SUPPLEMENT ARY MATERIALS

1. Dietary Factors and Natural Products

The concept that dietary factors may prevent cancer is largely derived from epidemiological studies showing an inverse association between cancer incidence and intake of certain nutrients such as selenium, vitamin E and β-carotene (Wynder, 1977; Reddy, 1980; Peto, 1981). Because of the involvement of reactive oxygen species (ROS) in carcinogenesis, the hypothesis that these antioxidant nutrients could prevent cancer was a very popular idea in the early 1980s. This hypothesis has been successfully tested in some studies in populations with insufficiencies in certain nutrients (Blot, 1993), but not in trials in populations that are sufficient in these nutrients (The Alpha-Tocopherol, Beta Carotene Cancer Prev. Study Group, 1994; Gaziano, 2009; Lee, 2005; Lippman, 2009). In the Linxian Nutrition Intervention Trial, supplementation with a combination of α-tocopherol, β-carotene and selenium was found to decrease mortality due to gastric (mainly gastric cardia) cancer by 21% and total cancer mortality by 13% (Blot, 1993). Nested case-control studies also showed that the blood levels of α-tocopherol and selenium were low and inversely associated with gastroesophageal cancer risk (Taylor, 2003, Mark, 2000). Results from a 10-year follow-up showed that the protective effects of the combination of α-tocopherol/β-carotene/selenium on gastric cardia cancer still persisted. A preventive effect of this nutrient combination against esophageal squamous cell carcinoma was observed only in subjects with enrollment ages younger than 55 years old (Qiao, 2009). It is possible that the intervention was effective only in younger subjects because they had lower grade or no precancerous lesions, while the older subjects had more severe lesions. This is consistent with the result of a parallel trial on subjects with esophageal dysplasia, showing that supplementation with multiple micronutrients did not produce a significant beneficial effect (Li, 1993). Studies in a rat model also demonstrated that deficiencies in vitamin E and selenium enhanced methylbenzylnitrosamine-induced esophageal carcinogenesis, and

supplementation with these nutrients at the early stage (but not the late stage) of carcinogenesis had a protective effect (Yang, 2011).

On the other hand, in the Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention Study, supplementation with β-carotene to Finnish smokers not only did not decrease but actually increased lung cancer incidence (The ATBC Cancer Prev. Study Gr. 1994). Similarly in the Nutritional Prevention of Cancer Trial, supplementation with selenium-enriched yeast failed to prevent skin cancer (Clark, 1996). However, secondary endpoint analyses of these studies, showed that supplementation with α-tocopherol or selenium reduced the incidence of prostate cancer (The ATBC Cancer Prev. Study Gr. 1994, Clark, 1996). It was also demonstrated that supplementation with selenium produced protective effects against prostate cancer in individuals with low, but not high, baseline serum levels of selenium (Duffield-Lillico, 2003). These results provided the rationale for launching the Selenium and Vitamin E Cancer Prevention Trial (SELECT). This large scale trial with daily supplementation of 400mg of α-tocopherol and 200 μg selenium (from L-selenomethionine) in a 2x2 design, however, yielded disappointing results (Lippman, 2009; Klein, 2011). The lack of cancer prevention effect by α-tocopherol, or in combination with vitamin C, was also demonstrated in other studies (Gaziano, 2009; Lee, 2005). There are many interpretations of these unexpected results (Yang, 2012). However, a simple explanation is that supplementation with nutrients would reduce the risk for certain cancers only in populations that are deficient in these nutrients. Since insufficiency in certain micronutrients is still common, even in some individuals in “well-fed” societies, predetermining the nutritional status of individual subjects is important before launching an intervention study with nutrients or related agents.

Non-nutritive natural products. The idea that plant-derived products can prevent cancer derived from early studies that rodents on a chow diet were less susceptible to carcinogenesis than those on a semi-purified diet, and that supplementation with the semi-purified diet with dried cabbage and orange oil inhibited carcinogenesis (Wattenberg, 1983). Subsequently, extensive research in this area has been conducted by many investigators. (Bode, 2009) While numerous interesting results from studies in animal models and cell lines have been published, only a small number of human studies (mostly small trials) have been conducted and the results have been inconsistent. The conditions of the human trials, which were usually conducted in high-risk populations, are quite different from the conditions used in laboratory studies. Because of the expenses and time required, many human cancer preventions trials cannot test agents that prevent cancer at the initiation (or promotion) stage of carcinogenesis. In many cases, we have to rely on biomarkers or surrogate markers. For example, both broccoli sprout preparations (rich in sulforaphane) and green tea polyphenols have been shown to increase carcinogen detoxifications (Kensler, 2005, Tang, 2008). Judging from the strong epidemiological data linking frequent consumption of plant-based food and low cancer risk (WCRF; a Global Perspective 2007), further research on cancer prevention by dietary constitutes is still needed, using either a “whole food or green chemoprevention” approach or a “single compound” drug approach. Many non-dietary phytochemicals, such as those in medicinal herbs, have strong anti-inflammatory activities (Yuan, 2000; Jiang, 2005; Zhou, 2015). Such anti-inflammatory agents could also be studied for developing cancer prevention agents. Many human intervention trials with nutrients and other natural products have failed (Martinez, 2012; Potter, 2014) because of insufficient understanding of the biochemical and pharmacological properties of the agent, misinterpretation of the epidemiological data, or over-interpretation of the laboratory results.

Dietary supplement trials resulted in largely negative findings (Bjelakovic, 2007; Mayne & Cartmel, 2006). The only study among the beta-carotene trials that demonstrated a beneficial

effect was conducted in individuals with persistent low intake of several micronutrients (Blot, 1993). For nutrients and bioactive food components, a bell-shaped curve with adverse effects at both ends of the curve is now a fairly well-established expectation (Mulholland & Benford 2007; Dwyer 2014). An alternative to the reductionist approach is to focus on and test effects of dietary modification.

Several intervention studies have examined the effect of dietary modification on cancer risk and progression, including large studies focused on the primary prevention of cancer (Prentice 2006; Klein 2011), as well as studies focused on reducing recurrence of preneoplastic lesions, and a few focused on reducing risk for new cancer events in patients with a history of cancer (Mayne & Cartmel 2006; Pierce 2007). Interpretation of the results of these studies involves consideration of several important issues.

One critical issue is the baseline nutritional status and dietary intakes of the target group, which affects whether or not the prescribed diet is likely to promote a change in risk status (Pierce, 2007). Data on the actual degree of change necessary to optimize status relative to cancer risk are limited. (Trumbo, 2008; Maki, 2014)

Few women in the large Women's Health Initiative diet trial met the goal of <20% energy from fat, and there was only a 5.7% increase in serum carotenoids (a dietary biomarker of vegetable/fruit intake) at year 3 of that study (Beresford, 2006). In the Polyp Prevention Trial, the difference in fruit and vegetable intake between intervention and control groups was 1.1 servings/1000 kcal (Lanza, 2001). Typically, adherence declines over time, so initial changes in diet will be reduced considerably throughout the course of the study. Actual exposure to differential intakes across groups is likely much less than anticipated or prescribed, and dietary recall data (with well-established inaccuracies) do not provide sufficient reassurance of compliance.

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2. Interpretation of the Nature of Carcinogenesis and Its Effect on Preventive Interventions

The major issue discussed in this supplement is the generally neglected consideration that carcinogenesis is not a linear continuum, but one that is interrupted; a consequence of the introduction of new genetic and epigenetic changes. This reconsidered revelation impacts the interpretation of chemoprevention effects in a fundamental way and hence forces a basic rethinking of the entire field.

Much has been written about the cancer process as a continuum (Figure 1a) including our own work. The central belief of this model is that by measuring a biological parameter early in the process, that this information can be used to predict therapeutic effectiveness and clinical outcome later. However, extensive studies of the genomics of cancer progression in a wide variety of cancers clearly indicates that the continuum is genetically discontinuous and dependent on key genetic and non-genetic changes that advance or inhibit the process (Figure 1b). Recent results from early stage intervention trials dramatically underscore the practical implications of this phenomenon (Figure 1c and 1d).

- Folate administration in patients at risk for colon cancer was effective in reversing early stage lesions but enhanced the progression of late stage lesions to an aggressive malignancy. (Cole, et al.)
- At the opposite extreme, NSAIDS failed to cause regression of the pre-malignant cutaneous lesion actinic keratoses, but over time decreased the development of cutaneous squamous cell cancers (Elmets, 2010; Guerrero, 2013; Elmets, 2014).

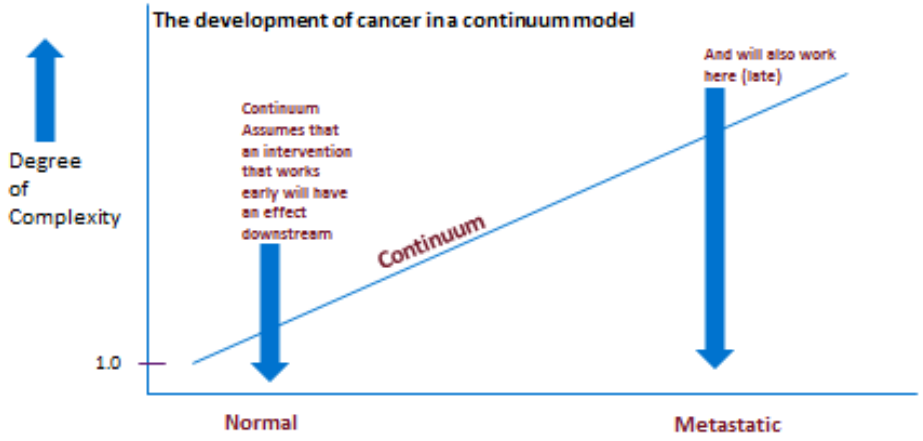
These types of results produce a real conundrum for chemoprevention agent development and also call into serious question the value of pre-clinical *in vitro* studies as a means to select compounds for clinical development and animal studies as predictive for the

disease process. At the very least, a fundamental reassessment of this process is in order as much time, effort, and expense has been expended in the past.

The process of development of biomarkers for preventive approaches of the carcinogenic and malignant process must also be challenged by the non-continuum paradigm (Baker and Kramer, 2007). On the one hand, the usefulness of tumor biomarkers once frank cancer is evident is clear in many malignancies and beyond reproach; however, the relatively new attempts to understanding dormancy and the metastatic process is still in its infancy and the role of biomarkers is less definitive for management of late relapses, (Hord, 2007) particularly important consideration for cancer survivors. Finally, an increased understanding of the genetic alterations present in cancers that drive the malignant process has resulted in new therapies in various cancers; two prominent examples in the treatment arena being the highly effective tyrosine kinase inhibitors (Imatinib and later related analogs) for CML (Desogus, 2015) and revealing and hopeful responses to $BRaf_{mut}$ inhibitors for incurable metastatic melanomas (Dossett, 2015).

We conclude: notwithstanding the issue of the relevant outcome unit for therapeutic analysis when N=1 and its impact on the development of preventive interventions evolving (Mathijssen, 2011; Doroshow, 2010; Kummar, 2011) an increased understanding of the carcinogenesis process in the human situation needs to occur in each tumor type for us to make progress in developing effective and non-toxic (chemo)prevention agents . The field needs to move beyond general concepts of carcinogenesis to targeted organ site prevention approaches in patients at high risk, as is now being done for several cancers.

1a.



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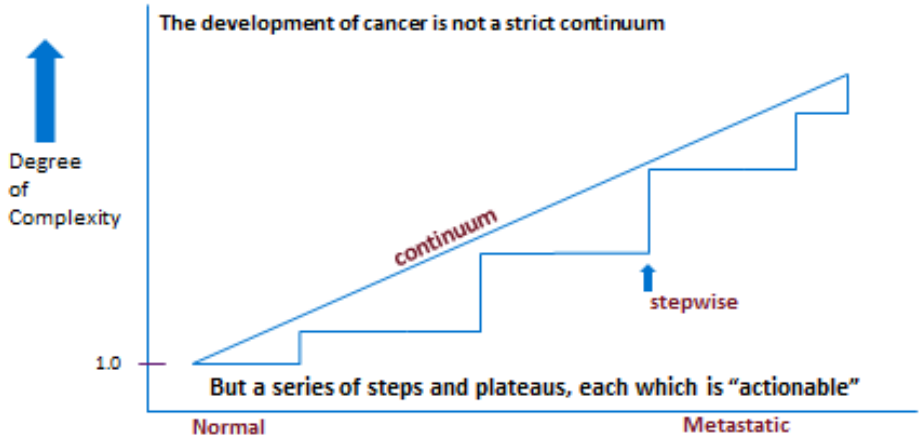
1b.



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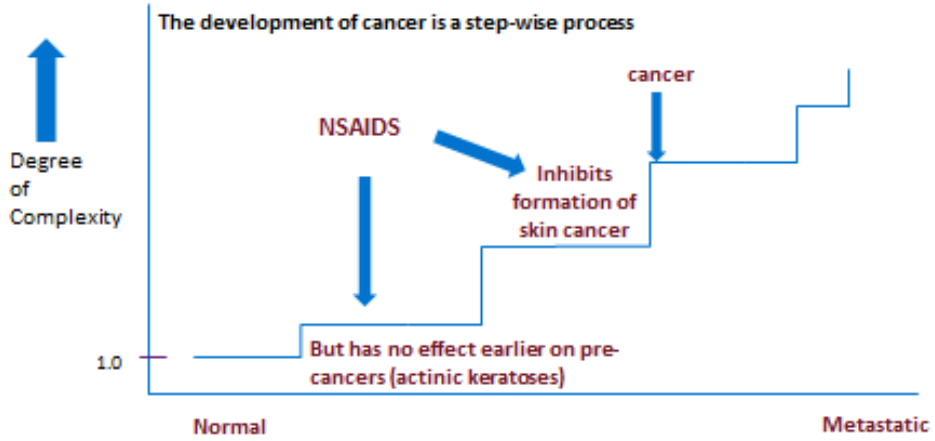
1c.



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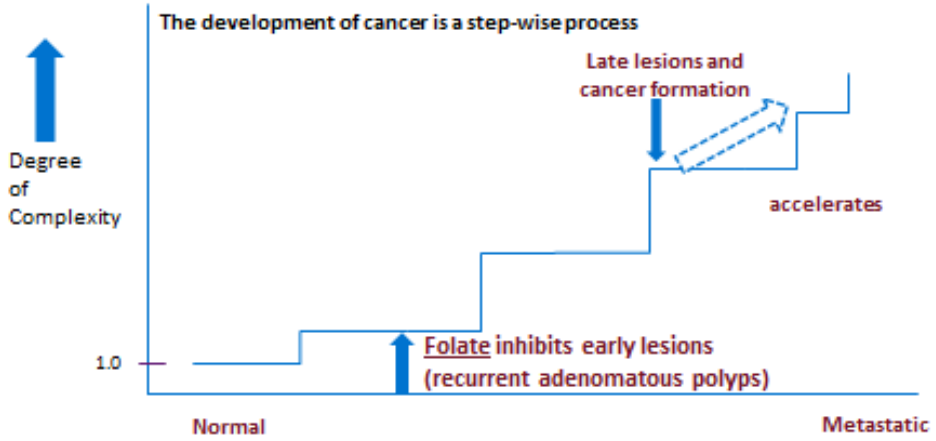
1d.



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3. Ancillary Issues

Cancer Survivorship. It is estimated that there are more than 14 million cancer survivors in the U.S. as of 2014 and this number is predicted to reach 19 million by 2024 (DeSantis, 2014). Just in the past 10 years, prospective clinical trials adding “best supportive care" to standard chemotherapy have documented significant quality of life and psychosocial improvements (Greer, 2012). While the focus of cancer management must be on the primary, multidisciplinary treatment of invasive disease, considerably more planning and effort is being targeted to both acute and chronic follow up of the surviving patients.

High impact cancer education and health policy driving organizations, like the American Cancer Society are developing guidelines on survivorship care. (Diguilo, 2014) Complicating such care is the very real threat of cancer recurrence as well as an overall 15% increased lifetime risk of a second primary cancer. Those with a much higher risk include adult survivors of Hodgkin's Lymphoma, tobacco - use -related cancers, and childhood survivors of retinoblastoma, and Ewing sarcoma (Fraumeni, 2006). Clearly, these high risk populations not only require close surveillance, but serious consideration for preventive interventions, like tamoxifen to reduce the risk of a second contralateral breast primary (Fischer, 1989). Cancer survivorship gets more complicated in relation to patient age. There are considerably different management requirements for patients falling into categories of pediatric, young adults, older adult and geriatric patients. In 2004, the Children's Oncology Group published evidence-based guidelines for pediatric aged cancer survivors. (Landier, 2004) Clearly, comparable guidelines are needed for cancer survivorship best practices for the other three age category patients.

An Institute of Medicine publication in 2005 concerning the extreme importance of cancer survivorship planning and implementation reenergized this field of research and service

(Hewitt, 2005); however, the work that must be done to improve the level of survivorship care in the U.S. is overwhelming, because each cancer provides it's very specialized challenges, related to the type of cytotoxic and biological therapy utilized, the heterogeneous disease related co morbidities, average patient age and gender, among many others. Unfortunately, comprehensive cancer survivorship research, guidance and services, despite their extreme importance to patient quality of life and long-term survival, continue to be difficult to fund and the common practice will not change until a much greater national survivorship "voice" is developed in our cancer centers and community oncology practices.

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Comparative Effectiveness The Institute of Medicine defines CER as, “The generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition, or to improve the delivery of care” (1). The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels. Because the vast majority of primary prevention necessarily involves behaviors *outside* of the health care system, it is imperative that prevention studies are designed with consideration of current health behavior and the challenges of behavior change. Studies must include multiple stakeholders, including those that would support or pay for the intervention (e.g., communities, governments, health insurers).

VOI involves the application of methods from economic theory and decision analysis to estimate the humanistic and economic value of performing additional research to better understand the safety, efficacy and cost of technologies and interventions (2-4). In the context of investing in prevention research, VOI is based on the premise that investments in large scale prevention trials are costly but have the benefit of reducing uncertainty about whether we should “adopt” a prevention technology. The potential payoff from investments in prevention research was well illustrated in a recent evaluation of the economic return from the Women’s Health Initiative study of hormone replacement therapy (5). Because the trial provided unequivocal evidence of the risks and harms of hormone replacement therapy, it had a profound influence on prescribing patterns. As a result, the $260 million investment from NIH in the WHI estrogen + progesterone study provided more than $37 billion in economic returns, both as direct medical care savings and the value of lives gained. VOI can be used to make trial investment decisions and to help design trials to maximize their value to society. In either case, VOI helps researchers understand the potential implications of trials on behavior—and essential consideration of prevention research.

Establishing the benefit of new cancer preventive interventions will take years and possibly decades depending on the outcome being evaluated. In addition, the sample size for studies designed to show the impact of preventive interventions on cancer incidence rates or survival will likely involve thousands of patients. We believe that these unavoidable issues necessitate consideration of CER and VOI in designs and estimates of the economic return on investment in large scale prevention studies.

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