

Mini-review

Nutrition and cancer: Essential elements for a roadmap

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Abstract

Personalizing nutrition for cancer prevention and therapy will require a comprehensive understanding of “genotypes/phenotypes” in order to identify, evaluate, and prioritize appropriate points for dietary intervention. This nutritional pre-emption roadmap must begin with accurately assessing intakes/exposures of which bioactive food component(s) is needed to bring about a desired response in critical cellular processes (carcinogen metabolism, DNA repair, cell proliferation, apoptosis, inflammation, immunity, differentiation, angiogenesis, hormonal regulation and cellular energetic) within an individual. Understanding this “individuality” through a better understanding of the “omics” is fundamental to arriving at the correct destination and thus interpreting biological variables which establish the magnitude or direction of a response to bioactive food components.

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1. Introduction

Belief in the medicinal powers of foods and its components is not a new concept, but has been passed down for generations as a strategy for improving health and productivity. In fact, almost 2500 years ago Hippocrates proclaimed it is best to “Let food be thy medicine and medicine be thy food.” While mounting evidence continues to point to eating behaviors as fundamental to health and disease prevention, there are numerous inconsistencies in the literature. Today, consumers are frequently confused by the mixed messages about the ability of foods and their constituents to influ-

ence health and/or the risk of chronic disease. The reason for scientific inconsistencies continues to be a major topic of research and debate among health professionals. Undeniably, the elucidation of appropriate strategies that utilize foods and dietary supplements to optimize nutrition to achieve one’s genetic potential, improve physical and cognitive performance, and to reduce risk of chronic diseases is indeed admirable in the current era of mounting health care costs [1,2]. While defining the most effective use of foods or components will not be simple, there is a growing body of scientific evidence to believe that such a personalized approach is feasible [3–5]. This review will discuss essential elements for developing a nutritional preemption roadmap for cancer prevention and therapy.

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2. Foods and bioactive food components

More than 25,000 different bioactive components are thought to occur in the foods consumed by human beings. More than 500 of these compounds have already been identified as possible modifiers of the cancer process and others will likely surface. These bioactive food components may arise from plants (phytochemicals), animal sources (zoochemicals), or mushrooms (fungochemicals) or from the metabolism of food components by bacteria within the gastrointestinal tract (bacterochemicals) [6]. This diverse array of dietary constituents may modify, either positively or negatively, cancer risk and tumor behavior [3]. Defining which food component is instrumental in bringing about a phenotypic change is exceedingly challenging because of the complexity of foods and the myriad of sites where food components may function. For example, some of the anticarcinogenic and antitumorigenic benefits attributed to garlic may arise from not only its allyl sulfur content, but also unique protein, flavonoids, specific minerals, or fructooligosaccharides [7]. Likewise, interactions among food may influence the overall response. For example, combining vitamin D₃ and genistein was more effective in suppressing the growth of prostate cancer cells at biologically achievable concentrations than when either agent alone. This response appears to relate to the ability of genistein to inhibit CYP 24 and thereby increase the half-life of vitamin D₃ [8]. It is likely that many other interactions among food constituents are occurring which have yet to be fully defined.

Rapid, accurate and inexpensive methods for assessing the intake of specific bioactive food components, both essential and non-essential nutrients, are fundamental to unraveling the relationship between dietary habits and cancer risk, yet represent a major methodological challenge. Undeniably errors in estimating food intakes, interactions among food components and incomplete data about nutrient content limit the usefulness of self-reported food consumption data. Because eating behaviors are exceedingly complex and may involve foods which are consumed intermittently and irregularly, self-reports for limited time periods are particularly prone to measurement error. Food frequency questionnaires (FFQ) and 24-h recalls are the two major dietary data collection instruments for estimating exposures, but are recognized to have significant limitations. Although FFQ are convenient, measure

long-term behaviors and are relatively inexpensive, they are limited by knowledge about particular foods and are hampered by the inability of individuals to accurately report their intakes retrospectively. A 24-h recall, while providing more in-depth information about the types and amounts of foods consumed, provides a rather poor estimate of long-term usual intakes. Despite the increased subject burden and cost, a 7-d diary has been reported to provide a far better estimate of exposures to dietary constituents, including protein and potassium, than found with the use of a FFQ [9,10]. Since absorption, metabolism, distribution and excretion may influence the amount of a bioactive food component that reaches the target site there is a need for methodologies which incorporate these variables. Combining intake assessments with analyses of tissue or fluid concentrations of a bioactive food component or metabolites (metabolomic profile), ideally at multiple time points, should offer special insights into individual responsiveness to individual and possibly prolonged term exposures.

Analytical problems associated with the compositional analysis of foods are in no way trivial issue for understanding the diet and cancer interrelationship. Reference standards are not always present and the matrix can have a profound influence on the bioavailability of components within foods and/or dietary supplements [11]. Growing conditions and processing can also markedly influence the composition of a food and represent another variable that needs to be considered in developing an effective roadmap [12]. The complexity of dealing with foods is illustrated by the known effects of genotype where glucoraphanin concentrations in broccoli can vary more than 25-fold [13].

3. Nutritional genomics

The study of nutritional genomics has the potential to help identify definitively which components in foods bring about either positive or negative consequences, and to clarify their relevant mechanisms of action and most importantly when they can be manipulated for health promotion and disease prevention [5,6,10,14–16]. Knowledge about how diet-induced phenotypic responses depend on an individual's genetic background (nutrigenetics), the expression of genes (epigenomics and transcriptomics), changes in the amounts and activities of proteins (proteomics), and shifts in small molecular weight compounds (metabolomics) – collectively referred

to as “-omics” – will be key to identifying responders from non-responders. The complexity of this undertaking is evident by the literally thousands of bioactive food components which can influence health, both positively and negatively [5,6,10]. Understanding the importance of the effective intakes/exposures of these food components necessary to influence key cellular processes is fundamental to unraveling the diet-health conundrum and to the establishment of a realistic roadmap for optimizing diet for health promotion [5,10].

Epidemiological studies continue to provide important clues about the likely importance of multiple foods and components as deterrents to cancer. However, controlled-intervention studies such as ATBC, Polyp Prevention Trial, WHEL, etc. also provide mixed messages about the physiological significance of dietary change [17–19]. Controlled-interventions may also provide erroneous information because of the quantities of the test agent examined, the duration of the intervention or the subjects examined. Unquestionably a meaningful roadmap must take into consideration the totality of information whether consistent or not with current hypothesis and beliefs. Variation in response may reflect timing of the amount and duration of exposure to a specific bioactive food component and to its interactions with multiple food constituents, environmental factors, the genetics of the consumer, or a combination thereof. Evidence of the variation across 11 studies that have examined colorectal cancer risk as a function of increased calcium intake [3]. The response was only statistically decreased in 3 cases. In one case higher intakes was associated with an increased risk in women, but not in men. When meta-analysis was restricted to 8 studies the summary estimate was 0.95 per 200 mg/day with no evidence of heterogeneity [3]. Thus, while calcium was associated with protection the overall response was relatively modest. While even a relative small change can have profound implications in large population, one wonders if the change in risk is really a reflection of a larger response in a subpopulation. Evidence this might be the case comes from studies which report that inadequate calcium intake is associated with increased colorectal cancer risk in those with the Ff and ff genotypes for Vitamin D Receptor FOK1 polymorphism [20]. Polymorphism in this receptor involving a T to C substitution at position 2 exon 2 has been identified with lower calcium accretion in children [21]. The biological bases by which this polymorphism might influence cancer

risk remains to be determined. Regardless, these data suggest that vulnerable individuals with inadequate calcium consumption may have an almost threefold higher risk of developing colon cancer; again considerably greater than the roughly 20% reduction seen in population studies with greater calcium exposures. Recently the association of VDR haplotypes has been examined in two large case-control studies [22]. While the CDX2 polymorphism was not independently associated with colon or rectal cancer nor several dietary components, the bLFA haplotype (*Bsm1* b, or B, poly(A) L, *Fok* F, and CDX2 A polymorphisms) was associated with an increased risk of colon cancer. It is important to recognize the frequency of a polymorphism can vary markedly across populations as evident of a frequency of the A allele of the CDX2 polymorphism which occurred in 19% of non-Hispanic whites, 21% of Hispanics, 76% of African-Americans, and 47% of Asians. These data suggest that haplotype analysis that encompasses different domains of the VDR gene might further enhance the understanding of importance of dietary calcium as a deterrent to cancer. The use of polymorphism information may offer opportunities for identifying individuals who will benefit maximally or be placed at risk because of dietary change.

Several additional polymorphisms have been linked to the ability of dietary components to modify cancer risk including glutathione peroxidase, glutathione-S-transferase, myeloperoxidase, estrogen receptor B, and cytochrome P450 genes [23–27]. Unfortunately, these findings remain largely observational and have not been consistently reproduced. More importantly, the biological bases by which polymorphisms influence cancer risk or tumor behaviors has not been substantiated in controlled preclinical or clinical intervention studies. Studies are desperately needed to verify the physiological significance of genetic polymorphisms in modifying the response of bioactive food component to influence one or more cancer related process. While individual variation in the genetic constitution may be key in determining the responses to diet the millions of SNPs in the human genome [28] make unraveling this connection extremely daunting. Regardless, genomic data for human and mouse (including SNPs, expressed sequence tags, gene expression patterns, and cluster assemblies) and cytogenetic information are increasingly becoming available through a number of databases; and thus provide opportunities to evaluating

genomics as a factor in explaining variation in response to food components in terms of growth, development, performance, and disease resistance.

3.1. Copy number is also a variable

Understanding gene constitution-nutrient interactions is further complicated by variations that can occur in copy number. Copy-number variation is the most prevalent structural variation in the human genome and thus can contribute significantly to genetic heterogeneity [29]. Variation in copy number has been reported for α -amylase and several cytochrome P450 genes [30,31] and likely occurs in many others. Increased α -amylase copy number has been related to prior history of starchy food intake [31]. Regardless of this historical reason for copy number this variation likely contributes to some of the differential response to food components across individuals.

3.2. Epigenetics as another biologic determinant

The classic view of cancer is that genetic alterations damage the structure of DNA and thereby induces mutations which manifest in abnormally functioning proteins that thereby precipitate diseased conditions. More recently, evidence has surfaced about the role of epigenetic alterations during disease development, including cancer [32–34]. Genes involving cell cycle regulation, DNA repair, angiogenesis, and apoptosis are all inactivated by the hypermethylation of their respective 5' CpG islands. Key regulatory genes – including E-cadherin, pi-class glutathione-S-transferase, the tumor suppressors cyclin-dependent kinases (CDKN2) and phosphatase gene (PTEN), and insulin-like growth factor (IGF-II) targeted histone acetylation and deacetylation – are influenced by DNA hypermethylation. The intake of multiple food components ranging from vitamin A to zinc and including both non-essential and essential components have been reported to influence DNA methylation patterns [33]. Classical studies demonstrate that methyl deficient diets lead to marked changes in methylation patterns at least some of which is consistent with alterations observed when a normal cell transforms to a neoplasm [35]. Restoring proper methylation may represent a fundamental process by which some bioactive food components may function to influence gene expression patterns. For example, Fang et al. [36] have

demonstrated that genistein and related soy isoflavones can reactivate methylation-silenced genes, partially through a direct inhibition of DNA methyltransferase.

Silencing and unsilencing of genes can occur through modification of histones, as well as by changes in DNA methylation [37–39]. In addition to factors that govern the overall recruitment and release of histones (histone occupancy), there is a complex interplay of reversible histone modifications that govern gene expression, including histone acetylation, methylation, phosphorylation, ubiquitination and biotinylation. Modification of histone deacetylase (HDAC) has surfaced as one strategy for changing tumor behavior [38,39]. Interestingly, several food components including butyrate, diallyl disulfide and sulforaphane have been reported to function as weak ligands for this enzyme and lead to reduced in vitro activity [38,40]. Sulforaphane, an isothiocyanate found in cruciferous vegetables, addition to cell cultures leads to a concomitant increase in global and local histone acetylation status including the promoter regions of P21 and bax genes. Most recently Dashwood and his research team have demonstrated that sulforaphane feeding markedly changes HDAC activity in humans [40].

4. Normal versus neoplastic conditions

A fundamental issue remains about under what circumstances bioactive food components bring about their primary affect; namely are they maintaining normal cellular function, influencing the transition of normal to neoplastic state, or altering the biological behavior of the neoplasm. Evidence exist that all three conditions can have importance in influencing cancer risk and tumor behavior but that the biological mechanism may be unique for each. A wealth of evidence points to the ability of several bioactive food components to modify phase I and II enzymes and thereby help maintain normalcy in a cell [6,41]. Unquestionably, modifying carcinogen metabolism and disposition is one of the major mechanisms by which dietary compounds can reduce cancer risk. The expression of phase I enzymes, which activate many carcinogens, is established by xenobiotics sensing nuclear receptors such as AhR, CAR, PXR, and RXR. Phase II enzymes catalyze the conjugations of carcinogens and frequently are transcriptionally controlled by the Nrf2/ARE signaling pathways. Thus, the Nrf2/ARE signaling pathway likely represents a major

target for several bioactive food components. If several food components are influencing the same site then potential synergistic or antagonist interactions are possible depending on the amounts consumed and the basal concentrations of the target proteins.

The excretion of carcinogens and their metabolites is likely mediated by phase III transporters, which share common regulatory mechanisms with phase I/II enzymes. Indeed, the expression of metabolizing enzymes and transporters is often coordinately regulated. In addition to transcriptional regulation, the activities of phase I/II enzymes and phase III transporters could be directly activated or inhibited by dietary compounds. The response to several bioactive components does not appear to be particularly tissue specific, yet is very dependent of the quantity consumed and the duration of exposure. Genetic polymorphisms may profoundly influence the response to a dietary component. Polymorphisms may influence the metabolism and excretion of dietary cancer preventive compounds and thereby alter their ability to induce or suppress metabolizing enzymes or transporters [41–43]. Differential response to dietary cancer preventive compounds may also relate to the variant of the enzyme being modified. For example garlic appears to lead to an autocatalysis of CYP2E1, but does not appear to influence other CYP450s in the same manner [44]. Likewise, polymorphisms in the regulator region of metabolizing enzymes/transporters, such as AhR, CAR and PXR, may also influence the overall response to bioactive food components [41,45].

There is limited evidence that bioactive food components can also influence the transition of normal to neoplastic cells. Classically, feeding a methyl donor deficient diet precipitates increased liver cancer, even in the absence of a carcinogen exposure [35]. More recently studies have demonstrated that feeding a diet high in fat, but low in calcium and vitamin D and thus similar to that consumed as part of a Western diet, has been demonstrated to markedly increase colon cancer in rodents [46]. It is unclear why there are few cases where deficiencies or inadequacies lead to cancer, but may relate to the ability of the cell to adjust and survive through changes in autophagic homeostasis [47].

A wealth of evidence also exist that multiple food components can alter neoplastic proliferation as well as scheduled cell death (apoptosis) [16,48–50]. Key transitions in the cell cycle are known to be regulated by the activities of various protein kinase

complexes composed of cyclin and cyclin-dependent kinases (CDK) molecules and to be influenced by multiple dietary components. Evidence that both essential and non-essential dietary agents can modulate cell cycle checkpoints, and thus contribute to reduced tumor proliferation, continues to mount [6,48–50]. Diverse agents such as apigenin (celery, parsley), curcumin (turmeric), (–)-epigallocatechin-3-gallate (green tea), resveratrol (red grape, peanuts and berries), genistein (soybean), and allyl sulfur (garlic) have been shown to markedly influence the cell cycle and possibly by differing mechanisms. At least some of these changes may be associated with posttranslational changes including shifts in the phosphorylation of key regulatory factors of cell division [51].

Many food components may alter tumors by precipitating cell death [16,52–53]. Apoptosis is recognized to occur primarily through two pathways including the intrinsic, mitochondrial-mediated pathway and the extrinsic, death receptor-mediated pathway [16]. Dietary components can modulate apoptosis through shifts in protein expression and function or mRNA expression, either directly or indirectly, to modulate gene expression in both pathways. At least some bioactive components may cause apoptosis by enhancing free radical formation in the cell [52,53]. While the evidence that multiple dietary components can induce apoptosis there are always concerns that the concentrations frequently used are excessive and may not therefore reflect what happens with more physiological exposures.

5. Multiple sties of action

Since cancer incidence is projected to increase during the foreseeable future (<http://seer.cancer.gov/>) there is a desperate need for defining effective prevention strategies. Fortunately, mounting evidence continues to highlight dietary change as an effective and cost-efficient approach for reducing cancer risk and for modifying the biological behavior of tumors [3]. Predictive, validated and sensitive biomarkers, including those that reliably evaluate “intake” or exposure to a specific food or bioactive component, that assess one or more specific biological “effects” that are linked to cancer, and that effectively predict individual “susceptibility” as a function of nutrient-nutrient interactions and genetics, are fundamental to establishing a roadmap for those who will benefit most from dietary

interventions. Collectively each suite of biomarkers must be accessible, reliably assayed, and predictive of one or more key process (es) involved with cancer (Fig. 1). Current information suggest that change in multiple cellular processes may account for the response to bioactive food components and thus represent a pleiotropic response, unlike that which frequently occurs with drugs. Multiple processes including carcinogen metabolism, DNA repair, cell proliferation, programmed cell death, inflammation, differentiation, and angiogenesis are likely modified by bioactive food components (Fig. 1) [6,10]. Since multiple biological changes can occur simultaneously, it is difficult to determine which is most critical in dictating the overall response. The ability of multiple nutrients to influence the same process suggest synergistic, as well as antagonistic interactions, may occur depending on exposures.

The monitoring of transcriptional mRNA expression (transcriptomics) caused by food compo-

nents represents another intriguing possibility for identifying those individuals who might be most responsive to dietary change. Vitamins, minerals, various phytochemicals, and macronutrients have been reported to significantly modify gene expression patterns associated with biological responses including those associated with metabolism, cell growth, apoptosis, differentiation, and immunocompetence. Genome-wide monitoring of gene expression using DNA microarrays allows the simultaneous assessment of signatures of tens of thousands of genes and of their relative expressions between normal and diseased conditions [54]. Adaptive processes are known to occur after ingesting foods or components for prolonged periods. Therefore, caution must be used with interpreting microarray analysis since often only a single point-in time observation is being made. Repeated temporal measures may be necessary to truly understand the responsiveness of individuals to dietary change.

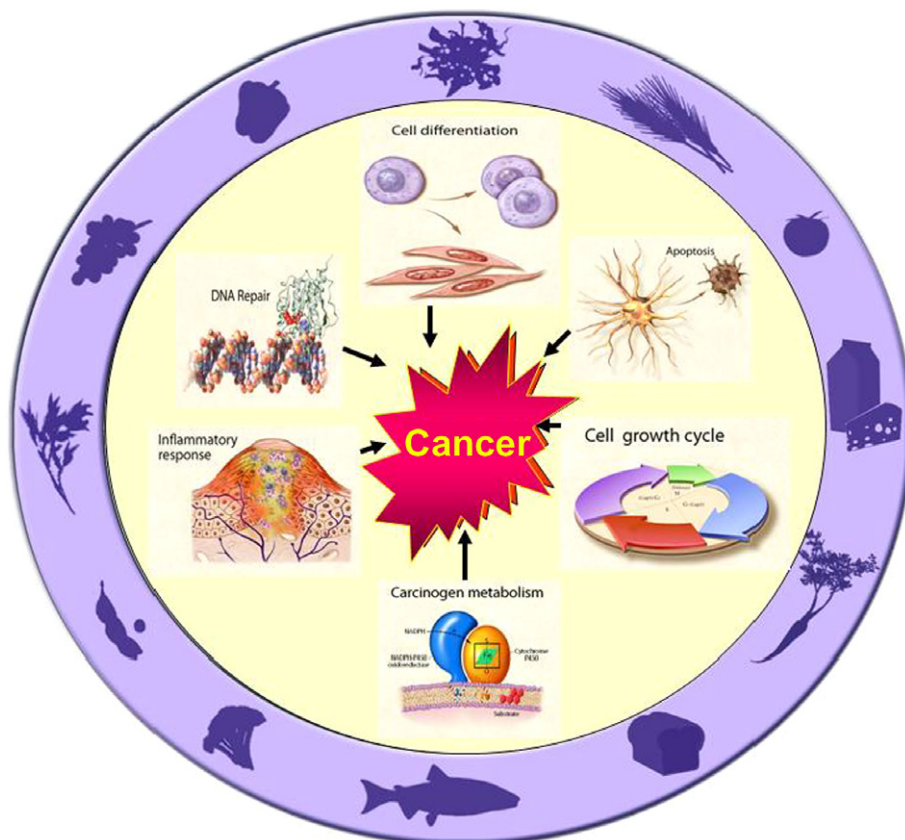


Fig. 1. Bioactive components present in food can influence molecular targets associated with multiple biological processes. Cell proliferation, apoptosis, angiogenesis, carcinogen metabolism, cell differentiation, hormonal regulation, DNA repair and inflammation have all been associated with cancer risk and tumor behavior. Evidence exists that each of these processes can be influenced by one or more foods and their constituents.

Regardless, recent intervention studies by Lin et al. [55] have reported that consumption of a low fat, low glycemic load diet can lead to marked changes in the expression of over 20 genes in human prostatic tissue for 6 weeks. These investigators suggest a molecular approach to health and disease may help individualized appropriate interventions based on cellular signature changes brought about by diet. It is noteworthy that significant changes in expression can occur within a few hours after consuming a food as reported by van Erk et al. [56] when breakfast cereals were provided. Thus, a bolus approach to a food or component may represent a relative inexpensive approach to determine if a nutritional intervention strategy is appropriate, especially if the price of chips continues to decrease. To prevent transcriptomics from becoming totally descriptive greater attention is needed to determine why patterns are being modified by food components. Linking transcriptomics with proteomics and metabolomics with add to the ability to interpret findings [4,57].

The use of animal models, transgenic and knockouts, will be fundamental to elucidating the specific site(s) of action of bioactive food components. Knockout mice have already assisted in identifying the nuclear factor E2 p45-related factor 2 (Nrf2) and the Kelch domain-containing partner Keap1 as the complex that is modified by sulforaphane [41,58]. Gene expression profiles from wild-type and Nrf2-deficient mice fed sulforaphane have shown several novel downstream events and thus more clues about the true biological response to this food component. Another potential target for retarding cancer recurrence that has surfaced is the over-expressed human epidermal growth factor receptor 2 (HER-2/neu), which is treated by the monoclonal antibody Herceptin. Interestingly, recent studies by Yee et al. [59] suggest that fish oil may be as beneficial in retarding over-expression of Her2-nu as is Herceptin.

6. Timing and quantity are critical factors

Timing and duration of exposures are likely important factors determining the overall response to foods or supplements. In rats the timing exposure to dietary genistein was determined to be exceeding important in determining mammary cancer risk [60]. In this mammary model treatment with genistein protective after prepubertal and combined prepubertal and adult genistein treatments, but was not

effective after prenatal- or adult-only treatments. Humans may also respond best with prolonged exposures since in a case-control study an inverse relationship was observed between adolescents, soy food intake and breast cancer incidence later in life, however protection was not evident when intakes began later in life [61].

The Women's Intervention Nutrition Study (WINS) study provides evidence that long-term exposure may be needed to detect a biological response to dietary change [62]. In this randomized, prospective, multicenter clinical trial the effect of a dietary intervention designed to reduce fat intake in women with resected, early-stage breast cancer receiving conventional cancer management was tested. This study provided evidence that approximately 4 years was required to detect a response to the reduced consumption of diet fat. The hazard ratio of relapse events in the reduced fat intervention group compared with the control group was 0.76. Additionally, this study provided evidence that a subgroup of individuals, namely ER negative individuals, were most responsive to a reduction in dietary fat.

Data from the General Population Trial in Linxian, China, demonstrated that individuals who received a supplement containing beta-carotene, vitamin E and selenium, had a 13% reduction in cancer mortality. Post-intervention follow up indicated that the beneficial effects of the supplement were evident and were magnified up to 10 years after termination of the supplementation program [63]. The benefits were greater in individuals who were <55 years at the beginning of the intervention. Cancer risk appeared to increase in those who started supplements usage when beyond 55 years of age [63]. These findings suggest that sustained exposure may not always be necessary to bring about a desired outcome. Undeniably a better understanding of temporal relationships will be needed if appropriate preemptive models are to be forthcoming. Finally, it is certainly conceivable that the observed response in risk as a function of age was possibly reflecting differences in the frequency of preneoplastic conditions.

7. Future

A roadmap is needed for nutrition and cancer prevention that builds on discovery, development and delivery (3Ds) and thus represents a seamless, integrated template for initiating and conducting

investigations. The importance of this 3Ds pathway comes from successes with tamoxifen and Herceptin [64,65]. Undeniably, greater attention is needed to characterize how specifically nutrition science relates to health and disease prevention. To define this path it is critical to identify cellular processes that are modifiable by physiologically relevant exposures to food or their components and how modifications of these pathway leads to a change in cancer risk or tumor behavior. Although there are many molecular pathways that may be influenced, they can likely be collated in essential elements for cancer as described previously [6,10,66]. Since the interaction between cellular metabolites and specific targets is dynamic, knowledge regarding genetics, susceptibility factors, timing, and degree of exposure to food components is fundamental to developing a realistic preemptive roadmap for cancer prevention. The future rests with the ability to detect subtle and predictive changes that occur prior to gross phenotypic changes reflecting cancer. The integrated analysis of the ‘omics’ should provide sensitive detection methodologies for evaluating which individuals may be most from dietary change. While the “discovery” phase of the roadmap is fundamental to identifying responsive subpopulations, its usefulness will depend on moving this knowledge into a “development” phase where actual interventions are examined for improved prevention, detection, diagnosis, and treatment. The final “delivery” phase will be to create appropriate strategies for provided preemptive information to those most in need. While creating a nutrition and cancer prevention roadmap will not be simple, the societal implications are enormous.

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