Oncology Nutrition *for* Clinical Practice

Second Edition

Oncology Nutrition Dietetic Practice Group
Editors: Anne Coble Voss, PhD, RDN, LDN, *and*
Valaree Williams, MS, RD, CSO, LDN, CNSC, FAND

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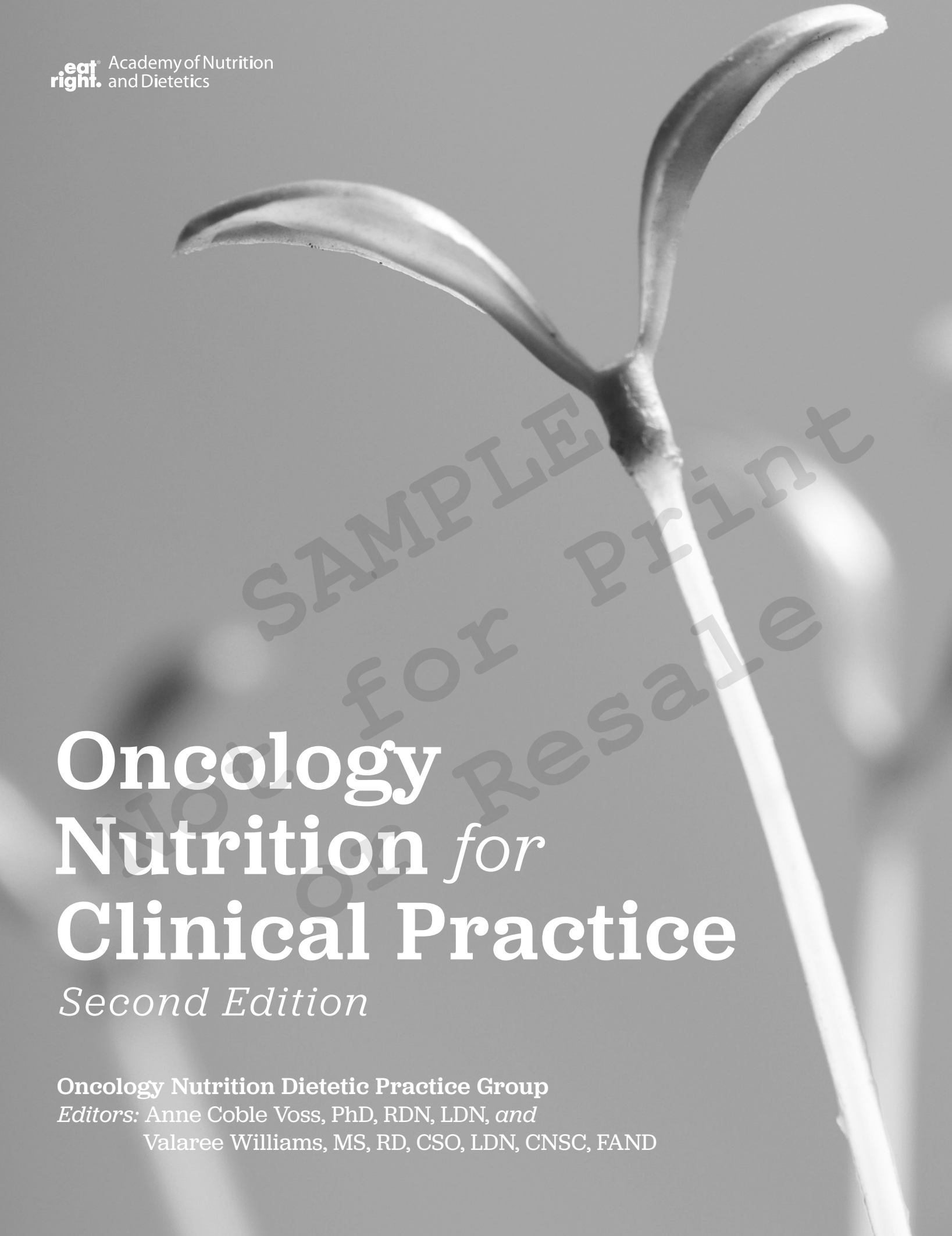

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Preface

Anne Coble Voss, PhD, RDN, LDN
Valaree Williams, MS, RD, CSO, LDN, CNSC, FAND
Editors, *Oncology Nutrition for Clinical Practice,* Second Edition

Oncology Nutrition for Clinical Practice, first published in 2013 by the Oncology Nutrition Dietetic Practice Group, has served as a vital text for registered dietitian nutritionists (RDNs) providing nutrition care to patients with cancer. The intent of this fully updated second edition is to provide both evidence- and experienced-based information for application in clinical practice.

Written and reviewed by knowledgeable RDNs practicing in oncology, this comprehensive resource can be read cover to cover, especially by those new to oncology nutrition, or individual chapters can serve as a guide for clinical practice for both experienced oncology practitioners as well as those who may only work occasionally with patients with cancer. To complement this edition, the new *Oncology Nutrition: Educational Handouts and Resources*, also developed by the Oncology Nutrition Dietetic Practice Group, provides handouts and practical guidance for the nutrition professional to use when counseling their patients with cancer.

This second edition addresses nutrition through the cancer continuum—from carcinogenesis and prevention to treatment, survivorship, and palliative care. All steps of the Nutrition Care Process are addressed with chapters covering nutrition screening, assessment, diagnosis and treatment of nutrition impact symptoms, and intervention and monitoring through medical nutrition therapy. Thirteen chapters address medical nutrition therapy of specific cancer sites, with a new chapter covering hematological malignancies. New to this edition is a chapter that provides rationale and guidance for the use of medical cannabis in cancer treatment.

To direct readers to the most current cancer treatments, in light of the rapidly changing nature of treatment regimens, an overview of treatment modalities and their associated nutrition impact symptoms are discussed in Chapters 9 and 10, and within the medical nutrition therapy chapters, readers are directed to the National Comprehensive Cancer Network (NCCN) guidelines for treatment of cancer by site for regimens for each specific cancer site discussed. NCCN Guidelines are available at www.nccn.org/professionals (free access after registration).

To demonstrate the use of standardized language, sample cancer-specific nutrition diagnosis (PES) statements, developed through collaboration with the Oncology Nutrition Dietetic Practice Group and Academy of Nutrition and Dietetics Nutrition Care Process staff, are included at the end of each medical nutrition therapy chapter. These sample nutrition diagnostic statements support the efforts of the Oncology Nutrition Dietetic Practice Group to increase use of standardized language in documentation of patient care by the RDN to support nutrition outcome measures in the future. In addition to concise, uniform, and complete documentation of nutrition interventions and outcomes by the RDN, standardized language is also essential to the evaluation and coordination of care, determination of the type, level, and complexity of the nutrition intervention, and—most importantly—to the generation of new understanding of the effectiveness and outcomes of nutrition intervention provided by the oncology RDN.

Of special note is the use of the term *cancer survivor* in this edition. Although the National Cancer Institute and some other groups consider a patient to be a survivor from the time of diagnosis until the end of life, this book uses cancer survivor to describe the period posttreatment, and separate from diagnosis, treatment, and end-of-life care. This definition helps to differentiate the nutrition care provided to those living after cancer therapy who may be disease-free or who have stable disease and desire medical nutrition therapy to maintain or improve quality of life and institute measures to prevent future cancers (see Chapters 2 and 8).

We are grateful to the contributors for sharing their expertise and to the reviewers for providing thoughtful, thorough review. With the known impact of nutrition on the development, treatment, and outcomes of cancer, we hope that readers find this second edition to be an essential and useful professional resource to further their expertise and practice.

About the Editors and the Oncology Nutrition Dietetic Practice Group

Anne Coble Voss, PhD, RDN, LDN, writes, lectures and consults on oncology nutrition and oncology nutrition research design following a career as an associate research fellow in the Volwiler Society at Abbott Nutrition.

Dr Voss has experience in the creation of national and international oncology nutrition guidelines and has extensive experience in oncology nutrition research. She held leadership positions in local and state dietetic associations and the Oncology Nutrition Dietetic Practice Group and sat on the Council on Research for the Academy of Nutrition and Dietetics. Dr Voss worked for The Ohio State University College of Medicine, The Ohio State University Hospitals, and Johns Hopkins Hospital. She has published over 75 journal articles, monographs, and book chapters.

Dr Voss earned her undergraduate degree in medical dietetics and a PhD in nutritional biochemistry from The Ohio State University. She recently received the Academy of Nutrition and Dietetics Distinguished Practice Award, The Ohio State University Distinguished Alumni Award, a President's Award, and a Luminary Award from Abbott Laboratories.

Valaree Williams, MS, RD, CSO, LDN, CNSC, FAND is a clinical dietitian at the Hospital of the University of Pennsylvania of the University of Pennsylvania Health System in Philadelphia. Over the past 9 years, she has specialized in caring for patients with cancer, focusing on cancers of the gastrointestinal tract. She serves in several volunteer roles for the Academy of Nutrition and Dietetics and is a commissioner for the Commission on Dietetic Registration. Additionally, she has contributed to textbooks on nutrition for patients with cancer.

Valaree received a bachelor of science degree in dietetics from the Indiana University of Pennsylvania, completed her dietetic internship at the University of Pittsburgh Medical Center Presbyterian-Shadyside, and obtained her master of health sciences degree from Chatham University.

Oncology Nutrition Dietetic Practice Group (ON DPG) is a dietetic practice group of the Academy of Nutrition and Dietetics with the mission of empowering members as oncology nutrition leaders and experts through advocacy, education, and research. Efforts of the ON DPG focus on oncology nutrition practice in areas including research, prevention, treatment, recovery, palliative care, and hospice. The ON DPG provides oncology nutrition resources for the public in addition to supporting dietetic professionals with evidence-based tools and professional networking opportunities to assist with managing the complexities of oncology nutrition practice.

Chapter 1
Overview of Cancer, Carcinogenesis, and the Role of Nutrition

Maki Inoue-Choi, PhD, MS, RD
Kim Robien, PhD, RD, LD, CSO, FAND

The term *cancer* refers to a group of neoplastic diseases characterized by the uncontrollable growth and spread of abnormal cells, which if left untreated may result in death. There are more than 100 types of cancer, each with its own etiology, progression, recommended treatment, and prognosis.[1]

This chapter addresses the following:

- cancer statistics in the US adult population
- health care expenditures for cancer care
- cancer screening
- cancer classification (staging) methods
- the role of nutrition across the cancer continuum

Box 1.1 lists the five most common types of new cancer cases in the United States for men and women in order of most to least common.

Box 1.1

The Five Most Common Types of New Cancer Cases in the United States[2]

Men	Women
1. Prostate	1. Breast
2. Lung and bronchus	2. Lung and bronchus
3. Colorectal	3. Colorectal
4. Urinary (bladder)	4. Uterine
5. Melanoma (skin)	5. Thyroid

Cancer Statistics

Using data from the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute (NCI), a premier source for cancer statistics in the United States, the American Cancer Society (ACS) estimated that approximately 1.8 million new cancer cases would be diagnosed in 2020.[1] Cancer is the second most common cause of death in the United States, after heart disease; it accounts for nearly one in every four US deaths and caused approximately 600,000 deaths in 2020.[2]

Approximately 40% of men and 38% of women in the United States will develop cancer during their lifetime.[1] Among all racial and ethnic groups in the nation, Blacks and non-Hispanic Whites have the highest cancer incidence rates.[3]

The 5-year survival rate for all cancers has improved from 49% for cancers diagnosed between 1975 and 1977 to 69% for cancers diagnosed between 2009 and 2015; yet it remains lower among Blacks (64%) than Whites (70%) (see Figure 1.1 on page 2).[2] Survival rates vary significantly by cancer type and stage at the time of diagnosis.

Cost of Cancer Care

The financial costs of cancer care are a burden for cancer patients, their families, and society. Individually, cancer survivors face not only direct costs related to health care expenses but also lost income due to illness, decreased productivity, and premature mortality.[4]

The NCI estimates that the cost of cancer care in 2010 was $157 billion. This figure was expected to reach $173 billion by 2020, given the growth and aging of the US population.[4,5] Additional costs will occur with the increase in cancer incidence expected with increased longevity.[6] Even if cancer incidence remains constant or decreases, the absolute number

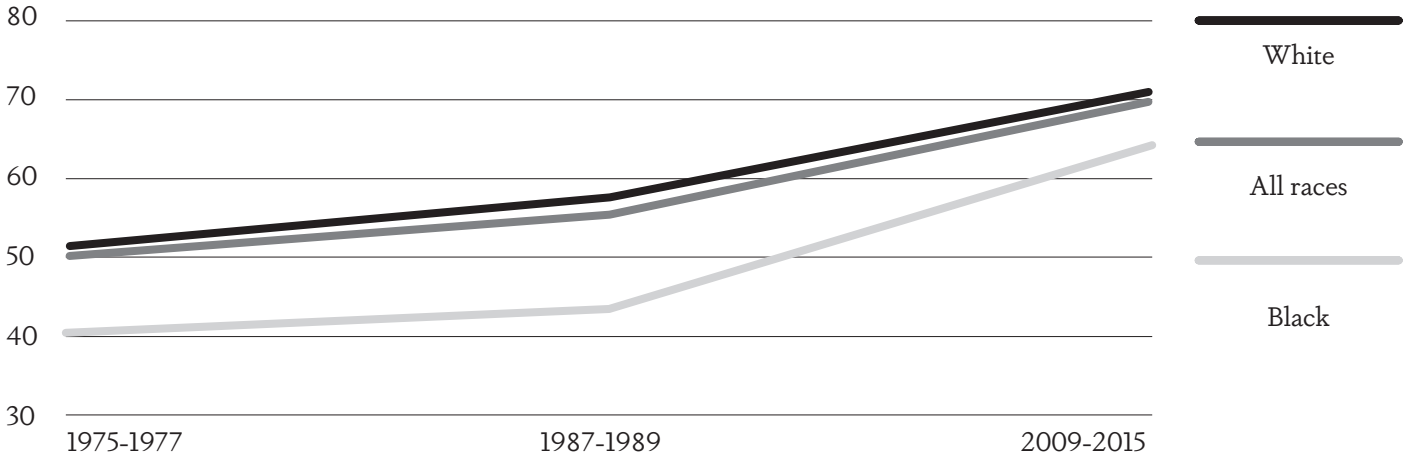


Figure 1.1
Trends in 5-year cancer survival rates by race

Adapted from American Cancer Society. Cancer Facts & Figures 2020. American Cancer Society; 2020. Accessed January 5, 2021. www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2020.html. See reference 2.

of people treated for cancer will increase, as the overall population increases and ages. The largest projected increase in costs for 2020 was expected to result from long-term continuing care for survivors of breast cancer and prostate cancer, the most common cancers in women and men, respectively.[5]

Cancer Screening

Regular screening can result in early detection of precancerous lesions and diagnosis of cancer at an early stage, when it is most treatable. "Early" cancer detection is the identification of tumors before they become palpable; early detection is an active area of cancer research with the potential to significantly decrease cancer morbidity, mortality, and health care costs.[5] Over the last few decades, significant decreases in death rates from certain cancers, such as breast and colorectal, have been attributed largely to increased screening, as well as to advancements in treatment options.[2] There are several types of screening that can be employed:

- Palpation (physical examination) (eg breast or testicle self-examination or a skin examination) is the most common type of screening; however, by the time a cancer is detected by palpation, it can be fairly advanced.
- Blood tests, such as prostate-specific antigen testing, are used to determine levels of circulating tumor cell metabolites.
- Imaging procedures, such as mammograms and colonoscopies, can detect cancers that are too small to feel by physical examination.
- Molecular techniques (for genetic biomarkers), such as genotyping or gene expression assays, look for certain genetic mutations that are linked to some types of cancer. Researchers are also exploring possible use in early cancer detection, as well as many radiographic techniques.

With all types of screening, false test results can occur. For example, test results might appear to be abnormal, even though there is no cancer. False-positive results can cause anxiety in patients and are usually followed by more invasive tests and procedures. Conversely, screening results might appear to be normal, even though a cancer

is present. False-negative test results may delay appropriate medical care. The ACS publishes annual cancer screening guidelines on its website (www.cancer.org).[7]

Cancer Staging

Staging is a process for describing the severity of a cancer based on the extent of disease and whether the primary tumor has spread to other areas of the body (metastasized) at the time of diagnosis. Staging is essential to determining the appropriate treatment plan and estimating prognosis at the time of diagnosis. A number of different staging systems are used to classify cancer, but the tumor, (lymph) node, metastasis (TNM) classification system[8,9] is one of the most widely used tumor staging tools, especially for solid tumors. Each tumor is assigned a grade for each letter: the T grade reflects the size and extent of the tumor; the N grade is for the extent of spread to local lymph nodes; and the M grade indicates the presence or absence of distant metastasis. The number added to each letter indicates the size or extent of the primary cancer and the extent of cancer spread (see Box 1.2).

For some cancers, the TNM classification is not the only system that determines the stage. For most cancers, a grading system is also used. Grade is a measure of how abnormal the cancer cells look under the microscope; this is called differentiation (see Box 1.3 on page 4). Grade can be important because cancers that look more abnormal, or that are more differentiated, tend to grow and spread faster. Each type of cancer has a unique grading

Box 1.2

Summary of the Tumor, Lymph Node, Metastasis (TNM) Classification System[9]

Primary tumor (T)

Grade	Definition
TX	Tumor cannot be evaluated
T0	No evidence of tumor
Tis	*Carcinoma in situ* (CIS): Abnormal cells are present but not spread to neighboring tissues Although not cancer, CIS may become cancer
T1	Tumor not palpable or visible by imaging
T2	Tumor confined to the primary cancer site
T3	Tumor extends to the neighboring tissue
T4	Metastatic disease

Lymph nodes (N)

Grade	Definition
NX	Regional lymph nodes cannot be evaluated
N0	No regional lymph node involvement
N1 N2 N3	Involvement of regional lymph nodes (number of lymph nodes indicates extent of spread)

Distant metastasis (M)

Grade	Definition
MX	Distant metastasis cannot be evaluated
M0	No distant metastasis
M1	Distant metastasis is present

system. Tumors also are described according to their nuclear grade, which describes the size and shape of the nucleus in the tumor cells and the percentage of tumor cells that are actively dividing.[8]

Box 1.3

Tumor Grading System of the American Joint Committee on Cancer[9]

Grade	Description
GX	Grade cannot be assessed (undetermined grade)
G1	Well-differentiated (low grade)
G2	Moderately differentiated (intermediate grade)
G3	Poorly differentiated (high grade)
G4	Undifferentiated (high grade)

Carcinogenesis

Carcinogenesis is the process by which normal cells transform into cancer cells, usually as a result of accumulated genetic damage. Carcinogenesis is commonly described as a process consisting of three phases:

1. Initiation, during which normal cells develop some type of DNA damage
2. Promotion, during which initiated cells are stimulated to grow
3. Progression, when the tumor grows rapidly and invades neighboring tissues

In the initiation phase, normal cells develop genetic damage as a result of exposure to environmental factors, such as radiation, chemicals, or viruses. DNA damage also can result from chronic inflammation due to long-term disease. Some of these factors damage DNA directly. Others, especially some chemicals, attach to the DNA and prevent normal transcription and translation of the DNA.[10]

Under normal conditions, cellular processes involving DNA repair enzymes allow cells to repair individual instances of DNA damage. If the damage cannot be repaired, it can trigger what is called cell cycle arrest, which results in a process known as apoptosis (programmed cell death). However, if the initiated cell does not undergo cell cycle arrest and apoptosis, it could progress to become cancer. Damage that occurs within the DNA repair genes can lead to alterations in these normal repair processes and stimulate uncontrolled tumor growth.[10]

Although genetic susceptibility increases the risk for developing certain types of cancer, other factors commonly associated with cancer incidence and progression include:

- internal environmental factors, such as hormones and the immune system;
- external environmental factors, such as infections and exposure to environmental toxins; and
- unhealthy behaviors, such as smoking, excessive sunlight exposure, and unhealthy diet.[11,12]

These factors may act in combination to initiate or promote carcinogenesis. Estimates are that one-third of cancer deaths are smoking-related, and another third are related to overweight or obesity, physical inactivity, and poor diet.[13]

Nutrition and Carcinogenesis

Evidence, primarily from in vitro studies, suggests that nutrients can play a protective role during all stages of carcinogenesis (see Figure 1.2 on page 6).[10] Chapter 2 addresses the role of nutrition in cancer prevention in more detail. In general, mechanisms by which food components might have protective effects in preventing cancer incidence and progression include:

- promotion of detoxification of carcinogens;
- prevention of oxidative damage to DNA;
- inhibition of the cell cycle or induction of apoptosis in initiated cancer cells; and
- support of DNA repair, cell differentiation, hormone regulation, carcinogen metabolism, and anti-inflammatory responses.

The roles that energy balance and body weight play in cancer incidence and treatment outcomes are becoming better understood; however, the exact mechanisms are complex and not fully known. Higher levels of adiposity and lower lean body mass have consistently been associated with increased risk for many types of cancers, as well as for poor treatment outcomes.[14] Excess adipose tissue has been shown to alter the interactions between insulin, growth hormone, insulin-like growth factors, sex hormones, and adipocyte-derived cytokine levels to precipitate favorable environments for cancer incidence and progression.[15] See Chapter 3 for more details about the relationship between energy balance and cancer incidence.

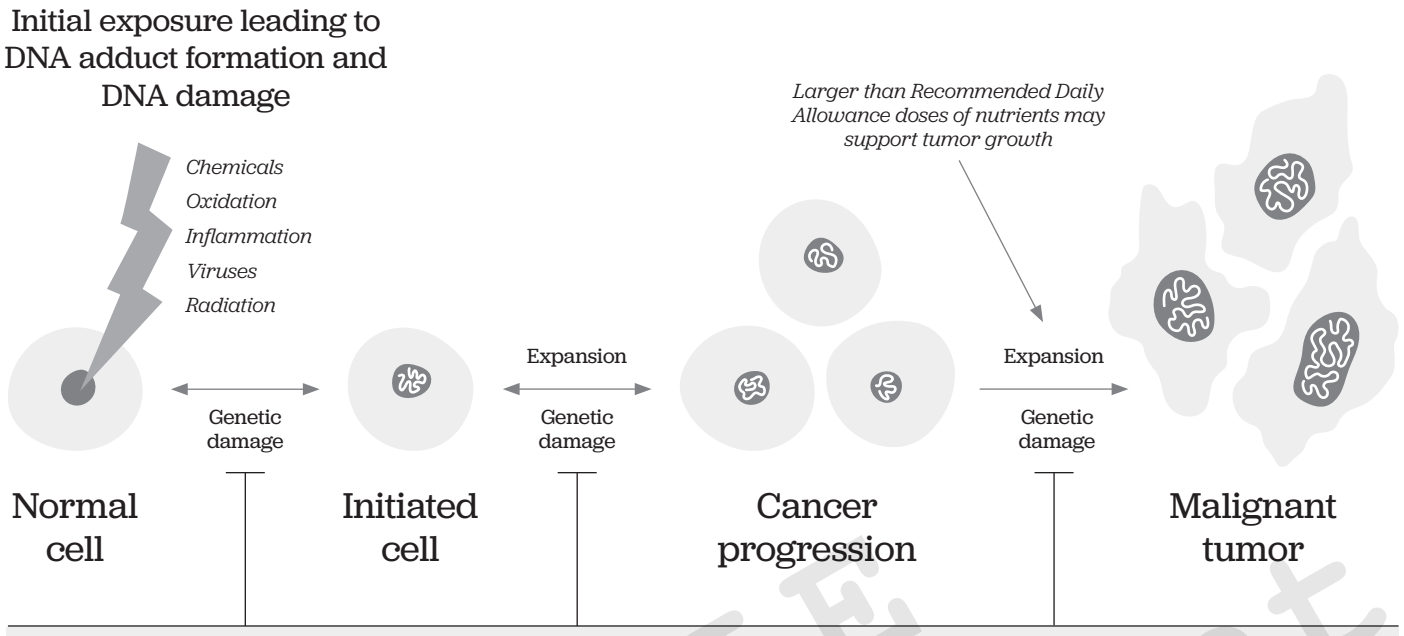
Certain diet-related factors also might increase the risk for developing cancer. For example, cooking meats at high temperatures (eg, grilling over an open flame) can precipitate formation of heterocyclic amines and polycyclic aromatic hydrocarbons, which have been shown to form DNA adducts (a portion of DNA attached to a cancer-causing chemical).[15,16] Foods also can serve as a vehicle for exposure to environmental toxins, such as aflatoxins (a family of fungal toxins associated with peanuts and other agricultural crops), which form DNA adducts,[17] or the endocrine-disrupting chemical bisphenol A (BPA, found in plastic bottles and food containers), which can stimulate proliferation of estrogen-mediated cancers, such as breast or ovarian cancer.[18] Excessive doses of nutrients more than the Recommended Dietary Allowance also might enhance progression of initiated cancer cells.[11,12]

Role of Nutrition in Cancer Treatment

Primary treatments for cancer include surgery, radiation, chemotherapy, hormone therapy, immunotherapy, biological therapy, targeted therapy, transplantation, and various combinations of these modalities.[19] Treatment selection depends on the cancer type, stage of disease, and other factors, such as the patient's age and comorbid conditions. Supportive care with nutrition and physical activity interventions, as well as complementary and alternative medicine approaches, is increasingly being used.

As noted previously, nutrients can play different roles at different stages of carcinogenesis (see Figure 1.2 on page 6). For example, folate is a vital nutrient for maintaining accurate DNA synthesis and repair; thus, adequate folate intake is important for preventing many types of cancers. However, once carcinogenesis has been initiated, folate can facilitate DNA synthesis in cancer cells, leading to proliferation and expansion of the tumor.[20] Methotrexate, an antifolate chemotherapeutic agent, targets this metabolic process by inhibiting folate-mediated DNA synthesis, thus stopping cancer-cell proliferation. Folate in the form of leucovorin calcium may be used to "rescue" patients from methotrexate toxicity or, alternatively, to enhance the effectiveness of drugs, such as fluorouracil (5-FU), that target enzymes that use folate as a cofactor.[21]

Chemotherapeutic agents are designed to kill cancer cells, which often grow and divide more rapidly than normal cells. However, most chemotherapy drugs are indiscriminate and also damage normal cells, such as blood cells in the bone marrow, cells in the digestive tract (including the mouth, esophagus, stomach, and intestines), cells in the reproductive system, and hair follicles.[19] Common side effects of chemotherapy, such as loss of appetite, nausea, mucositis, and diarrhea, result from this



Biological process protecting the cell, preventing cancer initiation and progression:	Examples of nutrients shown to support the process:
Detoxification of carcinogens	Isothiocyanates, flavonoids
Protection of DNA from oxidation	Vitamins A, C, D, and E, selenium
DNA repair	Folate, selenium, lycopene, retinoids
Cell cycle regulation	Polyphenols, retinoids, folate, selenium
Promotion of cell differentiation	Long-chain omega-3 fatty acids, vitamin D, retinoic acid
Induction of apoptosis in initiated cells	Curcumin, polyphenols, sulforaphane, isothicyanates, quercetin, lycopene
Prevention of angioneogenesis	Indol-3-carbinol, curcumin
Suppression of inflammation	Omega-3 fatty acids, indol-3-carbinol
Regulation of hormonal signals	Soy isoflavones, vitamin D, carotenoids

Figure 1.2
Possible effects of nutrients on various stages of carcinogenesis

Healthy cells can develop genetic damage from exposure to environmental factors, such as radiation, chemicals, or viruses. Nutrients can play a protective role in these early carcinogenetic processes.

Adapted from World Cancer Research Fund/American Institute for Cancer Research. The cancer process. In: *Diet, Nutrition, Physical Activity and Cancer: A Global Perspective. Continuous Update Project Expert Report 2018*. Accessed January 12, 2020. www.wcrf.org/dietandcancer/cancerprocess. See reference 10.

cellular damage. Radiation therapy can also cause side effects by damaging normal, healthy cells near the treatment site.[19] Nutrition and pharmacologic intervention can help prevent significant malnutrition and loss of muscle mass caused by treatment side effects. Studies suggest that nutrition intervention during cancer treatment is associated with fewer treatment-related side effects,[22-25] fewer hospitalizations,[24-26] and improved quality of life.[22,23,27] The role of nutrition interventions during site-specific cancer treatment is discussed in further detail in Chapters 13 through 25.

The Role of Posttreatment Nutrition

Nutrition remains a fundamental component of recovery after cancer treatment. Individuals who have completed cancer treatment might experience treatment-related late effects, such as changes in body composition, bone density, or cardiovascular complications. Cancer recurrence or second primary cancers also can be a concern. Healthy dietary choices are an important part of an overall strategy to prevent or manage these conditions. See Chapter 8 for further discussion of the role of nutrition after cancer treatment.

Summary

As shown in Box 1.4 on pages 8 and 9, nutrition plays a significant role across the cancer continuum. A healthy diet and lifestyle can help decrease the risk of cancer development and can improve cancer outcomes. More research is needed to gain a clearer understanding of the specific role nutrition plays in cancer biology, treatment regimens, and management of treatment side effects.

Box 1.4

Potential Nutrition-Related Concerns and Outcomes Across the Cancer Continuum

		Diagnosis
Stage in continuum	**Cancer prevention**	**Initial treatment**
Potential nutrition concerns	■ Obesity, loss of muscle mass ■ Energy-dense food intake ■ Excessive micronutrient intake from dietary supplements ■ Food contaminants (toxins, chemicals)	■ Treatment side effects (eg, nausea, vomiting, diarrhea, mucositis, taste changes) ■ Fatigue ■ Pain ■ Anorexia ■ Treatment-related cachexia ■ Immunosuppression ■ Weight or body-composition changes ■ Drug-nutrition interactions
Potential outcomes of nutrition interventions	■ Improved weight and body composition ■ Improved blood glucose control ■ Improved immune surveillance	■ Ability to adhere to scheduled treatment ■ Fewer infectious complications ■ Improved weight and body composition ■ Delay or prevention of disease progression ■ Improved chances of survival ■ Improved quality of life

Adapted from Robien K, Demark-Wahnefried W, Rock CL. Evidence-based nutrition guidelines for cancer survivors: current guidelines, knowledge gaps, and future research directions. *J Am Diet Assoc*. 2011;111(3):368-375. See reference 28.

	≥5 Years After Diagnosis
Early posttreatment	**Long-term cancer survivorship**
■ Fatigue ■ Pain ■ Endocrine disorders ■ Weight or body-composition changes ■ Cognitive deficits ■ Dental caries or complications	■ Weight loss or gain ■ Decreased bone density ■ Endocrine disorders ■ Cardiovascular complications ■ Cognitive deficits ■ Dental caries or complications
■ Decreased fatigue ■ Improved functional status ■ More rapid recovery from treatment ■ Improved weight and body composition ■ Decreased risk for cancer recurrence and subsequent primary cancers ■ Improved chances of survival ■ Improved quality of life	■ Fewer late effects of treatment ■ Improved functional status ■ Improved weight and body composition ■ Decreased risk of cancer recurrence and subsequent primary cancers ■ Improved chances of survival ■ Improved quality of life ■ Decreased health care costs

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Chapter 2
Nutrition and Cancer Prevention

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A substantial proportion of cancer cases in the United States are preventable. An estimated 40% of cases could be prevented through healthful dietary patterns, regular physical activity, maintaining a healthy weight (low body mass index and low adiposity), avoiding tobacco and excess sun exposure, and getting certain vaccines and regular screenings.[1]

In 2018, the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) jointly established recommendations for cancer prevention based on a structured and systematic approach of analyses and review of the literature on food, nutrition, physical activity, and cancer by an expert panel. These recommendations and the science behind them are outlined in this chapter.[2] The chapter also includes a section on emerging food and nutrition topics of special interest. These topics are being actively studied, but currently there is limited or inconsistent evidence regarding the effects of the various foods and practices on cancer risk.

Recommendations for Cancer Prevention

The 2018 World Cancer Research Fund and American Institute for Cancer Research (WCRF/AICR) cancer prevention recommendations are aimed at the overall prevention of cancer and are compatible with the *2020–2025 Dietary Guidelines for Americans*, which focus on promoting overall health, reducing the prevalence of overweight and obesity, and preventing diet-related chronic diseases.[3] They also align with the American Cancer Society (ACS) guidelines on nutrition and physical activity for cancer prevention.[4] Box 2.1 on pages 14 and 15 summarizes the WCRF/AICR recommendations for cancer prevention. Appendix A compares cancer prevention diet and lifestyle recommendations from various organizations. Each section that follows addresses a WCRF/AICR recommendation and describes the link to specific cancers, the proposed mechanisms, and key practice points.

Adiposity and Weight Gain

Maintaining a healthy body weight throughout life may be the most important lifestyle factor in reducing cancer risk, second only to not using tobacco products.[5] There is convincing evidence that a greater degree of body fatness—or greater adiposity—is a cause of cancers of the esophagus (adenocarcinoma), pancreas, colorectum, breast (postmenopausal), endometrium, liver, and kidney. Greater body fatness is probably also a cause of cancers of the stomach (cardia), gallbladder, ovaries, and mouth, pharynx, and larynx; and it has also been implicated in advanced prostate cancers.[2]

Excess body fatness could influence cancer risk through several possible mechanisms:

- Excess body fat is associated with insulin resistance, resulting in elevated levels of insulin and increased bioavailable insulin-like growth factor 1 (IGF-1).[2,6] Insulin and IGF-1 can activate signaling pathways that promote growth and proliferation of cancer cells and inhibit apoptosis (programmed cell death).[7-9]
- Overweight and obesity can lead to chronic low-grade systemic inflammation, which can

Appendix C
Select Dietary Supplements and Functional Foods

This information is designed to provide practitioners with available research on select dietary supplements and functional foods and how they relate to cancer. Its purpose is neither to condone nor to discourage use by patients. A patient's health care team can determine which supplements or foods are appropriate, if any.

616
Aloe
(*Aloe barbadensis* miller)

618
α-Lipoic acid

620
Black cohosh
(*Cimicifuga racemosa*)

622
Coenzyme Q10 (CoQ10)

624
Curcumin (*Cucurma longa*)

626
3,3'-Diindolylmethane (DIM) and indole-3-carbinol (I3C)

628
Flaxseed
(*Linum usitatissimum*)

630
Garlic (*Allium sativum*)

632
Ginger (*Zingiber officinale*)

634
Ginkgo biloba

636
Glutamine

638
Green tea
(*Camellia sinensis*)

640
Melatonin

642
N-acetylcysteine (NAC)

644
Omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)

646
Quercetin

648
Reishi mushroom
(*Ganoderma lucidum)*

650
Resveratrol

652
Selenium

654
Silymarin

656
St. John's wort
(*Hypericum perforatum*)

658
Theanine

660
Turkey tail mushroom or Yun Zhi (*Coriolus versicolor*, *Trametes versicolor*, *Polyporous versicolor*)

662
Vitamin D

Aloe (*Aloe barbadensis* miller)

A cactus-like plant, aloe is used predominantly in the form of a gel or a juice.[1-5]

Reported anticancer benefits	May be useful for constipation
Reported anticancer concerns	Well tolerated and good safety data on aloe juice and aloe vera gel Aloe latex used orally may be unsafe and may cause diarrhea
Evidence	Aloe use may delay radiation dermatitis in patients with head and neck cancer.[2] In a randomized study, patients with lung cancer who consumed aloe mixed with honey three times daily during chemotherapy significantly increased response compared with those who had chemotherapy alone.[3] Radiation proctitis significantly improved in patients who used aloe vera 3% ointment in a preliminary randomized controlled clinical trial.[4]
Comments	N/A

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α-Lipoic acid

α-Lipoic acid is a cellular antioxidant important for energy production that is naturally synthesized in the body.

Reported anticancer benefits	Improves insulin sensitivity and diabetes management Aids with hypertension May mitigate radiation damage May reduce symptoms of neurotoxicity Inhibits growth of breast, colon, lung, liver, and pancreatic cancer cells
Reported anticancer concerns	Generally, very well tolerated
Evidence	α-Lipoic acid used orally or intravenously seems to improve insulin sensitivity and fasting blood glucose levels in patients with type 2 diabetes.[1-4] α-Lipoic acid is reported to inhibit tumor cells both in vitro and in vivo.[5] α-Lipoic acid has been found to reduce neuropathic symptoms and triglycerides and improve quality of life.[6] α-Lipoic acid administration is ineffective at preventing neurotoxicity caused by oxaliplatin or cisplatin.[7] However, Opera (GAMFARMA), a combination product composed of α-lipoic acid, *Boswellia serrata*, methylsulfonylmethane, and bromelain, improved peripheral neuropathy symptoms in a prospective series of patients treated for neurotoxic chemotherapy; no significant toxicity or interaction was observed.[8] α-Lipoic acid reduced radiation-induced oral mucositis in rats with head and neck cancer in one study.[9]
Comments	α-Lipoic acid is both fat- and water-soluble and is thus able to function throughout the body.[10] Dietary sources rich in α-lipoic acid include spinach, broccoli, and brewer's yeast. The evidence for supplemental α-lipoic acid is still to be determined, but there appears to be potential benefit regarding insulin sensitivity, peripheral neuropathy, and mucositis.

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Vitamin D

Vitamin D is a fat-soluble vitamin with anti-inflammatory, immunomodulatory, bone protective, and anticancer effects.

Reported anticancer benefits	Regulates genes that influence cell proliferation and apoptosis[1]
Reported anticancer concerns	Toxicity, which can result in hypercalcemia[1]
Evidence	People living in geographic areas with greater sun exposure (which triggers vitamin D synthesis in the human body) have lower cancer rates.[2] Vitamin D helps regulate genes that influence cell proliferation, differentiation, and apoptosis.[1] Vitamin D controls immune cell regulation and differentiation, gut barrier function, and antimicrobial peptide synthesis, all of which may serve as protective factors against colon cancer.[3] An inverse association between cancer and 25-hydroxyvitamin D levels is strongest for colon cancer.[3-5] Several observational studies have supported an inverse association between vitamin D intake or 25-hydroxyvitamin D level and breast cancer,[6,7] while others have not.[8,9] A meta-analysis reported a significant inverse association between vitamin D and breast cancer in postmenopausal women[10] but not in premenopausal women.[11] Researchers reported a consistent prognostic association between 25-hydroxyvitamin D levels and survival in patients with colorectal cancer.[12] Most observational studies have found that vitamin D consumption is not associated with a risk for prostate[13,14] and ovarian cancers.[15] There may be an inverse association between vitamin D supplementation and overall mortality.[16] In a large prospective trial (1,260 cases vs 1,331 controls), men in the highest quartile for plasma 25-hydroxyvitamin D levels had a significantly lower risk for lethal prostate cancer than men in the lowest quartile.[17]
Comments	Vitamin D sufficiency is important for overall health, including cancer prevention. Because 25-hydroxyvitamin D has a longer half-life than 1,25 dihydroxyvitamin D (15 days vs 15 hours, respectively), 25-hydroxyvitamin D is used to assess vitamin D status.[1] The bioavailability of vitamin D3 (cholecalciferol) is significantly greater than that of vitamin D-2 (ergocalciferol).[18] The Dietary Reference Intakes for vitamin D were revised in 2010 and the Tolerable Upper Intake Level of vitamin D increased to 4,000 IU/d.[1] The Endocrine Society has suggested that maintenance of a 25-hydroxyvitamin D blood level of 40 to 60 ng/mL is ideal (this takes into account assay variability) and that up to 100 ng/mL is safe.[19]

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