Bioactive Compounds and Cancer

Nutrition and Health

Adrianne Bendich, PhD, FACN, Series Editor

For other titles published in this series, go to
http://www.springer.com/series/7659

Bioactive Compounds and Cancer

Edited by

John A. Milner

National Cancer Institute, Health and Human Services, Rockville, MD

Donato F. Romagnolo

Department of Nutritional Sciences, The University of Arizona, Tucson, AZ

Forewords by

David S. Alberts, MD

Arizona Cancer Center, The University of Arizona, Tucson, AZ

Maria Lluria-Prevatt, PhD

Arizona Cancer Center, The University of Arizona, Tucson, AZ

and

Scott M. Lippman, MD

Department of Thoracic/Head and Neck Medical Oncology, M. D. Anderson Cancer Center, The University of Texas, Houston, TX

Humana Press

Editors

John A. Milner
Nutritional Science Research Group
Division of Cancer Prevention
National Institutes of Health
Executive Plaza North
Suite 3164
6130 Executive Boulevard
Rockville MD 20892
USA
milnerj@mail.nih.gov

Donato F. Romagnolo
Department of Nutritional Sciences
The University of Arizona
Tucson AZ 85721-0038
Shantz Building
USA
donato@u.arizona.edu

Series Editor

Adrianne Bendich, PhD, FACN
GlaxoSmithKline Consumer Healthcare
Parsippany, NJ
USA

ISBN 978-1-60761-626-9 e-ISBN 978-1-60761-627-6
DOI 10.1007/978-1-60761-627-6
Springer New York Dordrecht Heidelberg London

Library of Congress Control Number: 2010922882

Printed on acid-free paper

Humana Press is part of Springer Science+Business Media (www.springer.com)

Series Editor Introduction

The Nutrition and Health Series of books have, as an overriding mission, to provide health professionals with texts that are considered essential because each includes (1) a synthesis of the state of the science, (2) timely, in-depth reviews by the leading researchers in their respective fields, (3) extensive, up-to-date fully annotated reference lists, (4) a detailed index, (5) relevant tables and figures, (6) identification of paradigm shifts and the consequences, (7) virtually no overlap of information between chapters, but targeted, inter-chapter referrals, (8) suggestions of areas for future research, and (9) balanced, data-driven answers to patient/health professionals questions which are based upon the totality of evidence rather than the findings of any single study.

The Series volumes are developed to provide valuable in-depth information to nutrition health professionals and health providers interested in practical guidelines. Each editor has the potential to examine a chosen area with a broad perspective, both in subject matter and in the choice of chapter authors. The international perspective, especially with regard to public health initiatives, is emphasized where appropriate. The editors, whose trainings are both research and practice oriented, have the opportunity to develop a primary objective for their book; define the scope and focus, and then invite the leading authorities from around the world to be part of their initiative. The authors are encouraged to provide an overview of the field, discuss their own research, and relate the research findings to potential human health consequences. Because each book is developed de novo, the chapters are coordinated so that the resulting volume imparts greater knowledge than the sum of the information contained in the individual chapters.

"Bioactive Compounds and Cancer," edited by John A. Milner, Ph.D., and Donato F. Romagnolo, Ph.D., is a very welcome addition to the Nutrition and Health Series and exemplifies the Series' goals. This volume is especially timely as the number of research papers and meta-analyses in the clinical nutrition arena of cancer research increases every year and clients and patients are very interested in dietary components that have bioactivity and may be able to impact cancer prevention as well as reduce the adverse effects of cancer therapies. The editors have made great efforts to provide health professionals with the most up-to-date and comprehensive volume that highlights the key, nutrition, and cancer information available to date. They have combined their broad backgrounds in research as well as clinical practice to help the reader to better understand the relevant science while providing background information so that the reader can understand and appreciate the importance of the mechanisms of action of the bioactive components in their diets.

Drs. Milner and Romagnolo are internationally recognized leaders in the field of nutrition and cancer biology and have actively investigated the physiological roles of dietary bioactive compounds as modifiers of cancer risk and tumor behavior. The editors are proven excellent communicators and they have worked tirelessly to develop

a book that is destined to be the benchmark in the field because of its extensive review of the current state of the science with regard to dietary bioactive compounds and the complex interactions between diet, health, and the development and the progression of cancer. Dr. Milner is the Chief of the Nutritional Science Research Group, Division of Cancer Prevention at the National Institutes of Health's National Cancer Institute (NCI). In this capacity, Dr. Milner is responsible for helping to set the national strategy for cancer research. Prior to joining the NCI, Dr. Milner led the Department of Nutrition at The Pennsylvania State University for over a decade. He also served as the Director of the Division of Nutritional Science at the University of Illinois. Dr. Milner has served as the President of the American Society for Nutrition and as chair of the World Cancer Research Fund/American Institute for Cancer Research Mechanisms Working Group. In 2008, Dr. Milner received the David A. Kritchevsky Career Achievement Award in Nutrition from the American Society for Nutrition. Dr. Romagnolo is Professor of Nutritional and Cancer Biology at the University of Arizona and is a member of the Arizona Cancer Center, BIO5, and the Center for Toxicology. He has served as the chair of the Environmental Gene Expression Group of the Southwest Environmental Health Sciences Center. Thus, both editors are immersed in the discovery and implementation of research to better understand the effects of bioactive molecules from the diet on cancer development and control.

The editors have chosen 76 of the most well-recognized and respected authors from around the world to contribute the 33 informative chapters in the volume. Hallmarks of all of the chapters include complete definitions of terms with the abbreviations fully defined for the reader and consistent use of terms between chapters. Key features of this comprehensive volume include the informative Key Points and key words that are at the beginning of each chapter and suggested readings as well as bibliography at the end of each chapter. The volume contains more than 150 detailed tables and informative figures, an extensive, detailed index and more than 4,300 up-to-date references that provide the reader with excellent sources of worthwhile information about the role of diet, foods, food components, essential nutrients, bioactive phytochemicals, and their potential mechanisms of action in affecting cancer risk.

This comprehensive volume is divided into two major sections beginning with six introductory chapters, followed by the section on bioactive molecules divided into three logical subsections – eight chapters on dietary macro-constituents; eight chapters covering carotenoids, vitamins, and minerals; and the final section including 10 chapters on the most researched of the myriad of non-nutritionally essential bioactive components in the diet. The final chapter examines the challenges of communicating food and cancer relationships to consumers, clients, and patients. The volume begins with an introductory chapter that examines the overall cancer rates in the United States, the major cancer types, and the populations most affected by cancer. We learn that about 1.5 million new cancers will be diagnosed each year and over half a million persons will die from this disease annually. For both men and women, lung and bronchus cancers are the leading cause of cancer deaths even though most individuals think that breast and prostate cancers are the major cancer killers. There is an extensive discussion of the Surveillance, Epidemiology and End Results (SEER) Program from the NCI, and the numerous tables and figures provide examples of the cancer statistics for incidence and survival rates in

the US population. The next chapter reminds us that only about 5% of cancer cases are genetically inherited, whereas 95% are linked to environmental factors including diet. There is a clear explanation of the developmental phases of cancer and the potential for bioactive molecules in the diet to affect the early stages of initiation and promotion. As an example, the interactions between nutritional factors and genes, defined as nutrigenomics, are carefully examined so that the reader is provided with the basics of this new area of research. An excellent explanation concerning the newest research tools including high-throughput proteomic and metabolomic approaches are placed in perspective to better understand their value in nutrition and cancer research. Examples of bioactive compounds found in foods include essential nutrients such as vitamins and minerals and essential lipids; plant polyphenols, carotenoids, xenobiotics, and numerous other molecular entities. The complex interactions between the bioactive molecules and genetic components including histones, DNA methylation, transcription factors, cell cycle regulators, and other factors are introduced and explanations are provided so that the reader can better understand the importance of these interactions.

Cancer begins with changes in the cell's DNA and the next chapter comprehensively reviews the major changes that result is cellular malignancy and examines the data suggesting that certain dietary factors can interfere with the progression of cells through the steps resulting in a cancerous cell. The reader is alerted that dietary factors that affect cells in cell culture may not be effective in vivo. Dietary substances that are briefly discussed include resveratrol, sulforaphane, apigenin (a flavonoid found in many fruits and vegetables), curcumin, EGCG and quercetin, and several other examples that are examined in greater depth in subsequent individual chapters. Within the cell, changes in single nucleotides (single nucleotide polymorphisms or SNPs) can result in changes to the structure, function, and/or the cellular content of a specific protein. If the SNP is located in genes involved in the metabolism of bioactive dietary factors, then this genetic change can result in alterations in cellular responses to potential carcinogens as one example. The next chapter, on nutrigenetics, closely examines nutrient–gene interactions. The epidemiological associations between antioxidants, folates, and dietary phytoestrogens, and reduced risk as well as the associations between meats and the compounds generated during cooking and increased cancer risk are reviewed with the aid of informative figures. Epigenetic processes that can alter the regulation of genes is the logical topic of the next chapter and it concentrates on the importance of dietary sources of methyl donors including folate, choline, and methionine. The final chapter in the introductory section examines the role of transcription factors that can initiate changes in the DNA in cells and the potential for dietary factors to modulate the actions of these transcription factors. The information contained within the first six chapters provides the reader with a firm grounding in the complexities of the cellular events that ultimately can lead to cancer and informs the reader of the newest research to identify key components in the diet that may be able to reduce the risk of forming cancerous cells.

The second section begins with the subsection on macro-constituents and the first chapter concerns the macronutrients, obesity, and the potential for calorie restriction (using diets that provide the full measure of essential nutrients in a calorie restricted matrix) and physical activity to reduce cancer risk by altering the synthesis of endogenous hormones and growth factors that are stimulated by caloric intakes. In addition

to macronutrients, diets contain fiber that is defined as the plant parts that are resistant to hydrolysis by human gastrointestinal (GI) enzymes. The importance of fiber (prebiotics) as well as metabolic products of the probiotic microbes that reside in the human alimentary tract and their role in the development of cancer – especially in the GI tract, is the topic of the next chapter. The following chapter explores the importance of the gut microbiota in greater detail and provides discussions of specific microbes in the gut and their influence on not only cancer risk but also potentially precancerous inflammatory responses in the colon and other organ systems as well.

Flame-cooked red meats and processed meat consumption is consistently associated with increased risk of cancers in the GI tract. The mechanisms by which these meats can increase cancer risk are clearly explained and strategies to reduce risk are included in the next chapter. Meats contain a higher proportion of saturated to unsaturated fats and the next chapter reviews the evidence linking higher intakes of most saturated fats with increased risk of cancer. The following chapter examines the early evidence from in vitro and animal studies that certain isomers of one fatty acid found in meat and dairy products, conjugated linoleic acid (CLA), may reduce the risk of certain cancers; the chapter includes almost a dozen relevant figures that help the reader to better understand the complexity of the findings with CLA. In contrast to most of the fats in meats, the polyunsaturated fats, primarily long-chain n−3 fatty acids from fish or other sources (discussed in a separate chapter), have been associated with a decreased risk of cancer possibly by affecting translational regulation of genes and thereby reducing cell proliferation. The next chapter, containing over 200 references and two detailed tables of the relevant clinical studies, reviews the data linking higher intakes of n-6 unsaturated fatty acids with increased risk of cancer that may be due to the increased cell proliferation and inflammation associated with n-6 fatty acid metabolites. These five chapters highlight the complexity of making generalizations about all fats; nevertheless, the authors, who are recognized leaders in this area of research, clearly present compelling arguments for maintaining overall fat intake at about 30% of calories/day, keeping saturated fat intake to 10% of calories, and maintaining a 1–2:1 ratio of n-6 to n-3 fatty acids in the daily diet.

In the section entitled carotenoids, vitamins, and minerals, there are individual chapters on carotenoids, vitamin A, vitamin D, folate, selenium, calcium, iron, and zinc contributed by the major researchers of these nutrients. The chapter on carotenoids highlights the consistent association between fruit and vegetable intakes with decreased cancer risks and examines in detail two individual carotenoids found in the human diet: β-carotene and lycopene. The authors remind the reader that even though the immediate headlines from the ATBC study published in 1994 suggested that Finnish smokers who were in the β-carotene arm had increased rates of lung cancer, data published 6 years later no longer found this association; four other β-carotene intervention studies found no increased risk of lung cancer in smokers although the number of smokers in these studies was not as great as in the ATBC and CARET studies. The entire literature concerning lycopene in major in vitro and all in vivo studies is tabulated for the reader. The authors conclude with a recommendation for individuals to eat five servings of fruits and vegetables/day and make five of those choices lycopene-containing tomato products each week. Certain carotenoids can be metabolized to vitamin A (retinol),

which is an essential nutrient critical for controlling cell growth and differentiation into normal cells in contrast to cancerous cells. Retinoic acid (RA), a metabolite of retinol, is a direct activator of genetic functions and has been examined as a chemopreventive drug over many years. Many RA derivatives have been synthesized and tested as cancer treatments. This chapter points out the difficulties found in moving from positive in vitro and animal studies to human studies of both chemoprevention and chemotherapy with vitamin A as well as the retinoids. With regard to vitamin D, discussed in the next chapter, its role in cancer development and potential in treatment is a very new area of research associated with the capability of non-renal tissues to locally synthesize the active form of the vitamin whereas cancerous tissue appears to lose this function. The epidemiology and the mechanism of action studies are carefully reviewed and a recommendation is made for increased intake of vitamin D. Synthesis of DNA as well as the methylation of this molecule and others within the body requires folate, an essential water-soluble B vitamin. Epidemiological data point to the inverse association between folate intake and risk of cancers of the colon and esophagus. However, intervention studies with folic-acid supplementation have not shown reduction in precancerous colon polyps. It may be that unrecognized genetic polymorphisms in the enzymes controlling folate and other B vitamin metabolism have reduced the potential to see the beneficial effects of folate and/or may even increase the risk of carcinogenesis. Given that many nations have implemented a folic-acid fortification program to reduce the occurrence of neural tube birth defects, it is critical to better understand the timing and dose of folate needed to reduce and not enhance cancer development and/or progression.

Selenium is the first essential mineral reviewed and as has been seen with many of the nutrients, there are several bioactive forms in the food supply as well as in the body. Likewise, selenium has a number of functions within the body as it is a component of an antioxidant enzyme and many other selenoproteins involved in cellular metabolism. In vitro, animal and epidemiological data support a chemopreventive role for selenium. However, the two clinical trials have provided inconsistent results for prostate cancer that may be due to many factors not the least of which could be the baseline selenium status of the cohort. Calcium, the mineral discussed in the next chapter, has been shown to significantly reduce the rate of colon polyp recurrence. Moreover, recent data from a large cohort suggests that supplemental intakes of calcium are associated with reduced risk of total cancers in post-menopausal women. The data for prostate cancer associations are inconsistent. Iron, another essential element, is required for the synthesis of energy in the form of ATP. There are no data suggesting that increased iron intake reduces the risk of cancers, rather in individuals with the homozygous genetic defect that causes iron overload, there is an increased risk of liver cancer and in heterozygotes there are increases in risks of several cancers. Other genes and proteins associated with iron metabolism and cancer risk are tabulated in this chapter. Epidemiological data show inconsistent associations between high iron intakes and cancer risks that may reflect red meat consumption (mentioned in the chapter on meat and cancer as well). The final chapter in this section looks at the role of zinc in cancer development and prevention. Zinc is an essential component of over 300 human enzymes and is thus involved in virtually all aspects of cellular function. Yet, the research on zinc and cancer is in its infancy. In vitro cell culture studies have shown important effects of zinc and studies

in zinc-deficient animal models find increased cancer development. There are consistent epidemiological associations of low zinc status and increased risk of oral and esophageal cancers, but no intervention studies of zinc alone have been initiated.

Non-nutritive bioactive molecules found in foods, spices, and herbs and their potential role in cancer prevention and/or treatment is an exciting and very active area of research. Drs. Milner and Romagnolo have chosen ten of the most well-studied bioactives and have also enlisted the investigators who have done the most work on these compounds to provide informative chapters. As the research on the effects of the bioactive compounds is at the early states of investigation, many have not been used in clinical intervention studies. Cruciferous vegetables contain isothiocyanates and indoles; these compounds have been shown to affect tumor cell cycles, gene expressions, apoptosis, inflammatory responses, and other factors associated with lowering the risk of initiation and growth of malignant cells. Broccoli is the most commonly consumed cruciferous vegetable in US diets at about once/week, and cooking inactivates some of the bioactive compounds. Genotypes likely affect the cancer preventive potential of these compounds. There are no full-scale clinical studies; the epidemiological studies are tabulated. Garlic and the bioactive sulfur compounds isolated from garlic have been shown to reduce cell proliferation and enhance DNA repair and in laboratory animal studies, garlic decreased cancer formation following exposure to carcinogens. However, epidemiological and clinical data are not available, so this is a new area for clinical investigation.

Two polyphenol compounds are reviewed in the next chapter that examines the anti-carcinogenic potential of resveratrol and genistein in animal models and cell culture studies. In rodent models of breast or prostate cancer, the two compounds individually and in combination appeared to reduce the size and progression of these tumors. Tea catechins, fruit and vegetable flavonols, and procyandins have also been shown to be of benefit against tumor development in animal models. The epidemiological evidence for tea consumption and reduced cancer risk is tabulated; results from small intervention studies are reviewed. The next chapter provides an in depth review of the isoflavones genistein and daidzein from soy (more than 200 cited references) and concludes that these compounds have anti-carcinogenic effects in animal models and a number of mechanisms of action. Because of their estrogenic activity, clinical investigations may concentrate on non-estrogen responsive cancers. Many culinary herbs and spices including rosemary, oregano, basil, chilies, turmeric, ginger, and cloves have demonstrated antioxidant and anti-inflammatory activities in cell culture and some have been tested in animal models of cancer. Emphasis in this chapter is placed on the data concerning curcumin from turmeric where there have been some small clinical investigations in cancer patients looking at biomarkers of activity. Berries, such as strawberries, blueberries, cranberries, and raspberries, have been consumed by humans throughout history. These fruits contain essential nutrients as well as other bioactive phytochemicals including phenolic acids and flavonoids. The anthocyanins are one of the most abundant flavonoids in berries. Extracts can reduce cellular carcinogenesis in culture and in certain animal models. Pilot intervention studies have shown that berry concentrates can modulate biomarkers of cancer development. Pomegranates have also been consumed by humans for centuries and there is interest in the phytochemicals in the rind and juice

produced from the whole fruit that contains a tannin, punicalagin. A pilot intervention study with pomegranate juice in men with prostate cancer found an increase in the time with no rise in prostate-specific antigen.

Alcohol use has been consistently associated with an increased risk of breast cancer in women and with cancers of the aerodigestive tract. Cell studies and animal models document that ethanol is the carcinogen in alcohol and the cancer risk is related directly to dose. The alcohol–cancer relationship can be modified by many factors including dietary status, concomitant smoking or other environmental toxins, gender, age, and by genetics. Over 200 references are included in this chapter. The other major classes of compounds that can increase the risk of cancer are the xenobiotics from the environment including polycyclic aromatic hydrocarbons and dioxins. The mechanisms of cancer formation and the potential to reduce the effects of exposure with the consumption of foods that contain beneficial bioactive molecules is the topic of the next chapter. Flavonols that can activate detoxifying enzymes may reduce the risk of cancer formation by lowering the body burden of these environmental toxins.

The final chapter of the volume is of great practical relevance and unique to this volume. The chapter examines the opportunities and challenges of communicating to consumers about foods and cancer risk. Effective communication is critically important as we do not appear to be able to stem the obesity epidemic; and obesity is a significant risk factor for many cancers. Consumer research from the 2008 International Food Information Council (IFIC) Food and Health Survey into attitudes and awareness of the role of dietary components in their health is reviewed. It is important to determine how clients, patients, and colleagues interpret the health messages that the media develop from research studies such as those presented in this volume.

In conclusion, "Bioactive Compounds and Cancer" edited by John A. Milner, Ph.D., and Donato F. Romagnolo, Ph.D., provides health professionals in many areas of research and practice with the most up-to-date, well-referenced volume on the importance of diet and its effects on cancer risk. This volume will serve the reader as the benchmark in this complex area of interrelationships between food, dietary intakes, and body weight, the myriad of mechanisms by which bioactive components in our diet can reduce the risk of initiation, promotion, and progression of malignancies. Moreover, the interactions between environmental and genetic factors are clearly delineated so that practitioners can better understand the complexities of these interactions. The editors are applauded for their efforts to develop this volume which now stands as the benchmark in the field of nutrition and cancer. This excellent text is a very welcome addition to the Nutrition and Health Series.

Adrianne Bendich, PhD, FACN

Foreword by David S. Alberts, MD, and Maria Lluria-Prevatt, PhD

While we have begun to see documented decline of both the incidence and death rates from all cancers combined in both men and women *(1)*, cancer still accounts for more deaths than heart disease in persons younger than 85 years of age. Our Western lifestyle literally is killing us! In order to extend the success in reducing cancer incidence and death, our knowledge of the effects of nutrition and physical activity in cancer causation, prevention, and intervention are essential. After all, there is a growing consensus that we must "get off the couch and out to the refrigerator" if we are to survive.

There is an expected more than 1.5 million new cases of invasive cancer and 560,000 cancer deaths in the United States in 2009 *(2)*. Alarmingly, with our present rate of increase in obesity, it is estimated that the current patterns of overweight and obesity in the United States could account for 14% of all deaths from cancer in men and 20% of those in women *(3)*. The vast majority of these cancer cases are preventable.

The multistage model of carcinogenesis demonstrates the stages of initiation, promotion, and progression as a multiyear process. If we understand that for most common cancer types there may be an estimated lag time of 20–30 years from the first initiated (i.e., DNA damaged) cancer cell to death from metastatic cancer, then there are between 11 million and 17 million people in the United States who currently have some phase of premalignant disease who, ultimately, will die from cancer. There is a wide window of opportunity within this long lag period or premalignant phase in which enhanced physical activity and nutritionally targeted cancer prevention can effectively influence the course of this disease process (Fig. 1).

The editors, Drs. John A. Milner and Donato F. Romagnolo, of "Bioactive Compounds and Cancer" have brought together 76 world renowned authors to provide the most up-to-date, comprehensive volume discussing numerous dietary components that have demonstrated an impact on cancer risk and prevention in preclinical models and/or clinically. This text provides health professionals the most relevant science-based knowledge with regard to dietary bioactive compounds and their effects on the progression of cancer.

There have been a large number of observational studies showing a reduction in the risk of several types of epithelial malignancies among populations with higher intakes of fruits and vegetables *(5)* or reduction in fat intake *(6)*. While a primary prevention strategy might involve the promotion of a high fruit and vegetable and/or low-fat diet to reduce the frequency of initiated cells or to repair damage manifested by initiated cells, the authors of this text have taken the process a step further by identifying the actual dietary component that specifically demonstrates bioactivity in a wide variety of cancers in preclinical and/or clinical settings. These authors provide scientific data of the mechanisms of action of these compounds and in many cases have been able to identify

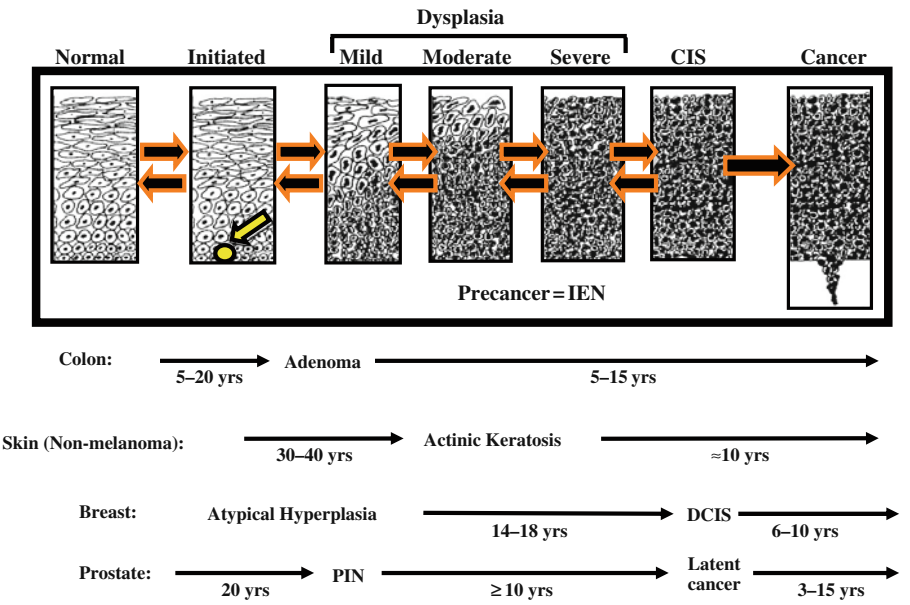

Fig. 1. Progression of precancer to cancer in humans is a multiyear process. Adapted from O'Shaughnessy et al. *(4)*.

specific cancer genes, signaling proteins, transcription factors, or epigenetic events that the bioactive components are able to regulate.

The initial section of this text gives an introduction to the potential influence of nutrition on cancer risk and prevention strategies and how investigators have begun to document the roles of bioactive compounds. One strategy to understand nutritional effects in cancer is nutrigenomics. Nutrigenomics is the study of the effects of food and food constituents on gene expression. This allows for the identification of bioactive food compounds, which affect specific targets that influence the carcinogenesis process. The identification of these bioactive compounds and the key molecular targets is attained through the use of high-throughput proteomics and metabolomic approaches. Here, the authors describe the potential interactions between bioactive molecules and genetic components such as histones, DNA methylation, transcription factors, and cell cycle regulators. The bioactive compounds found in food include essential nutrients such as vitamins and minerals and essential lipids, plant polyphenols, carotenoids, xenobiotics and numerous, other molecular entities. One specific transcription factor, AP-1, has been identified as a potential target for regulation and chemoprevention by nutrients, including epigallocatechin gallate (EGCG) *(7)*, theaflavins, caffeine *(8)*, [6]-gingerol *(9)*, resveratrol *(10)*, and flavonols such a as kaempherol, quercetin *(10)*, and myricetin *(11)*. This transcription factor appears to play a role in proliferation, differentiation, apoptosis, and angiogenesis *(12)*. In the case of DNA methylation, nutrients can supply the methyl groups in the formation of *S*-adenosylmethionine (SAM) and modify the utilization of methyl groups by DNA methyltransferases. In addition, nutrients may play a role in DNA demethylation

activity and DNA methylation may influence the specific response to a nutrient. Understanding the complexities of the cellular events in carcinogenesis has paved the road to identify the key components in the diet that may be able to reduce the risk of cancer development.

A comprehensive discussion of macronutrients, obesity, and the potential for calorie restriction and physical activity to reduce cancer risk are discussed in Chapters 7–14. These authors have pulled together much of the current knowledge, including their own extensive research to discuss the effect of dietary balance involving calorie restriction and specific dietary components involved in cancer risk and prevention. The authors in this section present data concerning the use of compounds such as bifidobacteria, lactobacilli, and *Clostridium butyricum* to modulate gut microbiota and the intake of fiber for colon cancer prevention. In addition to a discussion of the recommended reduction in red meat intake and the resulting exposure to their carcinogenic chemical compounds, polycyclic aromatic hydrocarbons (PAH) formed in grilled meat, these authors have extensively explained the bioactivity of two polyunsaturated fatty acids (PUFA): n-6 PUFA and n-3 PUFA. N-6 PUFA metabolites are associated with increased cell proliferation and inflammation providing a potential mechanism in the extensive clinical studies linking increased cancer risk with intake of high levels of this PUFA. In contrast, n-3 PUFA are often found in fish and other food sources and have been associated with a decrease risk of cancer by affecting translational regulation of genes and subsequently reducing cellular proliferation. Recent data have identified a family of isomers, conjugated linoleic acid (CLA), that are found in meat and dairy products. In vitro studies demonstrated CLA inhibited growth of several cancer cell lines and induced expression of apoptotic genes. A reduction in tumors by CLA was also seen in rodent models. However, there can be no recommendation for CLA consumption for prevention or therapy until more extensive preclinical and clinical studies can be undertaken. This section of the book brings forth the evidence needed for the recommended reduction of overall fat intake, discussing the specific compounds found in fat that are associated with increased cancer risk, and providing evidence of the mechanism by which they act to increase cancer risk.

Many patients today use alternative therapies to manage their health. It is difficult for the health-care professionals to keep up with the evolving field. With a large selection of combination of vitamins and supplements available to the individual and the frequent mention of the positive impact to health from the lay media, health professionals are undoubtedly left to answer the patient's request of vitamin and nutrient supplement selection. From a scientific perspective, the authors of Chapter 15–22 discuss the most recent studies of carotenoids, vitamin A, vitamin D, folate, selenium, calcium, iron, and zinc. Both the carotenoids, β-carotene and lycopene, are highlighted in this section. Lycopene found in tomato food sources has been associated with the reduction in prostate cancer risk potentially through a mechanism of decreasing the expression of androgen-producing enzymes. β-carotene levels have been used as a biomarker for fruit and vegetable intake which is associated with reduced cancer risk. Controversial studies of high doses β-carotene and increased lung cancer risk in heavy, current smokers are addressed. The authors of this chapter recommend the five-a-day servings of fruit

and vegetables and suggest that five of those in a week be lycopene-containing tomato products.

Vitamin A (retinol) is an essential nutrient involved in controlling cell growth and differentiation into normal cells; however, its use in cancer prevention has been limited to non-melanoma skin cancer chemoprevention due to the side effects associated with it. The authors do not present evidence that warrants a change in recommendations for dietary vitamin A for the purpose of cancer prevention. The discussions concerning vitamin D and its preventive cancer effects are quite limited; however, there is evidence that the ability to produce vitamin D3 is often lost as cancer develops. This leaves open the possibility that with restoration of this synthesis mechanism, there could be modulation of the carcinogenesis process.

Unfortunately, the role of folate in cancer prevention has been contradictory, especially since the mid-1990s when folic-acid supplementation of the US food supply was initiated. Essentially, too much of a "good thing" may not be so "good." The chapters on the minerals, selenium, and calcium provide well-documented preclinical and clinical data of their potential to prevent cancer. The putative mechanisms for cancer prevention are described for both. Selenium has been connected to antioxidant protection and anti-inflammatory effects while calcium provides protection by decreasing cell proliferation and stimulating cell differentiation in numerous types of cells. In contrast, excess iron accumulation can lead to increased risk of cancer and diseases associated with iron overload, but iron is required for many normal cell functions and therefore poses a dilemma with respect to long-term supplementation.

Currently, there has been an increased interest in zinc consumption because of its activity in boosting immune function and "fighting" the common cold. There is preclinical evidence to support that zinc has a potential role in cancer prevention. This concept has been formulated primarily because dietary zinc deficiency has been associated with increased tumors in epidemiological, clinical, and animal model studies. Esophageal cancer translational research efforts demonstrated an effect on NF-kB-COX-2 signaling pathway regulation by zinc that might contribute to prevention of this and other types of cancer.

Chapters 23–30 provide a large amount of reference supported research on specific compounds in different food components. One such compound is sulforaphane found in cruciferous vegetables and noted to block inflammatory responses. Cruciferous vegetable intake may reduce the risk of several cancers, including the hematologic malignancies, multiple myeloma, and non-Hodgkins lymphoma. Cruciferous vegetables contain isothiocyanates and indoles that have demonstrated advantageous cancer prevention effects on tumor cell cycles, gene expression, apoptosis, inflammatory responses, and other mechanisms associated with lowering of cancer risk. The bioactive sulfur compounds of garlic also have been shown to reduce cell proliferation and enhance DNA repair in animal models. Garlic decreased cancer formation subsequent to carcinogen exposure.

The polyphenols, resveratrol and genistein, individually and in combination reduced the size and progression of breast and prostate tumors in animal models. The benefits of tea intake are discussed and accompanied by a complete table of the epidemiological studies of tea consumption and the associated reduction in cancer risk. Another

set of bioactive compounds extensively reviewed in this text are the isoflavones, genistein, and diadzein from soy. These compounds demonstrate a multitude of mechanisms contributing to their anti-carcinogenic effects. Also the phytochemicals of berries and pomegranates are introduced. In berries, the most active compounds are the anthocyanins. Berries inhibit carcinogenesis by inhibiting growth of cells, inhibiting angiogenesis and inflammation, and stimulating apoptosis, cell differentiation, and cell adhesion. Topical ointments containing berry extract have been associated with a reduction in histological grade and restoration of loss of heterozygosity in oral dysplastic lesions. The authors go so far as to advise the daily consumption of several grams of berry powder to elicit protection from cancer development.

Pomegranate ellagitannins metabolize into urolithins by the gut flora, which have demonstrated bioactivity in inhibiting prostate cancer cell growth, NFκ-B, and HIF-1α-dependent activation of VEGF. The consumption of pomegranate juice appears to cause a decrease in the rate of PSA after radiation or surgery in prostate cancer treatment. The second to last chapter in this text brings forth the biological data on alcohol consumption and its contribution to the development of many types of cancers of the aerodigestive tract. Discussed in the final chapter is the aryl hydrocarbon receptor (AhR). When activated by agonists, the AhR leads to a decreased expression of the tumor suppressor genes p16 and BRCA-1 and may be a risk factor in various types of cancer. Under current investigations are the potential benefits of using natural modulators of the AhR, including resveratrol and other indole compounds to work as cancer chemoprevention drugs.

The authors of many of these chapters rightfully address the difficulties in moving positive in vitro and animal studies of these bioactive compounds to human studies of chemoprevention *(13)*. The suggested evidence necessary for a compound to qualify as a chemopreventive agent that could be developed naturally is shown in Fig. 2.

In an era where either the patients are asking "how and why" to prevent cancer or patients circumstances require the motivation for healthier living, "Bioactive Compound and Nutrition" provides the health-care professionals the concrete research behind calorie restriction, increased physical activity, reduction of intake of certain foods, including the moderation of vitamin and supplement consumption, and the increased intake of

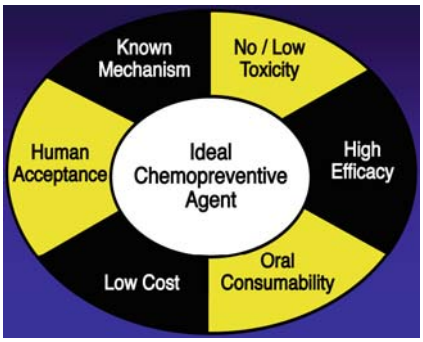

Fig. 2. Qualities of an ideal chemopreventive agent.

other healthful nutrients. With the identification of the actual bioactive compounds in the diet and understanding the molecular interactions that occur with these compounds, there will be greater confidence that effective chemoprevention agents can be developed from these dietary components.

David S. Alberts, MD
Maria Lluria-Prevatt, PhD

REFERENCES

1. Jemal, A., Thun, M.J., Ries, L.A., Howe, H.L., Weir, H.K., Center, M.M. et al. (2008) Annual report to the nation on the status of cancer, 1975–2005, featuring trends in lung cancer, tobacco use, and tobacco control. *J Natl Cancer Inst* **100**(23), 1672–94.
2. Jemal, A., Siegel, R., Ward, E., Hao, Y., Xu, J., Thun, M.J. et al. (2009) Cancer statistics, 2009. *CA Cancer J Clin* **59**(4), 225–49.
3. Calle, E.E., Rodriguez, C., Walker-Thurmond, K., Thun, M.J., Calle, E.E., Rodriguez, C. et al. (2003) Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults.[see comment]. *New Engl J Med* **348**(17), 1625–38.
4. O'Shaughnessy, J.A., Kelloff, G.J., Gordon, G.B., Dannenberg, A.J., Hong, W.K., Fabian, C.J. et al. (2002) Treatment and prevention of intraepithelial neoplasia: an important target for accelerated new agent development.[see comment]. *Clin Cancer Res* **8**(2), 314–46.
5. Alberts, D.S. (1999) A unifying vision of cancer therapy for the 21st century. *J Clin Oncol* **17**(11 Suppl), 13–21.
6. Prentice, R.L., Thomson, C.A., Caan, B., Hubbell, F.A., Anderson, G.L., Beresford, S.A. et al. (2007) Low-fat dietary pattern and cancer incidence in the Women's Health Initiative Dietary Modification Randomized Controlled Trial.[see comment]. *J Natl Cancer Inst* **99**(20), 1534–43.
7. Chen, W., Dong, Z., Valcic, S., Timmermann, B.N., and Bowden, G.T. (1999) Inhibition of ultraviolet B–induced c-fos gene expression and p38 mitogen-activated protein kinase activation by (-)-epigallocatechin gallate in a human keratinocyte cell line. *Mol Carcinog* **24**(2), 79–84.
8. Nomura, M., Ma, W.Y., Huang, C., Yang, C.S., Bowden, G.T., Miyamoto, K. et al. (2000) Inhibition of ultraviolet B-induced AP-1 activation by theaflavins from black tea. *Mol Carcinog* **28**(3), 148–55.
9. Bode, A.M., Ma, W.Y., Surh, Y.J., and Dong, Z. (2001) Inhibition of epidermal growth factor-induced cell transformation and activator protein 1 activation by [6]-gingerol. *Cancer Res* **61**(3), 850–53.
10. Lee, K.W., Kang, N.J., Heo, Y.S., Rogozin, E.A., Pugliese, A., Hwang, M.K. et al. (2008) Raf and MEK protein kinases are direct molecular targets for the chemopreventive effect of quercetin, a major flavonol in red wine. *Cancer Res* **68**(3), 946–55.
11. Jung, S.K., Lee, K.W., Byun, S., Kang, N.J., Lim, S.H., Heo, Y.S. et al. (2008) Myricetin suppresses UVB-induced skin cancer by targeting Fyn. *Cancer Res* **68**(14), 6021–29.
12. Cooper, S.J., and Bowden, G.T. (2007) Ultraviolet B regulation of transcription factor families: roles of nuclear factor-kappa B (NF-kappaB) and activator protein-1 (AP-1) in UVB-induced skin carcinogenesis. *Curr Cancer Drug Targets* **7**(4), 325–34.
13. Alberts, D.S. (2002) Reducing the risk of colorectal cancer by intervening in the process of carcinogenesis: a status report. *Cancer J* **8**(3), 208–21.

Foreword by Scott M. Lippman, MD

Natural agents have a long, exciting history in cancer prevention that extends back to 1925, when Wolbach and Howe reported early animal studies of vitamin A, foreshadowing the founding of the field of modern cancer chemoprevention by pioneers such as Lee Wattenberg, Michael B. Sporn, and Waun Ki Hong in the 1960s, 1970s, and 1980s. In the wake of several negative, some even harmful, major trials of natural agents for chemoprevention, however, a recent editorial stated that the prospects for cancer prevention through natural agents "have never looked worse" *(1)*. Although this observation is perfectly understandable, no one should rush to count natural bioactive compounds out, as the chapters of this book, *Bioactive Compounds and Cancer*, make abundantly clear.

This comprehensive textbook is an excellent research source of in-depth reviews in every chapter, illustrating the complexity of the field and useful both for research and for clinical practice. Every major area of natural-agent research is covered. Wide-ranging chapters on biology, technology, and mechanisms include one chapter each on nutrigenomics and nutrigenetics and a chapter on diet and epigenetics. Research varying from whole foods to extracts to specific compounds is presented in a clear, useable format. There are individual chapters on a host of bioactive compounds including folate, selenium, vitamin D, zinc, iron, garlic, isoflavones, berries and anthocyanines, herbs and spices, pomegranates, and many more. The book's broad scope is illustrated further by chapters on caloric restriction/energy balance, gut microbiotica, aryl hydrocarbon receptor-mediated carcinogenesis, carcinogenic effects of meat and alcohol, and (in four chapters) the double-edged sword of fatty acids.

Although illuminated in this book, much of the leading-edge methodology of natural-agent research did not enter into the backgrounds and rationales of the large randomized controlled trials (RCTs) beginning in the mid-1990s that led to the gloomy outlook quoted above. Beta-carotene and vitamin A analogues (retinoids) increased lung cancer incidence and mortality in smokers. Folic acid increased the risk of advanced colorectal adenomas and prostate cancer. Vitamin E (α-tocopherol) marginally increased prostate cancer in the largest cancer prevention RCT ever conducted (the Selenium and Vitamin E Cancer Prevention Trial [SELECT]), in addition to increasing mortality in meta-analyses of clinical trials. The only positive micronutrient RCT involved is calcium, which produced a significant, albeit modest, reduction in colorectal adenomas. RCTs of many other natural compounds, including complex combinations of vitamins and minerals, have yielded negative-neutral results. Many complex aspects of these results remain unresolved, including the apparent non-linear dose–response of many of the natural agents, potential effects in nutrient-deficient (not replete) populations, and pharmacogenomic considerations such as have been reported recently for selenium.

The primary basis of most of these RCTs was epidemiologic data, which can be confounded by many factors. The enormous SELECT went further, basing its rationale

largely on compelling secondary RCT data, which did not lead to positive results. In view of these trials' somewhat limited rationales and preponderantly negative results, cancer prevention experts have proposed a new model of natural agent development, a model that develops consistent cross-discipline preliminary data from preclinical models, epidemiology, pharmacogenetics, risk-modeling, and early-phase clinical trials prior to the launch of large, expensive, and time-consuming RCTs. Strong efforts are needed in the step of early-phase clinical trials, including presurgical studies within intraepithelial neoplasia or cancer and important correlative assessments such as of molecular profiles of efficacy.

The editorial mentioned in the opening paragraph also aptly said, "The primary lesson from our experience in the nutritional prevention of cancer is that it is not simple." Nevertheless, the complexity of feasible, desired early evidence will lead, at last, to the most-promising areas for registration or definitive RCTs of natural agents. These RCTs will represent the distillation of large, heterogeneous populations of somewhat-increased – risk individuals down into cohorts of highest-risk, pharmacogenomically appropriate individuals, who will receive formulations, doses, and durations of single or combined natural agents with the highest activity and safety profiles in preclinical and early-stage clinical studies. This proposed agent-development scheme applies not only to the natural agents described by world leaders in this remarkable book, but as well to the development of molecular-targeted or other synthetic agents for cancer prevention. Movement toward achieving the goal of fully stepped natural-agent development includes efforts of the new American Association for Cancer Research (AACR) journal *Cancer Prevention Research*, which is the leading home for preclinical (in vitro and in vivo), pharmacogenomic, molecular risk assessment, and early-phase clinical studies relevant to natural bioactive compounds.

In sum, the prospects for prevention through natural agents have never looked better, thanks to the growing impetus for effective drug development reflected in the extraordinary body of work represented in *Bioactive Compounds and Cancer*.

Scott M. Lippman, MD

REFERENCE

1. Kristal, A.R., and Lippman, S.M. (2009 Mar 18) Nutritional prevention of cancer: new directions for an increasingly complex challenge. *J Natl Cancer Inst* **101**(6), 432–35.

Preface

Cancer is a global issue. While cancer risk may vary depending on location there is mounting evidence that the incidence and associated morbidity and mortality will continue to mount. This increase is in part due to an aging society, but also to the escalating incidence of obesity throughout the world. Only a small percentage of cancers are familial suggesting that environmental factors including dietary intakes are critical for determining risk and tumor behavior. The impetus to developing this volume stems from the wealth of evidence pointing to specific dietary bioactive components as modifiers of cancer-related processes. Thirty-three chapters have been assembled from world renowned experts who have conducted a systematic review of the relevant literature and provided an assessment of cancer prevention opportunities using bioactive food compounds. The tone of this text is to establish a "proof-of-principle" about the importance of nutrition and cancer prevention while realizing that space limitations may not have allowed for all areas to be adequately addressed. The text has been divided into several sections to aid in the assimilation of the materials provided. *Part I: Understanding the Role of Nutrition in Health* addresses the cancer response to bioactive food components, how "omics" approaches have been used to investigate individual variability due to genetic and epigenetic nutrient regulation of signaling proteins and associated small-molecular-weight compounds. This section defines the cellular cancer processes and molecular targets for food components and identifies those individuals who are likely to benefit by assessing the relevance of selected polymorphisms. Part II: *Role of Dietary Bioactive Components in Cancer Prevention and/or Treatment* was developed realizing that cancer risk is influenced by dietary behavior and interactions among dietary *Macroconstituents* including dietary energy balance, protein, fats, and microflora. Moreover, the effects of certain macronutrients on the cancer process may be modified by synergies with other bioactive components including *Carotenoids, Vitamins, and Minerals*, and many *Bioactive Food Components* found in fruits and vegetables, which in concert may alter the susceptibility to cancer risk. Attention was given to the fact diet may also be a vehicle for cancer-promoting substances including *Alcohol* and to the biological basis of prevention by natural bioactive compounds against certain *Dietary Xenobiotics* with cancer-promoting effects. Finally, this volume provides a forum to discuss opportunities and challenges for communicating food and health relationships to *Consumers*.

In preparing this text, efforts were directed to presenting epidemiological, clinical, and preclinical experimental evidence supporting the role of selected bioactive food components in cancer prevention or causation. Because bioactive food components are promiscuous and influence a multitude of molecular and cellular targets, particular attention was given to discussion of the mechanisms of action, review of experimental data supporting tissue-specific cancer preventative effects, and whenever available, to the totality of evidence supporting the use of specific bioactive food components for the

prevention or management of specific types of neoplasms. Areas for future nutrition and cancer research are also highlighted throughout. When possible, global recommendations are provided as general guides for use by those committed to reducing cancer burden.

ACKNOWLEDGMENTS

Special thanks are due to Adrianne Bendich, Series Editor for her support through thought-full comments, suggestions, and encouragements. The editors acknowledge the editorial assistance of Amanda Rutherford of the Undergraduate Program in Nutritional Sciences and Theresa Spicer of the Department of Nutritional Sciences, at The University of Arizona; the grant support to Donato F. Romagnolo from the Susan G. Komen for the Cure and the Arizona Biomedical Research Commission, Phoenix, AZ. The editors would like to offer special accolades for the efforts of the multiple authors who have contributed to the development of this state-of-the-science text.

MEMORIAL

Professor Sheila Bingham, coauthor of Chapter 10 on Meats, Protein, and Cancer, was an international leader in nutritional epidemiology. She investigated the biological mechanisms underlying the effects of nutrition on health and chronic diseases, including cancer. Sadly, we acknowledge her death on 16th June 16, 2009.

Contents

Series Editor Introduction v

Foreword by David S. Alberts, MD, and Maria Lluria-Prevatt, PhD xiii

Foreword by Scott M. Lippman, MD xix

Preface xxi

Contributors xxvii

PART I: UNDERSTANDING THE ROLE OF NUTRITION IN HEALTH

1 Monitoring the Burden of Cancer in the United States 3
Nadia Howlader, Sean F. Altekruse, and Brenda K. Edwards

2 Cancer Biology and Nutrigenomics 25
John A. Milner and Donato F. Romagnolo

3 Cellular Cancer Processes and Their Molecular Targets for Nutritional Preemption of Cancer 45
Cindy D. Davis

4 Nutrigenetics: The Relevance of Polymorphisms 71
Susan E. McCann, Michelle R. Roberts, Mary E. Platek, and Christine B. Ambrosone

5 Diet and Epigenetics 101
Sharon A. Ross

6 Nutrient Signaling – Protein Kinase to Transcriptional Activation 125
Ann M. Bode and Zigang Dong

PART II: ROLE OF DIETARY BIOACTIVE COMPONENTS IN CANCER PREVENTION AND/OR TREATMENT: MACROCONSTITUENTS

7 Dietary Energy Balance, Calorie Restriction, and Cancer Prevention . . . 147
Stephen D. Hursting, Sarah M. Smith, Leticia Nogueira, Rebecca DeAngel, Laura Lashinger, and Susan N. Perkins

8 Fiber and Microbially Generated Active Components 165
Joanne L. Slavin and Maria L. Stewart

9 Gut Microbiota, Probiotics, Prebiotics and Colorectal Cancer 181
Gemma E. Walton and Glenn R. Gibson

10 Meats, Protein and Cancer 195
Gunter G.C. Kuhnle and Sheila A. Bingham

11 Saturated Fatty Acids and Cancer 213
Michele R. Forman and Somdat Mahabir

12 Conjugated Linoleic Acid and Cancer 235
Kent L. Erickson, Neil E. Hubbard, Alexander D. Borowsky, and Patrizia Damonte

13 Cancer and *n*–3PUFAs: The Translation Initiation Connection 253
B.H. Aktas, M. Chorev, and J.A. Halperin

14 *n*-6 Polyunsaturated Fatty Acids and Cancer 275
Marie Lof, Susan Olivo-Marston, and Leena Hilakivi-Clarke

PART III: ROLE OF DIETARY BIOACTIVE COMPONENTS IN CANCER PREVENTION AND/OR TREATMENT: CAROTENOIDS, VITAMINS AND MINERALS

15 Carotenoids 311
Brian L. Lindshield and John W. Erdman

16 Vitamin A 335
A. Catharine Ross

17 Vitamin D and Cancer Chemoprevention 357
James C. Fleet

18 Folate 387
Cornelia M. Ulrich, Xinran Xu, Amy Liu, and Jia Chen

19 Selenium 411
Margaret P. Rayman

20 Calcium and Cancer 449
Joan M. Lappe

21 Iron and Cancer 469
James R. Connor and Sang Y. Lee

22 Zinc in Cancer Development and Prevention 497
Louise Y.Y. Fong

PART IV: ROLE OF DIETARY BIOACTIVE COMPONENTS IN CANCER PREVENTION AND/OR TREATMENT: OTHER BIOACTIVE FOOD COMPONENTS

23 Cruciferous Vegetables, Isothiocyanates, Indoles, and Cancer Prevention 535
Cynthia A. Thomson, Sally Dickinson, and G. Tim Bowden

24 Garlic and Cancer Prevention 567
John A. Milner

25 Mammary and Prostate Cancer Chemoprevention and Mechanisms of Action of Resveratrol and Genistein in Rodent Models . . 589
Timothy G. Whitsett, Leah M. Cook, Brijesh B. Patel, Curt E. Harper, Jun Wang, and Coral A. Lamartiniere

26 Cancer Prevention by Catechins, Flavonols, and Procyanidins 613
Joshua D. Lambert and Chung S. Yang

27 Mechanisms of Action of Isoflavones in Cancer Prevention 633
Stephen Barnes

28 The Anticarcinogenic Properties of Culinary Herbs and Spices 671
Guy H. Johnson and Lyssa Balick

29 Cancer Prevention with Berries: Role of Anthocyanins 703
Gary D. Stoner, Li-Shu Wang, Christine Sardo, Nancy Zikri, Stephen S. Hecht, and Susan R. Mallery

30 Pomegranate 725
David Heber

31 Alcohol and Cancer: Biological Basis 735
Keith Singletary

32 Aryl Hydrocarbon Receptor-Mediated Carcinogenesis and Modulation by Dietary Xenobiotic and Natural Ligands 761
Donato F. Romagnolo, Stephanie C. Degner, and Ornella Selmin

33 Opportunities and Challenges for Communicating Food and Health Relationships to American Consumers 783
Susan Borra, Wendy Reinhardt Kapsak, and Elizabeth Rahavi

Subject Index 797

Contributors

B.H. AKTAS, PHD, DVM • *Laboratory for Translational Research, Brigham and Women's Hospital and Harvard Medical School, Cambridge, MA*

SEAN F. ALTEKRUSE, DVM, PHD • *Surveillance Research Program, National Cancer Institute (NCI), Bethesda, MD*

CHRISTINE B. AMBROSONE, PHD • *Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, NY*

LYSSA BALICK, MS, CNS • *Information Specialist, McCormick Science Institute, 18, Loveton Circle, Sparks, MD*

STEPHEN BARNES, PHD • *Department of Pharmacology and Toxicology, Center for Nutrient-Gene Interaction, University of Alabama at Birmingham, Birmingham, AL; Purdue University-University of Alabama at Birmingham Botanicals Center for Age-Related Disease, University of Alabama at Birmingham, Birmingham, AL*

SHEILA A. BINGHAM, PHD • *Medical Research Council, Dunn Human Nutrition Unit, Cambridge, UK*

ANN M. BODE, PHD • *The Hormel Institute, University of Minnesota, Austin, MN*

ALEXANDER D. BOROWSKY MD • *Department of Pathology, School of Medicine, Center for Comparative Medicine, University of California, Davis, CA*

SUSAN BORRA, RD • *Formally with International Food Information Council (IFIC) and the Foundation, Washington, DC*

G. TIM BOWDEN, PHD • *Department of Cell Biology and Anatomy, The Arizona Cancer Center, The University of Arizona, Tucson, AZ*

JIA CHEN, SCD • *Mount Sinai School of Medicine, New York, NY*

M. CHOREV, PHD • *Laboratory for Translational Research, Brigham and Women's Hospital and Harvard Medical School, Cambridge, MA*

JAMES R. CONNOR, PHD • *Department of Neurosurgery, Penn State Hershey Cancer Institute, The Pennsylvania State University College of Medicine & M.S. Hershey Medical Center, Hershey, PA*

LEAH M. COOK, MS • *Department of Pharmacology and Toxicology, University of Alabama at Birmingham, Birmingham, AL*

PATRIZIA DAMONTE, PHD • *Department of Pathology, School of Medicine, Center for Comparative Medicine, University of California, Davis, CA*

CINDY D. DAVIS, PHD • *Nutritional Science Research Group, Division of Cancer Prevention, National Cancer Institute, Rockville, MD*

REBECCA DEANGEL, MPH • *Department of Nutritional Sciences, University of Texas, Austin, TX*

STEPHANIE C. DEGNER, PHD • *Department of Nutritional Sciences, The University of Arizona, Tucson, AZ; Department of Veterinary Science and Microbiology, The University of Arizona, Tucson, AZ*

SALLY DICKINSON, PHD • *Arizona Cancer Center, The University of Arizona, Tucson, AZ*
ZIGANG DONG, MD, DR. PHD • *The Hormel Institute, University of Minnesota, Austin, MN*
BRENDA K. EDWARDS, PHD • *Surveillance Research Program, National Cancer Institute (NCI), Bethesda, MD*
JOHN W. ERDMAN JR., PHD • *Division of Nutritional Sciences, Department of Food Science and Human Nutrition, University of Illinois at Urbana-Champaign, IL*
KENT L. ERICKSON, PHD • *Department of Cell Biology and Human Anatomy, School of Medicine, University of California, Davis, CA*
JAMES C. FLEET, PHD • *Department of Foods and Nutrition, Purdue University, West Lafayette, IN*
LOUISE Y.Y. FONG, PHD • *Department of Pharmacology and Experimental Therapeutics, Kimmel Cancer Center, Thomas Jefferson University, Pennsylvania, PA, USA*
MICHELE R. FORMAN, PHD • *Department of Epidemiology, MD Anderson Cancer Center, Houston TX*
GLENN R. GIBSON, PHD • *Food Microbial Sciences Unit, Department of Food Biosciences, The University of Reading, Reading, UK*
J.A. HALPERIN, MD • *Laboratory for Translational Research, Brigham and Women's Hospital and Harvard Medical School, Cambridge, MA*
CURT E. HARPER, PHD • *Department of Pharmacology and Toxicology, University of Alabama at Birmingham, Birmingham, AL*
DAVID HEBER MD, PHD • *Department of Medicine, David Geffen School of Medicine at UCLA, UCLA Center for Human Nutrition, Los Angeles, CA*
STEPHEN S. HECHT, PHD • *Masonic Cancer Center, University of Minnesota, Minneapolis, MN*
LEENA HILAKIVI-CLARKE, PHD • *Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC*
NADIA HOWLADER, MS • *Surveillance Research Program, National Cancer Institute (NCI), Bethesda, MD*
NEIL E. HUBBARD, PHD • *Department of Cell Biology and Human Anatomy, School of Medicine, University of California, Davis, CA*
STEPHEN D. HURSTING, PHD, MPH • *Department of Nutritional Sciences, University of Texas, Austin, TX; Department of Carcinogenesis, University of Texas-MD Anderson Cancer Center, Smithville, TX*
GUY H. JOHNSON, PHD • *McCormick Science Institute, 18, Loveton Circle, Sparks, MD*
WENDY REINHARDT KAPSAK, MS, RD • *International Food Information Council (IFIC) and the Foundation, Washington, DC*
GUNTER G.C. KUHNLE, PHD • *Medical Research Council, Dunn Human Nutrition Unit, Cambridge, UK*
CORAL A. LAMARTINIERE, PHD • *Department of Pharmacology and Toxicology, University of Alabama at Birmingham, Birmingham, AL; UAB Comprehensive Cancer Center, University of Alabama at Birmingham, Birmingham, AL*

JOSHUA D. LAMBERT, PHD • *Department of Chemical Biology, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, NJ*
JOAN M. LAPPE, PHD, RN, FAAN • *Creighton University, Omaha, NE*
LAURA LASHINGER, PHD • *Department of Nutritional Sciences, University of Texas, Austin, TX; Department of Carcinogenesis, University of Texas-MD, Anderson Cancer Center, Smithville, TX*
SANG Y. LEE, PHD • *Department of Neurosurgery, Penn State Hershey Cancer Institute, The Pennsylvania State University College of Medicine & M.S. Hershey Medical Center, Hershey, PA*
BRIAN L. LINDSHIELD PHD • *Department of Human Nutrition, Kansas State University Manhattan, KS*
AMY LIU, MPH • *Fred Hutchinson Cancer Research Center, Cancer Prevention Research Program, Seattle, WA*
MARIE LOF, PHD, MSC • *Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden*
SOMDAT MAHABIR, PHD, MPH • *Department of Epidemiology, MD Anderson Cancer Center, Houston TX*
SUSAN R. MALLERY, DDS, PHD • *Division of Oral Surgery, Pathology and Anesthesiology, College of Dentistry, The Ohio State University, Columbus, OH*
SUSAN E. MCCANN, PHD, RD • *Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, NY*
JOHN A. MILNER, PHD • *Nutritional Science Research Group, Division of Cancer Prevention, National Cancer Institute, Rockville, MD*
LETICIA NOGUEIRA, BS • *Department of Nutritional Sciences, University of Texas, Austin, TX*
SUSAN OLIVO-MARSTEN, PHD, MPH • *Cancer Prevention Fellowship Program, Office of Preventive Oncology, Division of Cancer Prevention National Cancer Institute, NIH, Bethesda, MD*
BRIJESH B. PATEL, MS • *Department of Pharmacology and Toxicology, University of Alabama at Birmingham, Birmingham, AL*
SUSAN N. PERKINS, PHD • *Department of Nutritional Sciences, University of Texas, Austin, TX*
MARY E. PLATEK, PHD • *Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, NY*
ELIZABETH RAHAVI, RD • *International Food Information Council (IFIC) and the Foundation, Washington, DC*
MARGARET P. RAYMAN DPHIL, RPHNUTR • *Nutritional Sciences Division, Faculty of Health and Medical Sciences, University of Surrey, Guildford, UK*
MICHELLE R. ROBERTS, MA • *Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, NY*
DONATO F. ROMAGNOLO, PHD, MS • *Department of Nutritional Sciences, The University of Arizona, Tucson, AZ*
A. CATHARINE ROSS, PHD • *Department of Nutritional Sciences, Pennsylvania State University, University Park, PA; Huck Institute for the Life Sciences, Pennsylvania State University, University Park, PA*

SHARON A. ROSS, PHD • *Nutritional Science Research Group, Division of Cancer Prevention, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD*

CHRISTINE SARDO, MPH, RD • *Comprehensive Cancer Center, The Ohio State University College of Medicine, Columbus, OH*

ORNELLA SELMIN, PHD • *Department of Nutritional Sciences, The University of Arizona, Tucson, AZ*

KEITH SINGLETARY, PHD • *Department of Food Science and Human Nutrition, University of Illinois, Urbana, IL*

JOANNE L. SLAVIN, PHD, RD • *Department of Food Science and Nutrition, University of Minnesota, St. Paul, MN*

SARAH M. SMITH, PHD • *Department of Nutritional Sciences, University of Texas, Austin, TX; Department of Carcinogenesis, University of Texas-MD Anderson Cancer Center, Smithville, TX*

MARIA L. STEWART, MS • *Department of Food Science and Nutrition, University of Minnesota, St. Paul, MN*

GARY D. STONER, PHD • *Division of Hematology and Oncology, Department of Internal Medicine, Innovation Centre, The Ohio State University College of Medicine, Columbus, OH; Comprehensive Cancer Center, The Ohio State University College of Medicine, Columbus, OH*

CYNTHIA A. THOMSON, PHD, RD • *Department of Nutritional Sciences, The University of Arizona, Tucson, AZ*

CORNELIA M. ULRICH, PHD • *Fred Hutchinson Cancer Research Center, Cancer Prevention Research Program, Seattle, Washington, WA; NCT Division of Preventive Oncology, German Cancer Research Center, Heidelberg, Germany*

GEMMA E. WALTON, PHD • *Food Microbial Sciences Unit, Department of Food Biosciences, The University of Reading, Reading, UK*

JUN WANG, MD • *Department of Pharmacology and Toxicology, University of Alabama at Birmingham, Birmingham, AL*

TIMOTHY G. WHITSETT JR., PHD • *Department of Pharmacology and Toxicology, University of Alabama at Birmingham, Birmingham, AL*

LI-SHU WANG, PHD • *Comprehensive Cancer Center, The Ohio State University College of Medicine, Columbus, OH*

CHUNG S. YANG, PHD • *Department of Chemical Biology, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, NJ*

XINRAN XU, PHD • *Mount Sinai School of Medicine, New York, NY*

NANCY ZIKRI, PHD • *Department of Cardiovascular Medicine, The Ohio State University College of Medicine, Columbus, OH*