. 2008; 40:499–507. [PubMed: 18443585]
41. Langelier B, Linard A, Bordat C, et al. Long chain-polyunsaturated fatty acids modulate membrane phospholipid composition and protein localization in lipid rafts of neural stem cell cultures. J Cell Biochem. 2010; 110:1356–64. [PubMed: 20564231]
42. Trosko JE. Role of diet and nutrition on the alteration of the quality and quantity of stem cells in human aging and the diseases of aging. Curr Pharm Des. 2008; 14:2707–18. [PubMed: 18991690]
43. Alexander LS, Mahajan A, Odle J, et al. Dietary phosphate restriction decreases stem cell proliferation and subsequent growth potential in neonatal pigs. J Nutr. 2010; 140:477–82. [PubMed: 20053936]
44. Kussmann M, Affolter M. Proteomics at the center of nutrigenomics: comprehensive molecular understanding of dietary health effects. Nutrition. 2009; 25:1085–93. [PubMed: 19665868]
45. Rahman MA, Amin AR, Shin DM. Chemopreventive potential of natural compounds in head and neck cancer. Nutr Cancer. 2010; 62:973–87. [PubMed: 20924973]
46. Thongboonkerd V. Proteomics. Forum Nutr. 2007; 60:80–90. [PubMed: 17684403]
47. Xiao Z, Blonder J, Zhou M, Veenstra TD. Proteomic analysis of extracellular matrix and vesicles. J Proteomics. 2009; 72:34–45. [PubMed: 19068243]
48. Mitchell BL, Yasui Y, Lampe JW, et al. Evaluation of matrix-assisted laser desorption/ionization-time of flight mass spectrometry proteomic profiling: identification of alpha 2-HS glycoprotein B-chain as a biomarker of diet. Proteomics. 2005; 5:2238–46. [PubMed: 15841498]
49. Yuan Q, Fontenele-Neto JD, Fricker LD. Effect of voluntary exercise on genetically obese Cpefat/fat mice: quantitative proteomics of serum. Obes Res. 2004; 12:1179–88. [PubMed: 15292483]
50. Wenzel U, Herzog A, Kuntz S, Daniel H. Protein expression profiling identifies molecular targets of quercetin as a major dietary flavonoid in human colon cancer cells. Proteomics. 2004; 4:2160–74. [PubMed: 15221776]
51. Oliver SG. Functional genomics: lessons from yeast. Philos Trans R Soc Lond B Biol Sci. 2002; 357:17–23. [PubMed: 11839178]
52. Kim YS, Maruvada P. Frontiers in metabolomics for cancer research: Proceedings of a National Cancer Institute workshop. Metabolomics. 2008; 4:105–13.
53. Ellis DI, Dunn WB, Griffin JL, et al. Metabolic fingerprinting as a diagnostic tool. Pharmacogenomics. 2007; 8:1243–66. [PubMed: 17924839]
54. Gatenby RA, Gillies RJ. Glycolysis in cancer: a potential target for therapy. Int J Biochem Cell Biol. 2007; 39:1358–66. [PubMed: 17499003]
55. Kim YS, Milner JA. Bioactive food components and cancer-specific metabonomic profiles. J Biomed Biotechnol. 2011; 2011:721213. [PubMed: 21113295]
56. Solanky KS, Bailey NJ, Beckwith-Hall BM, et al. Biofluid 1H NMR-based metabonomic techniques in nutrition research—metabolic effects of dietary isoflavones in humans. J Nutr Biochem. 2005; 16:236–44. [PubMed: 15808328]
57. Davis CD, Milner JA. Gastrointestinal microflora, food components and colon cancer prevention. J Nutr Biochem. 2009; 20:743–52. [PubMed: 19716282]
58. O'Keefe SJ, Ou J, Aufreiter S, et al. Products of the colonic microbiota mediate the effects of diet on colon cancer risk. J Nutr. 2009; 139:2044–8. [PubMed: 19741203]
59. Lampe JW. Emerging research on equol and cancer. J Nutr. 2010; 140:1369S–72S. [PubMed: 20505018]
60. Larrosa M, Gonzalez-Sarrias A, Garcia-Conesa MT, et al. Urolithins, ellagic acid-derived metabolites produced by human colonic micro-flora, exhibit estrogenic and antiestrogenic activities. J Agric Food Chem. 2006; 54:1611–20. [PubMed: 16506809]
61. Corthesy B, Gaskins HR, Mercenier A. Cross-talk between probiotic bacteria and the host immune system. J Nutr. 2007; 137:781S–90S. [PubMed: 17311975]

Table 1

Major plant constituents with evidence of epigenetic modifications

Major plant	Bioactive component
Tomatoes	Lycopene
Turmeric	Curcumin
Cinnamon	Coumaric acid
Cashew nuts	Anacardic acid
Apples	Phloretin
Soybean	Genistein
Tea	Epigallocatechin gallate (EGCG)
Grapes	Resveratrol
Citrus	Hesperidin
Coffee	Caffeic acid
Broccoli	Isothiocyanates
Garlic	Allyl mercaptan

(*Adapted from* Link et al. [22].)