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Nutrigenomics in cancer prevention and therapeutic strategies

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Abstract

As an increasingly prevalent disease and a leading cause of death, cancer is a major threat to human health. Although cancer research has provided us with a better understanding of cancer biology, we still face numerous challenges in cancer treatment and prevention. Current therapies are largely limited to surgery, radiation therapy, and chemotherapy, which remain unsatisfactory. In particular, there are many problems in chemotherapy, such as low response rate, poor specificity, drug resistance, and severe side effects. Thus, we still have much to do in order to improve the current situation. It is our priority to identify and develop alternative treatment options that can increase efficacy, reduce side effects, and improve quality of life for cancer patients. In this context, nutrigenomics is emerging as a field that holds great promise for this endeavor because of its capability to modulate cancer metabolism and tumorigenesis through nutritional intervention. The crucial role of nutrigenomics in the field of cancer therapy is apparent. By elucidating the network of nutrient-gene interactions related to cancer, we can ultimately synthesize this information into integrated metabolic interventions for cancer therapy. As these nutritional interventions can target multiple mechanisms, they could prove to be more effective than conventional therapies – in addition to being safer, more cost-effective, and more accessible for cancer patients. However, to implement nutrigenomics for cancer therapy, much translational research is still to be done. It is particularly important to develop clinically effective dietary protocols and supplement formulas for specific conditions as well as biomarkers to identify utility criteria and monitor efficacy. Nutrigenomics therefore offers a novel approach to cancer management; conversely, cancer therapy is a critical field for the practice of nutrigenomics.

Keywords: Nutrition, genomics, cancer, cancer prevention, cancer therapy.

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Nutrigenomics and Cancer

Cancer incidence is projected to increase in the future and an effectual preventive strategy is required to face this challenge. Alteration of dietary habits is potentially an effective approach for reducing cancer risk. Assessment of biological effects of a specific food or bioactive component that is linked to cancer and prediction of individual susceptibility as a function of nutrient - nutrient interactions and genetics is an essential element to evaluate the beneficiaries of dietary interventions. It is believed that dietary habits as an important modifiable environmental factor, influence cancer risk and tumor behavior. It is estimated that diet influences about 30-40% of all cancer cases, however, the actual percentage is not known and depends on the specific type of cancer and the specific components of diet [1]. In general, the use of biomarkers to evaluate individuals susceptibilities to cancer must be easily accessible and reliable. However, the response of individuals to bioactive food components depends not only on the effective concentration of the bioactive food components, but also on the target tissues. This fact makes the response of individuals to food components vary from one individual to another. Many studies indicate that breast, prostate, liver, colon and lung cancers are

linked to the dietary intakes [2]. Nutrigenomics focuses on the understanding of interactions between genes and diet in an individual and how the response to bioactive food componentsis influenced by an individual's genes. Nutrients have shown to affect gene expression and to induce changes in DNA and protein molecules. Nutrigenomic approaches provide an opportunity to study how gene expression is regulated by nutrients and how nutrition affects gene variations and epigenetic events. Some of these bioactive components such as calcium, zinc, selenium, folate, vitamins C, D and E, carotenoids, flavonoids, indoles, allyl sulfur compounds, conjugated linoleic acid and N-3 fatty acids may influence carcinogen metabolism, cell signaling, cell cycle control, apoptosis, hormonal balance and angiogenesis [3]. Finding the components involved in interactions between genes and diet in an individual can potentially help identify target molecules important in preventing and/or reducing the symptoms of cancer. Studies of variations in cancer incidence among and within populations under similar dietary habits suggest that an individual's response to food may reflect genetic predisposition of an individual as well as differences in gene and protein expression patterns in the individual. Recently the effects of nutrition on DNA methylation and the role of epigenetic events in cancer prevention have also been reviewed [4].

Evidences suggest that foods offer advantages over their isolated constituents in treatment of cancer. This may be due to presence of multiple bioactive compounds within the food that exert additive or synergistic effects. For example, in treatment of human lung cancer cells which undergo apoptosis, whole green tea is more effective than the individual constituents of the green tea in inhibiting TNF-α release [5]. These effects appear to be mediated through enhanced incorporation of the tea polyphenols into the cells. In a rat study in which prostate carcinogenesis was induced by N-methyl-N-nitrosourea (NMU) - testosterone, tomato powder was shown to inhibit carcinogenesis. These effects were suspected to be at the levels of absorption, retention, or metabolism [6]. In another study a fat-soluble extract from vegetable powder was found to be more efficacious than ß-carotene in inhibiting cell proliferation in a lung cancer cell line [7]. There have been also cases wherein, the foods were found not to be as effective as their isolated components, suggesting that the food may contain constituents that inhibit the cellular response. Although the mechanisms involved in these processes are not known yet, it may be due to modification of components involved in absorption, metabolism, or site of action of the bioactive food constituent in the body. An example for this may be the reduced ability of soy flour and full fat soy flakes to inhibit aberrant crypt foci compared to isolated genistein [8]. At the present time, there is not much known about the food matrix and the bioactive components in them and how they influence cancer prevention.

Patterns of gene, protein and metabolite expressions in response to particular nutrients or dietary protocols can be viewed as 'dietary signatures'. Nutrigenomics studies these dietary signatures in specific cells, tissues and organisms. Nutrigenomics also attempts to understand how nutrition influences homeostasis. Furthermore, nutrigenomics aims to identify the genes that affect the risk of diet related diseases at the genome level and understand the mechanisms that underlie genetic predispositions in individuals. Two strategies are used in molecular nutrition research. The first strategy is the traditional hypothesis-driven approach in which the expression of specific genes and proteins influenced by nutrients are identified [9]. In this approach genomic tools such as transcriptomics, proteomics and metabolomics are used to identify specific regulatory pathways which are affected by diet [9, 10]. Also transgenic mouse models and cellular models are also used which can allow new genes and pathways to be identified. In future, the use of such models may lead to better understanding of the interactions between metabolic and inflammatory signaling routes. In the second strategy, systems biology approach is used. In this approach gene, protein and metabolite signatures that are linked with specific nutrient or dietary protocols are systematically organized to serve as molecular biomarkers for early detection of diseases in response to nutrient induced changes in the body. The first strategy provides detailed molecular data on the interaction between genome and nutrition. The second strategy will potentially provide variety of biomarkers to stage and track the health of an individual at any time point during his/her lifetime.

Many of the techniques used to unravel nutritional genomics are the same as those used in modern molecular genetics research. These techniques are used to study the interrelations between diet and cancer risk and tumor behavior [10, 11, 12, 13]. Application of such techniques lead to a better understanding of genetics and associated

polymorphisms in diet related diseases, nutrient-induced changes in chromatin structure, nutrient-induced changes in gene expression, and altered formation and/or bioactivation of proteins as they relate to nutrient-induced effects in an individual. The response to a bioactive food component may be very subtle; therefore, characterization and quantification of small cellular changes are very important.

However, nutrigenetics studies the effect of genetic variation on the interaction between diet and disease. Based on a number of studies on population differences in single nucleotide polymorphisms (SNPs), it is thought that genetics plays a major role in determining an individual's risk of developing a certain disease [14]. Inter-individual genetic variation is also likely to be an important factor in nutrient requirements. For example, it has been shown that individuals with a C→T substitution in the gene for methylenetetrahydrofolatereductase (MTHFR) might require more folate than those with the wild type allele [15]. Several studies have indicated that diet has an important influence on the risk of developing certain diseases and genetic predisposition has been shown to play a role in these cases [16, 17, 18, 19]. Cancer prevention studies have shown that all of the major signaling pathways deregulated in different types of cancer, are affected by nutrients. Pathways studied include: carcinogen metabolism, DNA repair, cell proliferation/apoptosis, differentiation, inflammation, oxidant/antioxidant balance and angiogenesis [20]. So far, more than 1000 different phytochemicals have been identified with cancer preventive activities [21].

Dietary components can also induce many enzymes through activation of signal transduction pathways. The three known signaling pathways, mitogen activated protein kinase (MAPK), protein kinase C (PKC), and phosphatidylinositol 3-kinase (PI3K) pathways are known to be modulated by dietary components [22]. Bioactive components present in fruits and vegetables can prevent carcinogenesis by several mechanisms such as blocking metabolic activation through increasing detoxification. In-vitro studies and preclinical models have shown many constituents of plant foods can modulate detoxification enzymes; examples are flavonoids (e.g. quercetin, rutin, and genistein), phenols (e.g. curcumin, epigallocatin-3-gallate and resveratrol), isothiocyanates, allyl sulfur compounds, indoles, and selenium [23, 24].

Deficiency of dietary components have been found to disrupt DNA repair pathways and many dietary components such as flavonoids, vitamins E and C, and isothiocyanates that scavenge ROS, have been shown to stimulate repair of oxidative DNA damage [25]. Dietary supplementation with cooked carrots have been shown to increase the repair of 8-oxod G (an indicator of oxidative DNA damage) in white blood cells [26].

Dietary components are likely to be major determinants of cancer risk in humans. Genetic polymorphisms lead to alteration of response to dietary components by influencing the absorption and metabolism. Epigenetic events can induce changes in DNA methylation patterns and thus influencing overall gene expression that can be modified in response to food components. Many dietary constituents affect post translational events and may account for at least part of the variations in response to dietary components. Bioactive food components may affect cellular and molecular events that are important in cancer prevention. Studies of dietary components using tissue/cell model systems can help have a better understanding of inter-relations among nutrigenetics, nutritional epigenomics, nutritional transcriptomics, proteomics and metabolomics in the near future. As the field of molecular nutrition expands and the functions of human genome are better understood, a greater understanding of how foods and their components influence cancer will ensue.

The main goal of nutrigenomics is to profile global changes induced by nutrients and develop dietary-intervention strategies to maintain homeostasis and prevent diseases including cancer [27]. The main challenge is that of integrating information pertaining to expression of more than 30,000 genes, for most of which the function is not known, and computing changes in expression for more than 100,000 proteins and several thousand metabolites [28]. A major drawback in developing prevention strategies comes from differences in approach between preclinical and clinical research. Most, if not all, preclinical studies with in vitro and animal models tend to focus on single bioactive food components without considerations of the complex interactions that occur among bioactive food components present in the human diet. This problem is addressed in part by epidemiological studies that focus on the average anticarcinogenic or procarcinogenic effects of specific groups of bioactive compounds (e.g., n-3 fatty acids) in the context of dietary exposure (e.g., Western vs. Asian diet). Nevertheless, results of population studies may not find statistical differences or be biased if the

analysis comprises individuals with mutations in tumor suppressor genes or carrying specific polymorphisms. For example, individuals with the TT polymorpshism at nucleotide 677 for methylenetetrahydrofolatereductase (MTHFR) (~5–20% population worldwide) appear to be at decreased risk for colorectal adenomas in the presence of high plasma levels of folate [29]. Therefore, the interaction between levels of exposure to certain bioactive food components and genetics (nutrigenetics) may influence the risk of cancer in certain subpopulations and is an important component of nutrigenomic studies. Whereas it is recognized that cancer requires multiple molecular changes, it is also known that certain genetic alterations play a hierarchical role in cancer development in certain tissues. For example, loss of BRCA-1 expression through epigenetic silencing may confer a high probability of breast cancer [30]. Loss of DNA repair functions controlled by BRCA-1 may lead to subsequent genetic alterations in genes that control proliferation and apoptosis. During the last two decades a tremendous amount of information has been gathered concerning the role of signaling pathways in cancer development. Nutrigenomic strategies are an important tool to decode pyramidal effects and establish the minimum requirements for cancer development and prevention.

Conceptually, nutrigenomics represents a strategy that can be applied to the study and prevention of many diseases. It provides a pyramidal approach that encompasses the study of molecular relationships between nutrients and genes (nutrigenetics), how these interactions influence changes in the profile of transcripts (transcriptomics), proteins (proteomics), and metabolites (metabolomics) [31]. The underpinning concept is that thousands of bioactive compounds function as signals and influence the organism's response [32]. The opportunity of targeting nutrients–gene interactions to influence the cancer process is modulated by genetic variations in human populations, epigenetic modifications that selectively and permanently alter gene expression, by complex interactions/ associations among dietary components, and heterogeneity of cells within a certain tumor. Therefore, integration of information about gene polymorphisms, identification of gene targets that regulate cell and tissue-specific pathways, and development of diagnostic strategies to control for clinical heterogeneity are important to understand how nutrigenomics may be used in cancer prevention [33]. Other chapters in this volume will discuss specifically how nutrigenetics, epigenetics, transcriptomics, and metabolomics may help to assess the effects of specific nutrients on the cancer process. Here, we will highlight examples of how integration of nutrigenomic data may be useful to understand the correlation between consumption of specific bioactive compounds and protection toward specific tumor types.

A specific target for nutrigenomic strategies is endocrine cancers, including breast, ovarian, endometrial, and prostate cancers. The vast majority of breast cancers is estrogen receptor (ER)-positive and occurs in postmenopausal women. Because breast tissues undergo complex programs of growth and development that are under the influence of ovarian steroids, studies have considered nutrition factors that alter or interfere with estrogen and progesterone-dependent regulation. The interest on isoflavones in breast cancer prevention derives from the fact breast cancer risk for women residing in geographical areas of high consumption of soy products during puberty is lower compared to that of women living in Western countries or Asian women who had a low soy intake [34]. However, clinical trials reported small [35] or no effect of supplementation with isoflavones on breast cancer risk [36-39], and administration of isoflavones elicited in some cases an estrogen-like effect. Other studies indicated that the reduction in breast cancer risk due to soy intake was limited to Asian populations [40]. A case–control study conducted in Southeast China in 2004–2005 reported that premenopausal and postmenopausal women in the highest quartile of total isoflavone intake had a reduced risk for all receptor (ER/PR) status of breast cancer with a dose–response relationship. The protective effect was more pronounced for women with ER+/PR+ and ER–/PR– breast tumors [41].

Several factors may be responsible for the inconsistent effects of soy-related diets on cancer outcome. These include age, reproductive history, genetic background, dose and timing of exposure, and dietary patterns. For example, because of their binding affinity for the ER, isoflavones may function as agonists or antagonists depending on the concentration. The differential binding of isoflavones to the ER may interfere with or activate the genomic actions of the ER. Moreover, the agonist/competing effects of isoflavones for the ER may be modified by interactions with polymorphisms for the ER [42]. For example, polymorphisms in the ERβ have been shown to modify the association between isoflavone intake and breast cancer risk [43]. Given the role of

cross talk between ER and isoflavones in breast cancer risk, genome-wide studies are required to examine the effects of isoflavones and exposure levels on promoter sequences that are targeted by the ER. DNA microarray technologies have been used to monitor genomewide effects by isoflavones. For example, studies measured patterns of gene expression in the developing uterus and ovaries of Sprague-Dawley rats on GD 20, exposed to graded dosages of 17alpha-ethynyl estradiol (EE), genistein, or bisphenol A (BPA) from GD 11 to GD 20. Analysis of the transcript profile of these tissues was used to determine the estrogenicity of different compounds [44]. Studies that examined the impact of isoflavones on the epigenetic process reported that elevation of histone acetylation and coactivator activity of ER may reduce the risk of estrogen-related diseases [45].

Nutrigenetics takes into account how the cellular response to specific nutrients is influenced by interindividual genetic variations including single nucleotide polymorphisms(SNPs). The cell response to isoflavones may also be influenced by the presence of mutations in specific tumor suppressor genes. For example, the growth of *BRCA1* mutant cells (SUM1315MO2) carrying the 185delAG *BRCA1* mutation was strongly inhibited by genistein, whereas this isoflavone only had a weak effect in cells expressing wild-type BRCA1 protein. The responsiveness of BRCA1 mutant cells was linked to higher expression of ERβ gene. These data suggested that genistein may be an efficient inhibitor of cancer development in *BRCA1* mutant breast cancer cells [46].With respect to BRCA-1 status in ovarian cancers, genistein induced apoptosis in both wild-type and mutated BRCA-1 ovarian cancer (BG-1) cells. However, this effect was mediated by different pathways since genistein inhibited ERα in BRCA-1 deficient cells, whereas itactivated ERβ when BRCA-1 was present [47].

Isoflavones may also alter gene expression by inducing chromatin modifications at target promoters. For example, genistein was shown to suppress DNA-cytosine methyltransferase-1 (DNMT) and reverse DNA hypermethylation in mammary cancer cells in vitro [48]. Therefore, epigenetic changes such as alterations in DNA methylation could account for the preventive effects of genestein and other soy isoflavones. A recent study reported that intake of soy isoflavones had an antiestrogenic effect and altered mammary promoter hypermethylation in healthy premenopausal women [49]. Low circulating levels of genistein were associated with decreased methylation of RARβ2 and CCND2, whereas promoter methylation of these genes increased with high circulating levels. Hypermethylation of both RARβ and CCND2 is correlated with breast carcinogenesis. The fact that the circulating levels of genestein may influence the direction and methylation levels represents important evidence of potential for epigenetic regulation by isoflavones in breast tissue.

The effects of isoflavones in mammary tissue have been related to either stimulation or repression of a number of processes. Pathways and processes that are stimulated by isoflavones include cell cycle arrest, apoptosis, cyclin-dependent inhibitors (p21 and p27), BRCA-1 and BRCA-2, PPARγ,MAPK signaling (p38 phosphorylation and JNK), and IGF-1 plasma levels. Conversely, isoflavones have been reported to downregulate cdc2 activity, Akt1, NFκB, AP-1, phosphorylation of ERK1/2, levels of VEGF and cell migration, xenobiotic metabolism, and enzymatic activities of estrogen sulfotransferases (SULT) [34]. The SULT enzymes regulate in endocrine tissue such as breast and endometrium the sulfonation of various substrates including estrogens and phenols [50].The chemical reactivity of isoflavones compared to that of estrogens may influence their preventative role in breast cancer. For example, genistein is metabolized to quinones with a short half-life, and it is subsequently hydrated to generate a catechol genistein which has estrogen-like properties, but low reactivity with DNA. Conversely, catechol estrogen quinones have a longer half-life and can damage DNA via depurination reactions [51]. Therefore, competition for quinone formation by genistein may reduce the formation of genotoxicquinone metabolites.

Epidemiologic evidence suggests that early-life environmental exposures are related to disease risk; it has been hypothesized that epigenetic dysregulation may be involved [52]. 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 [53].

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 [54].

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 [55] 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 [55].

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 [56]. 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 [57].

Histone modification may cause the silencing and unsilencing of genes [58-60]. 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 [58, 59]. 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 [61].

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 [62]. Other animal studies are beginning to identify specific sites of action of food components [63]. 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 [64].

Cancer prediction using embryonic stem cell gene signatures may be an area of growing importance [65, 66]. Several dietary components, including PUFAs, have been found to influence stem cells [67-69]. The response between healthy and cancer stem cells may ultimately lead to a better understanding of using bioactive food components for cancer prevention.Nutritional proteomics can identify and quantify bioactive proteins and peptides and address questions of nutritional bioefficacy [70]. 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 [71-73].

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 [74]. Metabolomic methods have been used to profile cells at various stages in carcinogenesis based on shifts in glucose metabolism [75]. Bioactive food components can modify these metabolic profiles at

various steps in glucose metabolism [76]. Metabolomics can also be used to determine mechanisms of action and/or bioavailability of bioactive food components. For example, Solanky et al. [77] measured urinary metabolites in premenopausal women who consumed soy in the form of textured vegetable protein containing conjugated isoflavoneglucosides 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 [77].

Conclusion

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 targets and also regulate the constitutive amount of the molecular targets requiring modification. Findings to date demonstrate that nutrigenomics and the downstream events like 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. The increase in cancer worldwide along with other non-communicable diseases, the impact of incorporating a personalized approach for using diet to curb risk holds enormous potential to improve quality of life.

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