This completely revised second edition of the gold-standard reference on cancer rehabilitation provides a state-of-the-art overview of the principles of cancer care and best practices for restoring function and quality of life to cancer survivors. Authored by some of the world’s leading cancer rehabilitation experts and oncology specialists, the book opens with primer-level discussions of the various cancer types and their assessment and management, including potential complications, as a foundation for providing safe and effective rehabilitation. Subsequent sections thoroughly explore the identification, evaluation, and treatment of specific impairments and disabilities that result from cancer and the treatment of cancer. Described to serve the needs of the entire medical team, this singular resource is intended for any clinician working with cancer survivors to improve function and quality of life.

With several new chapters on topics such as inpatient cancer rehabilitation, pediatric oncology, research issues, and barriers to accessing cancer rehabilitation and building a cancer rehabilitation program, the book keeps pace with recent advances in the growing field of cancer rehabilitation. This new edition features updates throughout and expansions to major topics, including imaging in cancer and key disorders such as aromatase inhibitor-induced arthralgias. Presenting the most current medical, clinical, and rehabilitation intelligence, this is a mandatory reference for anyone in the field.

**Praise for the previous edition:**

“This book is a milestone and must-have for anyone involved in the care of those with cancer.”
—American Journal of Physical Medicine and Rehabilitation

“This reference provides a comprehensive, pragmatic approach for physical medicine physicians, speech, occupational, and physical therapists, and nurses with cancer survivor responsibilities. (A)ny cancer program with significant rehabilitation services will find this a useful addition to its library.”
—JAMA (Journal of the American Medical Association)

**Key Features:**

- New edition of the only contemporary comprehensive text covering the field of cancer rehabilitation
- Revised and updated to reflect current knowledge, practice, and emerging topics
- Covers essential aspects of oncology and medical complications of cancer to inform rehabilitation decisions and strategies
- Provides evidence-based principles and important issues in cancer rehabilitation, including pain assessment and management, neurorehabilitation, and functional outcomes of cancer survivors
- Digital access to the ebook included

**Recommended Shelving Category:**

Physical Medicine and Rehabilitation; Oncology
Cancer Rehabilitation
Michael Dean Stubblefield, MD, received his medical degree from the Columbia University College of Physicians and Surgeons and completed a combined residency in internal medicine and physical medicine and rehabilitation (PM&R) at Columbia Presbyterian Medical Center in New York City. He is triple board certified in PM&R, internal medicine, and electrodiagnostic medicine (EMG).

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Dr. Stubblefield joined Kessler Institute for Rehabilitation as Medical Director of Cancer Rehabilitation in 2015. He also serves as the National Medical Director of the ReVital Cancer Rehabilitation Program for Select Medical where he supervises the development of comprehensive cancer rehabilitation programs across their vast national network of rehabilitation facilities.

Dr. Stubblefield is globally recognized as a leader in the field of cancer rehabilitation. His clinical expertise is in the identification, evaluation, and rehabilitation of neuromuscular, musculoskeletal, pain, and functional disorders resulting from cancer and its treatment, particularly those caused by radiation and neurotoxic chemotherapy. He is an expert electromyographer and performs procedures such as botulinum toxin (Botox) injections for the relief of pain and spasm in cancer survivors.

Dr. Stubblefield has been on the Castle Connolly list of America’s top doctors, America’s top doctors for cancer, and New York metro area’s top doctors for many years. He is an accomplished researcher who has published extensively authored numerous review articles and book chapters, and frequently lectures on a wide range of cancer rehabilitation-related topics. In addition to his role as editor of *Cancer Rehabilitation: Principles and Practice*, the only comprehensive textbook in the field, Dr. Stubblefield is on the editorial board of the journal *Muscle and Nerve* and is a peer reviewer for more than 30 journals.
Cancer Rehabilitation
Principles and Practice
Second Edition

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To my wife Elyn without who’s love and support this project could never have come to fruition. Also for my parents Linda and Willie to whom I owe so much and my sister Shelia whose presence we shall always miss.
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Foreword

This is an exciting time to be in the field of cancer rehabilitation... we are redefining what cancer rehabilitation is, how and when it is delivered, who is on the rehabilitation team, and how services are coordinated to ease the burden on patients and the healthcare system.

—Catherine M. Alfano, PhD

Nearly 1.7 million Americans (1) and 14.1 million people worldwide (2) are diagnosed with cancer each year. Decades of research have documented that cancer and its treatment can cause significant morbidity including fatigue, pain, neuropathies, balance problems, mobility issues, lymphedema, bladder and bowel problems, dysphonia and other communication difficulties, dysphagia, cardiopulmonary function declines, sexual dysfunction, and cognitive and psychosocial problems, among others (3). While the prevalence of toxicity varies by treatments received, patient age, and other factors: as many as 20% of childhood cancer survivors (4) and 53% of adult onset cancer survivors (5) report limitations in their functioning. Adding to these problems that arise during treatment are late effects of treatment affecting bone, cardiac, and other organ systems that can emerge years after cancer treatment (6,7). The functional limitations from cancer-related impairments contribute to depression, anxiety, and poor quality of life (8–10). Together these problems limit the ability to work (11–14) and increase healthcare utilization, driving up healthcare costs (15), and increasing risk of mortality (16,17).

The good news is that cancer rehabilitation interventions including physical, occupational, or speech therapy; exercise training; psychosocial and cognitive interventions; and physician-directed diagnostic imaging, injections, and pharmacologic symptom management have the potential to treat many impairments from cancer treatment, thereby improving functioning and quality of life (3,18,19). Multimodal rehabilitation interventions have also been shown to improve return to work compared to usual care (20). The chapters of this book review the latest evidence about which interventions should be used to treat specific impairments thereby constituting the most comprehensive and up-to-date reference on this topic.

The challenge for our field is that despite the benefits of cancer rehabilitation interventions, these services are currently under-utilized with referral rates as low as 1% to 2% (21). There are several historical reasons for this (22). The National Cancer Act of 1971 funded clinical cancer research centers and demonstrations projects to assess rehabilitation needs and evaluate rehabilitation interventions and by the early 1980s, a number of hospital-based multidisciplinary cancer rehabilitation teams provided services to cancer patients (23). Since the 1980s, the cancer survivorship movement has taken hold bringing increased focus on quality of life among long-term survivors. However, changes in cancer treatment to less-intensive surgery requiring shorter or no hospital stays coupled with the rise of community cancer centers with no multidisciplinary rehabilitation teams have resulted in a disconnect between cancer rehabilitation and cancer survivorship (22). Driving this point home, the first National Cancer Policy Board report in 1999, “Ensuring Quality Cancer Care” did not include recommendations for integrating cancer rehabilitation into cancer care (24).

As a result of these historical trends, the current cancer care system neither routinely screens patients for impairments nor is there a focus on preventing disability. Without these key components as a part of standard cancer care, referrals to cancer rehabilitation are not made and impairments often go unidentified and unaddressed (21). Additionally, the fragmentation of rehabilitation providers means that when cancer rehabilitation services are prescribed today, they tend to have a one-dimensional focus rather than comprehensive assessment and coordinated delivery of interventions by a multidisciplinary team. Some highly efficacious interventions, especially aerobic exercise (25–27), are rarely prescribed at all and are not routinely covered by insurance when they are prescribed. Compounding this situation, the shortage of oncologists means that post-treatment follow-up care is often being delivered by primary care providers who lack training and awareness of the long-term and late effects of cancer treatment (29) and are thus unlikely to be a source for rehabilitation referrals. The confluence of these factors means that impairments are often detected very late if at all, and survivors struggle with these problems years after treatment ends (30).

We are emerging from that history, however, and there is currently reason for significant enthusiasm. National efforts aim to educate providers and patients about the benefits of cancer rehabilitation and better integrate cancer rehabilitation with oncology and follow-up care. These are co-occurring with scientific research efforts that aim to outline the most effective interventions for given patients and test efficient and effective models of care delivery that limit burden on patients and healthcare systems. In 2005, The National Cancer Policy Forum’s landmark second survivorship report, “From Cancer Patient to Cancer Survivor: Lost in Transition” included cancer rehabilitation as part of cancer survivorship care (6). These recommendations and
a subsequent report (31) emphasized the role that rehabilitation providers play as part of a coordinated cancer care team in optimizing patient recovery. Since 2005, there has been a dramatic increase in the number of published scientific papers devoted to cancer rehabilitation interventions and numerous “calls to action” to increase research and clinical efforts to improve referral and delivery of cancer rehabilitation interventions (3,22,32–37). Current U.S. guidelines for cancer follow-up (survivorship) care include referrals for rehabilitation interventions as the standard of care (38–41). There is a growing understanding of the benefit of rehabilitation among oncologists: cancer rehabilitation sessions are now highlighted at the annual meetings of the American Society of Clinical Oncology. As a further testament to the progress in establishing the role of cancer rehabilitation, in 2015, the National Institutes of Health convened a meeting of cancer rehabilitation experts to prioritize future efforts that promote quality cancer rehabilitation care. The report recommended implementing a model of care that integrates cancer rehabilitation with oncology care beginning at diagnosis (42).

These efforts represent a paradigm shift for the field. Today is an exciting time to be in the field of cancer rehabilitation. To achieve the goal of integrated cancer care and comprehensive rehabilitation care, current national efforts are redefining what cancer rehabilitation is, how and when it is delivered, who is on the rehabilitation team, and how services are coordinated to improve patient outcomes and ease the burden on patients and the healthcare system. A team of stakeholders has developed (43) and refined (32) a prospective surveillance model as a best practice model for cancer rehabilitation. In this model, rehabilitative efforts begin at the time of cancer diagnosis and continue through treatment and after treatment ends, using a multidisciplinary team approach. A multidimensional, comprehensive assessment is conducted at the preoperative evaluation to establish baseline functioning, identify patients with preexisting conditions that may place them at higher risk for the development of treatment toxicities and impairments during and after treatment, and refer patients with current problems for interventions to improve their symptoms and function. Ongoing surveillance efforts with repeated assessments occur throughout and beyond cancer therapy, allowing for monitoring of the development of treatment toxicities or impairments, and facilitation of timely referrals to cancer rehabilitation providers.

Implementing this new approach to cancer rehabilitation will involve generating referrals for both traditional and nontraditional cancer rehabilitation interventions and streamlining this care. To optimize patient functioning and quality of life, a prospective surveillance model for comprehensive cancer rehabilitation must incorporate assessment and referral for physical, psychosocial, and cognitive sequelae of cancer. The goals of this care are to evaluate the sum total of problems that a survivor faces and coordinate their treatment, address preexisting or cancer treatment–related comorbid conditions, and reduce risk of late effects (e.g., the cardiac, pulmonary, endocrine, or bone complications). This may involve providers including physical or occupational therapists, speech-language pathologists, physiatrists, audiologists, dieticians, exercise physiologists, psychologists, social workers, endocrinologists, cardiologists, and other specialists along with the oncology team. This multidisciplinary team of providers must work together to design coordinated interventions that minimize burden to the patient and deliver them initially at the cancer center, and then in outpatient or home settings once treatment for cancer is complete.

The prospective surveillance model has the potential to lead to early identification of symptoms and impairments and appropriate referral and timely treatment. This should in turn increase patient functioning, quality of life, and the ability to engage in work and life roles; improve healthcare utilization, relieving the burden on the primary care workforce unprepared to deal with cancer toxicities; and decrease long-term healthcare costs. For this model to become the standard of care, however, research will need to demonstrate that it helps achieve the triple aim set forth by the Institute for Healthcare Improvement (IHI) (44): facilitating better care for individuals, better health for populations, and lower per capita costs.

Current research is driving three paradigm shifts in cancer rehabilitation that will help assure this model meets the IHI triple aim criteria. First, the expanded prospective surveillance model presents a framework for creating personalized cancer rehabilitation interventions rather than a “one size fits all” approach. The disciplines and services who provide these different interventions, the type and dose of interventions, the environment in which they are provided, and the degree of integration of the team will differ depending on numerous factors including the strengths and expertise of individual providers and existing services, geographic proximity and communication among services, and facility and system resources (32,37). An exemplar here involves current efforts to personalize exercise training prescription (45). Data showing response to exercise training demonstrates considerable heterogeneity (45,46) and data raising safety concerns about exercise training in patients with impaired ability to respond to repeated stress (47–49) suggest that personalized exercise prescriptions may be preferable to the general public health prescription (45,50). Better personalizing cancer rehabilitation interventions also involves leveraging diverse types of patient and clinical data to understand how to predict the best intervention for a given problem in a given patient (51). For example, current research is testing whether multidimensional patient data (e.g., from blood tests and clinical markers, comorbidities, omic data, behavioral data) can be aggregated to phenogroup patients to tailor their exercise prescription to optimize response to exercise and outcomes (52).

Second, researchers are increasingly testing the efficacy of prehabilitation, or initiating cancer rehabilitation interventions before the initiation of cancer therapy, either to prevent problems from occurring or to treat already existing impairments and preserve functioning. Recent reviews of this emerging literature suggest that prehabilitation interventions can reduce functional impairments, improve psychosocial symptoms, and at least for lung cancer patients, some of these interventions may reduce surgical complications and the length of hospitalization (53–55). However, this research is just the beginning. Research priorities for this science include determining which patients are most likely to benefit from prehabilitation and determining the effects of these interventions on response to surgery and perioperative complications, timeliness and adherence to
oncology treatment, and healthcare utilization, in addition to patient functioning outcomes (54).

Third, cancer rehabilitation research is testing models of care delivery that will make these interventions more feasible for patients, addressing logistical and cost hurdles. Telemedicine interventions are being tested that deliver care electronically, in geographic areas that lack formal cancer rehabilitation providers, or by engaging rehabilitation providers with limited cancer expertise. These will provide improved access to rehabilitation interventions but do little to address the cost challenges. Financial problems stemming from cancer are evident in up to 50% of survivors leading survivors to delay or forgo medical care and prescriptions (56–58). Travel costs and copayments for cancer rehabilitation add to this financial burden and make care unfeasible for financially distressed survivors. Taking time off from work for additional outpatient visits is an additional barrier to cancer rehabilitation care for survivors who are employed in jobs with limited sick leave or who have exhausted their sick leave with oncology care visits. Finding ways to deliver cancer rehabilitation care that is coordinated with oncology care, limits out of pocket costs (e.g., through bundled co-pays with oncology care), or other ways to make cancer rehabilitation more feasible for patients are greatly needed.

Perhaps the greatest reason for current enthusiasm about the future of cancer rehabilitation is the increasing numbers of providers—those currently in the workforce and students—who are passionate about learning how to use these interventions to help patients with cancer maximize their functioning and quality of life. This textbook is the most comprehensive and up-to-date source of evidence-based information for them. The information in these pages comes at a critical time as we face increasing numbers of patients and shortages in oncology and primary care providers who can care for the chronic and late effects of cancer and its treatment. Training additional providers in cancer rehabilitation is crucial to meet the growing need for this care. Using the wealth of information presented in these pages to improve clinical practice and inform novel research questions that further drive care improvements has the potential to improve the lives of the over 14 million patients diagnosed around the world each year who are counting on us for help.

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REFERENCES


44. Institute for Healthcare Improvement. IHI Triple Aim Initiative. Institute for Healthcare Improvement.


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Preface

The first version of this textbook took four years and countless hours to complete. For those curious why anyone would take on such an onerous project again, you need look no further than the patient stories accompanying the cover photos. These inspiring cancer survivors and hundreds of others like them have touched me deeply both professionally and personally. I consider it a privilege to be in a position where I can help improve their lives. That said, like many clinicians who care for this extremely challenging population, I am troubled by those instances where my knowledge and skill was inadequate. It is a desire to bolster my own, and my colleague’s, ability to relieve suffering and restore function and quality of life to cancer survivors that motivated this revision.

Like all textbooks, this one is a repository of the essential knowledge concerning the medical specialty of cancer rehabilitation at the time of its publication. It includes not only the latest scientific research, but every bit as important, the clinical approach and thinking of many of the top clinicians in the field. This is the beauty of a textbook—it tolerates and even encourages the marriage of science with the nebulous art of medicine in a way that purely evidence-based scientific manuscripts cannot and should not. This heavy valuation of the art of medicine is extremely important to a discipline as early in its development as cancer rehabilitation is. For many of the impairments we treat, we cannot base our decision making and interventions solely on scientific evidence simply because there is none. Where oncology produces thousands of high-quality studies annually, cancer rehabilitation produces only a handful. While this gap is closing, it will take many more years for our field to mature. In the meantime, we have no less of an obligation to the patients we serve and must use the knowledge and tools at hand to that end as we strive to improve the scientific foundations of our discipline.

This textbook is intended to be used by anyone involved in the rehabilitation of cancer survivors. Safe and effective rehabilitation in this population requires specialized knowledge that is not central to the training of most clinicians. A physical therapist does not learn the details of breast cancer treatment as a part of their schooling at any more than a superficial level. Similarly, a medical oncologist newly minted by a fellowship is unlikely to have a working knowledge of neuromuscular medicine. The truly exceptional cancer rehabilitation clinician will have mastered not only their core specialty but also be extremely knowledgeable about the specifics of the various cancers, their treatment, their complications, and how they impact function.

Many of the world’s leading cancer rehabilitation experts and oncology specialists contributed to this book. As noted earlier, I view an understanding of the principles of oncology as foundational to successful cancer rehabilitation. To that end, primer-level discussions of the various cancer types and their assessment and management, including potential complications, are included. Subsequent sections thoroughly explore the identification, evaluation, and treatment of specific impairments and disabilities that result from cancer and the treatment of cancer. With several new chapters on topics such as inpatient cancer rehabilitation, prehabilitation, pediatric oncology, imaging, dermatologic issues, research issues, barriers to accessing cancer rehabilitation, and building a cancer rehabilitation program, the book keeps pace with recent advances in the growing field of cancer rehabilitation. This new edition features updates throughout and expansions to major topics including imaging in cancer and key disorders such as aromatase inhibitor-induced arthralgias.

Michael D. Stubblefield, MD
Cancer Patients and Their Stories of Perseverance

Susan Choe was diagnosed with a 4-cm low-grade glioma in the right frontal lobe in 2005. Following resection of the tumor, she developed significant left-side hemiparesis, requiring admission to a rehabilitation hospital to re-learn how to walk, speak, and take care of herself and her two young children (ages 4 and 8). Her rehabilitation did not end following discharge. To regain and maintain her function and quality of life, she has required extensive and ongoing outpatient therapy and management by a rehabilitation physician specializing in the care of cancer survivors. In addition to regular botulinum toxin injections to control her spasticity, she has benefited from weekly physical therapy and a modified exercise regimen.

Susan’s hard work, perseverance, and dedication to recovery has paid off. She has since passed the social work board examination and now works full time as a medical social worker in an early intervention program serving 0- to 3-year-old children with developmental delays. Even with significant residual spastic hemiparesis she has earned the physical prowess to resume her favorite pastime—tennis.

Susan knows that her survivorship journey is not over. A recent small regrowth of the glioma prompted the need for proton radiation and subsequent chemotherapy treatment. Going forward, Susan plans to continue with all her rehabilitation efforts so she can maintain a healthy and independent lifestyle that includes extensive traveling to Europe and spending time with her two “almost” adult children, Emma and Grayson, who are now 17 and 21 years old respectively!

Former Minnesota Vikings cheerleader Kelly’s Flaten’s battle with cancer started in 2007 with a burst of pain and a lump in her left breast. The initial lumpectomy did not get the entire tumor so she elected to have a double mastectomy and reconstruction. Her third bout with breast cancer started in January 2009 when the plastic surgeon who performed her reconstruction found a new lump. The lesion was biopsied and confirmed her greatest fear—the cancer was back. She underwent a wide excision to remove the cancerous tissue as well as some of the surrounding muscle. After that, chemotherapy, radiation, and additional reconstruction were needed. Fortunately, the cancer has not returned since.

Ms. Flaten endured the multiple surgeries, chemotherapy, and radiation therapy but the journey left her weak and drained. Migraines that had been only an occasional nuisance before her battle with cancer became a major issue. Not only were they more frequent and severe, but they would also often last for two weeks or more. “I had migraines that were off the charts -- the ones where you have to darken room and vomit. The pain was unbearable,” Kelly said. To make matters worse, Kelly suffered from extreme allergic reactions to virtually every medicine that was prescribed to address her migraines and other side effects of her years of cancer treatment.

Undeterred, Kelly ultimately identified a cancer rehabilitation physician to help her manage the multiple issues that resulted from her cancer treatment. A multimodal approach to her migraines including specialized physical therapy helped loosen the tissues scarred by radiation and surgery, targeted pharmacotherapy with medications she could tolerate, and botulinum toxin injections. Once the migraines were controlled, a program of progressive exercise helped restore her body and mind. She was able to go back to work and participate in the active lifestyle she had enjoyed before her cancer diagnosis, including coaching her son’s baseball and basketball teams.

Today, the 43-year-old mom is president and CEO of Minnesota-based KC Consulting Group. She’s a polished strategist who creates winning results for clients that range from the Minnesota Twins to Mattel and Minnehaha Creek Watershed District. Kelly specializes in pulling off complex events. She loves to test her mettle and gets a sense of accomplishment when events are completed. “Bring me a challenge and I’ll find a way to solve it,” she said.

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It was a persistent sore throat and a misdiagnosis of tonsillitis that heralded Sean Flaherty’s tonsil and throat cancer in 2011. At the time he was only 42 years old and had everything to live for, including a wonderful marriage to his high-school sweetheart, two small children, and a job as a financial advisor. With all the stress and uncertainty of his new cancer diagnosis, he was comforted by the words of his doctor, “You know, Sean, there’s life before cancer, with cancer, and after cancer; and yours is treatable.” Fortunately, his cancer was HPV-associated, which generally means a better prognosis than those caused by smoking and other causes. He did not receive surgery but was treated with combined chemotherapy and high-dose external beam radiation therapy. While his cancer is long gone, he suffers greatly from the effects of the radiation treatment that saved his life.

In 2014, Mr. Flaherty noticed painful spasms in the left neck radiating to the shoulder. The muscles would become as “hard as a rock” and limit the use of his left shoulder. He tried acupuncture and massage without help. His oncologist tried medications but side effects limited their use.

Sean had always been athletic. Now, with constant painful neck spasms he was unable to fully participate in the sports he loved, including golf, tennis, and especially surfing which had always been a release for him. Worse still, the progressive nature of the neck spasms was starting to interfere with his family life and work.

Ultimately, he was referred to a specialist in cancer rehabilitation. He was diagnosed with radiation-induced cervical dystonia caused by damage to the nerves and muscles in the radiation field. Through the use of specialized physical therapy and botulinum toxin injections into the neck, Mr. Flaherty is a new man. He can now participate in the activities he loves.

While deciding on a medical specialty, Dr. Ashish Khanna was given sage advice: “Find patients that inspire you and the rest will fall into place.” As he progressed through his training, he met plenty of amazing patients, but none inspired him as much as cancer survivors. He feels blessed to have found a career that puts him in close proximity to ordinary people exhibiting remarkable courage and determination under extraordinary conditions. His patients have confronted their own mortality and have bravely resisted the numerous opportunities to give up. They possess a unique courage to persevere, day after day, in spite of great pain and an uncertain reward. When he first encountered these patients and their inspiring determination, he knew where he belonged. Ultimately, he sees his career in cancer rehabilitation to be mutually beneficial. As he works to guide patients down their path to recovery, their stirring spirit becomes a perpetual source of inspiration, continuously feeding his own tenacious sense of optimism.

Dr. Khanna completed his residency in physical medicine and rehabilitation at the Kingsbrook Rehabilitation Institute in Brooklyn, New York, where he became interested in cancer rehabilitation early on. He subsequently did a specialized fellowship in cancer rehabilitation at Medstar Georgetown University and the National Rehabilitation Hospital in Washington, DC. Currently, he is an Assistant Attending in cancer rehabilitation at the Kessler Institute for Rehabilitation in West Orange, New Jersey, and an Assistant Professor at Rutgers New Jersey Medical School.
Cancer Statistics

Kimberly D. Miller, Rebecca L. Siegel, Rabia Khan, and Ahmedin Jemal

Cancer is a complex group of hundreds of distinct diseases (1), with occurrence that varies by cancer type, age, sex, race/ethnicity, socioeconomic status (SES), geographic location, and time. The disparities and patterns revealed by examining these variations provide strong evidence that much of cancer is caused by environmental factors and could potentially be avoided (2). Monitoring temporal trends in cancer occurrence is also important for assessing the need for and effectiveness of cancer prevention and control efforts in the overall population and in subgroups that may be at higher risk. This chapter describes cancer occurrence patterns in the United States for all cancers combined and for seven select cancer sites.

DATA SOURCES
In the United States, the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) program has been collecting cancer incidence data in nine population-based cancer registries since 1975. These registries, which provide information on historic temporal trends in incidence and survival, cover approximately 10% of the U.S. population. Subsequent expansions of the SEER program to include additional registries provide coverage of approximately 28% of the U.S. population (www.seer.cancer.gov). The Centers for Disease Control and Prevention’s National Program of Cancer Registries (NPCR) was established in 1994 to improve existing non-SEER population-based cancer registries and to establish new statewide registries (www.cdc.gov/cancer/npcr). Through the NPCR and SEER programs, cancer data are collected in almost all parts of the United States, although data quality varies across registries. The North American Association of Central Cancer Registries compiles and reports data from registries that participate in either program (www.naaccr.org) (3).

Mortality data based on information from death certificates have been collected for most of the United States since 1930. The underlying cause of death is classified according to the most current International Classification of Diseases (ICD), which is currently in its 10th edition. Since 1999, underlying causes of death have been classified according to ICD-10 coding and selection rules, replacing ICD-9, which was used from 1979 to 1998 (4). The ICD-10 codes for malignant cancer are C00-C97 (5). Mortality data are available from the National Center for Health Statistics (www.cdc.gov/nchs/nvss.htm).

MEASUREMENTS OF CANCER OCCURRENCE

Incidence and Mortality
Age-standardized incidence and mortality rates are measures of cancer occurrence that allow for comparisons across populations and time. They quantify the number of new cancer cases or deaths in a specified population at risk over a defined time period and are commonly expressed per 100,000 people. Age standardization is necessary to account for differences in population age distribution because of the strong correlation between age and cancer risk. Incidence rates are also adjusted for delays in case reporting when assessing temporal trends.

Prevalence
Prevalence measures the proportion of people living with a history of a cancer diagnosis at a certain point in time. The number of prevalent cases includes newly diagnosed cases, those who are undergoing treatment or in hospice care, and people who are in remission. Prevalence is influenced by cancer incidence and survival rates, as well as the growth and aging of the population. Because population-based cancer incidence and survival data in the United States only date back to 1975 and are for a limited geographic area, complete cancer prevalence estimates are model based. In addition, they do not distinguish between people with active disease and long-term survivors because information on cure rates is unavailable. There were 15.5 million people living with a history of cancer in the United States as of January 1, 2016 (Table 2.1) (6).

The Probability of Developing or Dying From Cancer
The probability that an individual will develop or die from cancer during a lifetime or a certain age interval is a measure used to describe average cancer risk in the general population. It is expressed as a percentage or as one in x number of persons. These estimates are based on the average experience of the general population and may over- or underestimate individual risk because of family history or individual risk factors. The probabilities are calculated using the Probability of Developing or Dying of Cancer (DevCan) software developed by the National Cancer Institute (www.surveillance.cancer.gov/devcan/). Based on cases diagnosed from 2012 to 2014, the lifetime
probability of developing invasive cancer was about 40% among men and 38% among women (Table 2.2).

**Estimated New Cancer Cases and Deaths**

Each year, the American Cancer Society estimates the total number of new cancer cases and deaths that will occur in the nation and in each state in the current year. These estimates are of interest because observed data lag 2 to 4 years behind the current year. While these estimates cannot be used to track cancer trends over time, they are useful because they provide estimates of the contemporary cancer burden. The estimates are produced by using historic information on the observed number of cancer cases and deaths in past years to project ahead to the current year (7,8).

**Survival**

Relative cancer survival rates are a type of net survival measure that takes into account causes of death other than cancer by adjusting for normal life expectancy. It is calculated by comparing the proportion of cancer patients alive at a specified period after diagnosis, usually 5 years, to that of a population of equivalent age, sex, and race without the disease.

### Table 2.1 Estimated Number of Prevalent Cases of Selected Cancers,* by Sex (United States, 2016)

<table>
<thead>
<tr>
<th></th>
<th>MALES</th>
<th>FEMALES</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td>7,377,100</td>
<td>8,156,120</td>
</tr>
<tr>
<td>Prostate</td>
<td>3,306,760</td>
<td>3,560,570</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>724,690</td>
<td>757,190</td>
</tr>
<tr>
<td>Melanoma</td>
<td>614,460</td>
<td>727,350</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>574,250</td>
<td>630,660</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>361,480</td>
<td>612,790</td>
</tr>
<tr>
<td>Kidney and renal pelvis</td>
<td>305,340</td>
<td>324,890</td>
</tr>
<tr>
<td>Testis</td>
<td>266,550</td>
<td>288,210</td>
</tr>
<tr>
<td>Lung and bronchus</td>
<td>238,300</td>
<td>282,780</td>
</tr>
<tr>
<td>Leukemia</td>
<td>230,920</td>
<td>235,200</td>
</tr>
<tr>
<td>Oral cavity and pharynx</td>
<td>229,880</td>
<td>204,040</td>
</tr>
</tbody>
</table>

*Prevalence estimates for specific cancers allow for multiple primaries of different cancer types, whereas the estimate for all cancer types combined only includes each individual once. Therefore, the estimate for all cancer types combined does not represent the sum of estimates for specific cancer types.


### Demographic and Geographic Factors

As mentioned, the risk of developing cancer is affected by age, race, sex, SES, geographic location, and calendar year.

**Age**

Incidence rates increase with age for most cancers because of cumulative exposures to risk factors such as tobacco use and excess body weight. Figure 2.1 (left panel) depicts the age-related increase in the average annual incidence rate for all cancers combined in men and women during 2010 to 2014 (9). Age-specific incidence generally increases with advancing age until age 84. Cancer occurrence in ages 85 and older may be particularly influenced by underdiagnosis or competing causes of death. The median age at diagnosis for most cancer sites is 60 or above. Cancers with a median age at diagnosis of 50 or younger include cancers of the testis, bones and joints, and cervix; acute lymphocytic leukemia; and Hodgkin lymphoma (9), in addition to several rare childhood cancer types. While cancer diagnosis during childhood or adolescence is rare, accounting for about 1% of all cancers in the United States, certain cancers are more common at younger ages (e.g., acute lymphocytic leukemia, neuroblastoma, and retinoblastoma) (9).

**Sex**

Among young adults, cancer incidence rates are higher in women than in men (Figure 2.1, left panel), largely because of the younger age of onset both for cancers more common in women, such as thyroid and breast cancer. However, overall incidence and mortality rates are higher in men than in women for most cancer types, with rates in men more than fourfold those in women for Kaposi sarcoma, mesothelioma, and cancers of the esophagus, larynx, and urinary bladder (Table 2.3). The few exceptions include cancers of the breast, thyroid, anus, and gallbladder. The overall incidence of cancer is higher in women, however, reflecting differences in cancer distribution and survival, as well as greater longevity of women compared to men. Of the 15.5 million people living with a history of cancer in January 2016, about 8.2 million were women compared to 7.4 million men (Table 2.1).

**Race/Ethnicity**

Cancer occurrence varies widely across racial and ethnic groups. Non-Hispanic Blacks (hereafter, Blacks) generally have higher cancer rates compared to non-Hispanic Whites (Whites; Table 2.4). During the most recent 5 years of available data, cancer incidence and death rates were 10% and 23% higher, respectively, in Black men than in White men. Notably, cancer death rates were nearly 14% higher in Black women than White women, despite 7% lower incidence rates. While Hispanics and Asian American/Pacific Islanders have lower incidence and mortality rates for all sites combined compared to Whites and Blacks, these populations have higher rates of many infection-related cancers (stomach, liver and intrahepatic bile duct, and, among Hispanic women, cervix). This is thought to reflect greater exposure to specific infectious agents; lower access to or use of screening for cervical cancer; and higher consumption of preserved rather than fresh foods (stomach cancer) (10,11).
### TABLE 2.2
Probability of (Percentage) Developing Invasive Cancers Over Specified Age Intervals,* by Sex (United States)

<table>
<thead>
<tr>
<th></th>
<th>BIRTH TO 49 YEARS (%)</th>
<th>50–59 YEARS (%)</th>
<th>60–69 YEARS (%)</th>
<th>70 YEARS AND OLDER (%)</th>
<th>BIRTH TO DEATH (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All sites†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3.4 (1 in 30)</td>
<td>6.1 (1 in 16)</td>
<td>13.4 (1 in 7)</td>
<td>32.2 (1 in 3)</td>
<td>39.7 (1 in 3)</td>
</tr>
<tr>
<td>Female</td>
<td>5.5 (1 in 18)</td>
<td>6.1 (1 in 16)</td>
<td>9.9 (1 in 10)</td>
<td>26.0 (1 in 4)</td>
<td>37.6 (1 in 3)</td>
</tr>
<tr>
<td><strong>Breast</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.9 (1 in 52)</td>
<td>2.3 (1 in 43)</td>
<td>3.4 (1 in 29)</td>
<td>6.8 (1 in 15)</td>
<td>12.4 (1 in 8)</td>
</tr>
<tr>
<td><strong>Colon and rectum</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.3 (1 in 287)</td>
<td>0.7 (1 in 145)</td>
<td>1.2 (1 in 85)</td>
<td>3.4 (1 in 29)</td>
<td>4.5 (1 in 22)</td>
</tr>
<tr>
<td>Female</td>
<td>0.3 (1 in 306)</td>
<td>0.5 (1 in 194)</td>
<td>0.8 (1 in 122)</td>
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<td>&lt;0.1 (1 in 4,334)</td>
<td>&lt;0.1 (1 in 2,040)</td>
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<td>0.2 (1 in 573)</td>
<td>0.4 (1 in 260)</td>
<td>1.4 (1 in 71)</td>
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<td>1.9 (1 in 54)</td>
<td>6.1 (1 in 16)</td>
<td>6.9 (1 in 15)</td>
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<td>2.6 (1 in 38)</td>
<td>3.6 (1 in 27)</td>
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<td>0.5 (1 in 202)</td>
<td>1.1 (1 in 91)</td>
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<td>0.6 (1 in 174)</td>
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<td>0.2 (1 in 480)</td>
<td>0.4 (1 in 248)</td>
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<td>1.9 (1 in 54)</td>
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<tr>
<td>Male</td>
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<td>0.2 (1 in 555)</td>
<td>0.4 (1 in 236)</td>
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<td>1.6 (1 in 63)</td>
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<td>0.3 (1 in 320)</td>
<td>1.3 (1 in 77)</td>
<td>1.5 (1 in 65)</td>
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<tr>
<td><strong>Uterine cervix</strong></td>
<td>0.3 (1 in 368)</td>
<td>0.1 (1 in 845)</td>
<td>0.1 (1 in 942)</td>
<td>0.2 (1 in 605)</td>
<td>0.6 (1 in 162)</td>
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<tr>
<td><strong>Uterine corpus</strong></td>
<td>0.3 (1 in 342)</td>
<td>0.6 (1 in 166)</td>
<td>1.0 (1 in 103)</td>
<td>1.3 (1 in 75)</td>
<td>2.8 (1 in 35)</td>
</tr>
</tbody>
</table>

*For people free of cancer at the beginning of age interval.
†All sites exclude basal cell and squamous cell skin cancers and in situ cancers except urinary bladder.
‡Probabilities for non-Hispanic Whites only.

An important limitation of cancer statistics is that data are generally only available for the five broad racial and ethnic groups shown in Table 2.4, masking substantial heterogeneity within these diverse populations. For example, overall cancer incidence rates in Asians/Pacific Islanders have been reported to vary up to threefold by subgroup, with rates for some populations approaching those of Whites (12).

### Socioeconomic Status
Lower SES, sometimes approximated via educational attainment or county-level poverty, is associated with higher death rates from cancer and many other causes because it is strongly associated with higher prevalence of cancer risk factors, such as smoking, obesity, and alcohol consumption, and with less access to high-quality healthcare (13,14). For example, in one study, colorectal...
cross-state regional areas that would benefit from colorectal cancer screening interventions (19).

Temporal Trends
Changes in cancer incidence over time result from changes in the prevalence of risk factors and detection practices (e.g., screening tests or diagnostic techniques). Incidence trends can also be affected by changes in disease classification. Trends in mortality rates may also be affected by most of the previously mentioned factors, with the exception of delay in reporting, in addition to improvements in cancer treatments over time.

CANCER OCCURRENCE PATTERNS FOR ALL CANCERS COMBINED
An estimated 1,735,350 newly diagnosed cancer cases and 609,640 cancer deaths are expected in the United States in 2018 (18). This case estimate excludes basal cell and squamous cell skin cancers, as well as in situ carcinoma.

cancer death rates among those with the least education (≤12 years) compared to those with the most (≥16 years) were about 80% higher for Blacks and more than double for Whites (15). Conversely, higher SES is positively associated with the incidence of some screening-related cancers, such as breast cancer (16).

Geographic Location
Variability in cancer occurrence by place of residence has stimulated important hypotheses about the etiology and potential preventability of many cancers (2,17). Geographic patterns in lung cancer incidence and mortality are particularly striking, with mortality rates in Kentucky threefold those in Utah, reflecting historic patterns in smoking prevalence and cessation (18). However, high-risk areas for some cancers may not be well characterized by state or other official boundaries. For example, the highest colorectal cancer death rates in the United States are clustered in the Mississippi Delta, west central Appalachia, and parts of eastern North Carolina and Virginia, highlighting cross-state regional areas that would benefit from colorectal cancer screening interventions (19).

TABLE 2.3  Average Annual Cancer Incidence Rates* by Sex (United States, 2010–2014)

<table>
<thead>
<tr>
<th></th>
<th>MALE RATE</th>
<th>FEMALE RATE</th>
<th>RATE RATIO, MALE VS. FEMALE†</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td>501.9</td>
<td>417.8</td>
<td>1.20</td>
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<tr>
<td>Kaposi sarcoma</td>
<td>0.7</td>
<td>0.1</td>
<td>9.75</td>
</tr>
<tr>
<td>Esophagus</td>
<td>8.0</td>
<td>1.8</td>
<td>4.49</td>
</tr>
<tr>
<td>Larynx</td>
<td>6.0</td>
<td>1.4</td>
<td>4.47</td>
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<tr>
<td>Mesothelioma</td>
<td>1.7</td>
<td>0.4</td>
<td>4.12</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>35.8</td>
<td>8.8</td>
<td>4.06</td>
</tr>
<tr>
<td>Liver and intrahepatic bile duct</td>
<td>12.1</td>
<td>4.2</td>
<td>2.89</td>
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<tr>
<td>Oral cavity and pharynx</td>
<td>17.4</td>
<td>6.4</td>
<td>2.73</td>
</tr>
<tr>
<td>Stomach</td>
<td>9.2</td>
<td>4.7</td>
<td>1.98</td>
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<tr>
<td>Kidney and renal pelvis</td>
<td>21.9</td>
<td>11.3</td>
<td>1.93</td>
</tr>
<tr>
<td>Leukemia</td>
<td>17.6</td>
<td>10.7</td>
<td>1.64</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>26.5</td>
<td>16.3</td>
<td>1.63</td>
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<td>Myeloma</td>
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<td>1.53</td>
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<td>Non-Hodgkin lymphoma</td>
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<td>1.46</td>
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<tr>
<td>Soft tissue, including heart</td>
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<td>1.42</td>
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<td>Brain and other nervous system</td>
<td>7.7</td>
<td>5.6</td>
<td>1.39</td>
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<tr>
<td>Lung and bronchus</td>
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<td>52.8</td>
<td>1.39</td>
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<tr>
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<td>0.7</td>
<td>1.33</td>
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<tr>
<td>Bones and joints</td>
<td>1.1</td>
<td>0.8</td>
<td>1.32</td>
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<td>Colon and rectum</td>
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<td>34.9</td>
<td>1.32</td>
</tr>
<tr>
<td>Small intestine</td>
<td>2.7</td>
<td>2.0</td>
<td>1.32</td>
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<td>Hodgkin lymphoma</td>
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<td>11.1</td>
<td>1.29</td>
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<tr>
<td>Anus, anal canal, and anorectum</td>
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<td>2.2</td>
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<td>Gallbladder</td>
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<td>1.4</td>
<td>0.60</td>
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<td>Thyroid</td>
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<td>21.1</td>
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<tr>
<td>Breast</td>
<td>1.3</td>
<td>123.4</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Note: Incidence rates from the North American Association of Central Cancer Registries public use database (excludes data from six states: Maryland, Minnesota, Kansas, New Mexico, Nevada, and Vermont).

* Rates are per 100,000 and age-adjusted to the 2000 U.S. standard population.
†Rate ratios are based on unrounded rates; reference group = males.

except that of the urinary bladder. Five-year relative survival rates for all cancers combined have increased significantly, from 49% during the period 1975 to 1977 to 69% during 2007 to 2013 (Table 2.5).

Overall cancer incidence trends are substantially influenced by those of the major cancer sites. Among men, increasing incidence rates for all cancers combined from 1975 to 1988 (Figure 2.2) reflect the rise in lung and prostate cancers due to historical increases in smoking prevalence and diagnosis from transurethral resection, respectively (20,21). Similarly, the subsequent sharp rise and fall in rates for all cancers combined from 1988 to 1992 was driven by trends in prostate cancer incidence rates (Figure 2.3, left panel) as a result of the introduction, saturation, and leveling off of prostate-specific antigen (PSA) testing (22). During the most recent 10 years of available data (2005–2014), incidence rates for all cancer sites combined decreased among men by about 2% per year, reflecting declines in lung, prostate, and colorectal cancers (9).

Among women, the increase in incidence rates during the late 20th century (Figure 2.2) predominantly reflects rises in lung cancer, because of increased cigarette smoking in women born in the 1930s (20), and breast cancer, because of increased mammography utilization and prevalence of reproductive risk factors (e.g., fewer and later age childbirths) (23). Incidence rates among women during the most recent 10 years of available data (2005–2014) were stable, largely due to declines in lung and colorectal cancers being offset by increasing or stable rates for cancers of the breast, thyroid, and uterine corpus, and for melanoma of the skin.

Trends in overall cancer death rates (Figure 2.2) among men are largely determined by lung cancer patterns (24). Lung cancer death rates (per 100,000) rose from 4.3 in 1930 to 90.6 in 1990, representing a 21-fold increase, and subsequently declined to 49.7 in 2015 (18,25). These trends reflect historical cigarette consumption, which peaked during the mid-20th century and gradually decreased following the Surgeon General’s report in 1964 (26). Improved treatments, increased screening, and changes in risk factors may have also contributed to the reduction in death rates from all cancers combined since the early 1990s.

Among women, the overall cancer death rate decreased from the 1930s through the early 1970s, increased until the early 1990s, and decreased thereafter (Figure 2.2). The long-term decline before the 1970s reflects decreases in deaths from cancers of the stomach, uterus (uterine corpus and cervix combined), and colorectum. The dramatic decrease in stomach cancer mortality, which has occurred in most industrialized countries, is largely the result of reduced prevalence of Helicobacter pylori infection due to improved sanitation and antibiotics, in addition to greater availability of fresh produce and improvements in food preservation (27). Among women, the historic decreases in mortality from stomach and uterine cancers were eventually offset in the late 20th century by increases in lung cancer mortality. Decreases in the overall cancer death rates since the early 1990s reflect reduction in death rates from cancers of the colorectum, breast, and, more recently, lung (Figure 2.4, right panel).
<table>
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<th>NON-HISPANIC WHITE</th>
<th>NON-HISPANIC BLACK</th>
<th>ASIAN/PACIFIC ISLANDER</th>
<th>AMERICAN INDIAN/ALASKA NATIVE†</th>
<th>HISPANIC LATINO‡</th>
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<td></td>
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<td></td>
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</table>

Note: Incidence rates from the North American Association of Central Cancer Registries public use database (excludes data from six states: Maryland, Minnesota, Kansas, New Mexico, Nevada, and Vermont). Death rates from National Center for Health Statistics, Centers for Disease Control and Prevention.

*Per 100,000, age-adjusted to 2000 U.S. standard population.
†Rates for American Indians/Alaska Natives are based on the Contract Health Service Delivery Area counties.
‡Hispanics/Latinos may be of any race and are not mutually exclusive from Asians/Pacific Islanders and American Indians/Alaska Natives.
### Table 2.5 Changes in 5-Year Relative Survival Rates* (%), by Race and Year of Diagnosis (United States, 1975–2013)

<table>
<thead>
<tr>
<th>Site</th>
<th>ALL RACES</th>
<th></th>
<th>WHITE</th>
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<td>12†</td>
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<td>76</td>
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<td>6†</td>
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<td>6†</td>
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<tr>
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<td>85</td>
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</tbody>
</table>

*Survival rates are adjusted for normal life expectancy and are based on cases diagnosed from 1975–1977 to 2007–2013 and followed through 2014.
†The difference in rates between 1975–1977 and 2007–2013 is statistically significant (p < .05).
‡The standard error is between 5 and 10 percentage points.

### Cancer Occurrence Patterns for Select Sites

The most commonly diagnosed cancers in the United States are prostate, lung and bronchus, and colorectum in men and breast, lung and bronchus, and colorectum in women (Figure 2.5). These cancers account for 42% and 50% of new diagnoses in men and women, respectively. Lung and bronchus cancer is the leading cause of cancer death in both men and women, followed by prostate and colorectal cancers in men and breast and colorectal cancers in women. The remainder of this section focuses on these four cancer types, as well as three additional cancers (liver and intrahepatic bile duct, esophagus, and pancreas) that are unique with respect to risk factors, distribution and trends by histologic subtype, and low survival. Combined, these seven cancers account for about 53% of new cases and 60% of cancer deaths in the United States.
Lung and Bronchus Cancer

An estimated 234,030 new cases of lung and bronchus (lung) cancer were expected to be diagnosed in 2018, accounting for about 13% of new cancer diagnoses (18). Lung cancer accounts for the most cancer-related deaths in both men and women—about one-fourth of all cancer deaths—with an estimated 154,050 lung cancer deaths in 2018. The lifetime probability of developing invasive lung cancer is 7% for men and 6% for women (Table 2.4). Although lung cancer is one of the most commonly diagnosed cancers, only about 526,510 individuals were living with a history of lung cancer in the United States as of January 1, 2016 (Table 2.1), partly reflecting the low survival for the disease (6).

Overall, men have higher rates of lung cancer compared to women and Black men have the highest rates of all racial/ethnic groups (Tables 2.2). The incidence rate for lung cancer has declined substantially in men, from a high of 102.0 (per 100,000) in 1984 to 60.9 in 2014 (Figure 2.3, left panel) (9). In women, rates began declining in the mid-2000s after a long period of increase (Figure 2.3, right panel). Lung cancer death rates have continuously decreased in men since 1991, with the pace of the decline accelerating in more recent years (Figure 2.4, left panel). Among women, mortality rates increased until 2007 and have since declined by about 2% per year (Figure 2.4, right panel). Gender differences in incidence and mortality...
trends reflect historical patterns in smoking and cessation. Cigarette smoking is by far the most important risk factor for lung cancer, accounting for about 80% of lung cancer cases and deaths (28). Risk increases with quantity of cigarettes smoked and smoking duration. Other risk factors for lung cancer include secondhand smoke, occupational or environmental exposures to radon and asbestos (particularly among smokers), certain metals (chromium, cadmium, arsenic), some organic chemicals, radiation, air pollution, and tuberculosis (29).

The 5-year relative survival rate for all stages of lung cancer combined has increased slowly compared to other cancers, from 12% in 1975 to 1977, to 20% in 2007 to 2013 (Table 2.5), largely due to improvements in surgical techniques and combined therapies. Although 5-year survival is 56% for cases detected when the disease is still localized, only 16% of lung cancers are diagnosed at this early stage (9).

Breast Cancer

Breast cancer is the most frequently diagnosed cancer in women, with an estimated 266,120 newly diagnosed invasive cases in the United States in 2018 (Figure 2.5). Breast cancer ranks second among causes of cancer death in women, with 40,920 deaths expected in 2018 (18). The lifetime probability of developing invasive breast cancer is 12%, or about 1 in 8 women, with a median age at diagnosis of 62 years. More than 3.5 million female breast cancer survivors were estimated to be living in the United States as of January 1, 2016 (Table 2.1). Breast cancer can also develop in men, but is rare (Table 2.3), with about 2,500 cases and 500 deaths estimated in 2018.

Breast cancer incidence rates are highest in White women, followed closely by Black women, with rates in other major racial and ethnic groups substantially lower (Table 2.4). Despite Black women having slightly lower incidence than White women, their breast cancer death rate
is about 40% higher, in part due to later stage at diagnosis and poorer stage-specific survival (30).

Breast cancer incidence rates increased rapidly among women from 1980 to 1987, likely due to the increasing uptake of mammography and the use of menopausal hormone therapy (estrogen plus progestin) (23); rates stabilized until 1994, then continued to increase at a slower pace through 1999 (Figure 2.3, right panel) (9). A precipitous decline in incidence from 2002 and 2003, primarily among White women, followed a landmark report that the use of menopausal hormone therapy (estrogen plus progestin) was associated with an increased breast cancer risk (31). The slight increase in breast cancer incidence overall from 2005 to 2014 was the result of annual increases of 1.7% in Asian/Pacific Islander women and less than 0.5% in Black and Hispanic women; rates were stable in White and American Indian/Alaska Native women (30). Death rates for breast cancer have steadily decreased in women since 1989 (Figure 2.4, right panel), although declines have slowed among women younger than 50 years in recent years (30). The substantial decreases in female breast cancer mortality are thought to reflect uptake of mammography, which can detect breast cancer early, and improvements in treatment (32,33).

There are a number of established risk factors for breast cancer. Although risk is increased among women with a family history of the disease, most women who develop breast cancer have no such history (34). A personal history of breast cancer at a young age or a history of ductal or lobular carcinoma in situ, inherited genetic mutations in the \( \text{BRCA}1 \) or \( \text{BRCA}2 \) genes, high breast tissue density, certain high-risk types of benign breast disease, and high-dose radiation to the chest also increase risk (35,36). Reproductive factors associated with increased risk include a long menstrual history, never having children or delayed childbearing, use of postmenopausal hormone therapy (especially combined estrogen and progestin therapy), and the recent use of oral contraceptives (31,37,38).

**FIGURE 2.5** Ten leading cancer types for the estimated new cancer cases and deaths, by sex (United States, 2018). Excludes basal and squamous cell skin cancer and in situ carcinomas except urinary bladder. Estimates are rounded to the nearest 10, and percentages may not total 100%. (Data from Cancer Facts and Figures, 2018.)

*Source: American Cancer Society.*

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modifiable factors associated with increased risk include being overweight or obese after menopause, physical inactivity, and excess alcohol consumption (39).

The 5-year relative survival rate for all stages of breast cancer has increased from 75% in 1975 to 1977, to 91% in 2007 to 2013 (Table 2.5). The 5-year relative survival rate for localized breast cancer is 99%, while the rate for cancer that has spread regionally or distally is 85% or 27%, respectively (9).

Prostate Cancer
An estimated 164,690 new cases of prostate cancer and 29,430 prostate cancer deaths are expected in the United States in 2018 (Figure 2.5) (18). Prostate cancer is the most frequently diagnosed cancer in men, with a lifetime risk of about 12%, or about 1 in 9 men (Table 2.2). More than 3.3 million men with a history of a prostate cancer diagnosis were living in the United States as of January 1, 2016 (Table 2.1). More than half (57%) of all prostate cancer cases are diagnosed in men 65 years and older (9).

For reasons that remain unclear, incidence rates are significantly higher in Black men than in White men (Table 2.4). Incidence rates of prostate cancer have changed substantially over the past 30 years (Figure 2.3, left panel). These trends, in large part, reflect patterns in prostate cancer screening with the PSA blood test (40). Protracted declines in prostate cancer incidence since 2010 likely reflect decreased PSA screening following recommendations from the United States Preventive Services Task Force in 2008 against routine use of the test for men ages 75 and older and subsequently in 2011 for men of all ages (41). Death rates have been declining among White and Black men since the early 1990s, reflecting, in part, earlier detection and improvements in treatment (42). However, rates in Black men remain more than twice as high as those in Whites (Table 2.4).

The only well-established risk factors for prostate cancer are age, ethnicity, and family history of the disease (43). However, prostate cancer associated with a strong family component accounts for 5% to 10% of cases. Well-characterized hereditary conditions associated with increased risk include Lynch syndrome and mutations in the BRCA1 or BRCA2 genes.

More than 90% of all prostate cancers are discovered in the local and regional stages, and the 5-year relative survival rate for these patients approaches 100% (9). The 5-year survival rate for all stages combined has increased from 68% in 1975 to 1977, to 99% in 2007 to 2013 (Table 2.5). More than half (57%) of all prostate cancer cases are diagnosed in men 65 years and older (9).

Colon and Rectum Cancer
An estimated 97,220 colon and 43,030 rectal cancer cases are expected to be diagnosed in 2018 (18). Colorectal cancer accounts for about 8% of all cancer deaths, with an estimated 30,630 deaths in 2018 (mortality estimates for colon and rectal cancers separately are not available because a substantial proportion of rectal cancer deaths are misclassified as colon cancer). In 2016, more than 1.4 million men and women were estimated to be living in the United States with a history of colorectal cancer (Table 2.1). There are substantial racial and ethnic disparities in colorectal cancer occurrence, with rates in Alaska Natives more than 80% higher than those in Blacks and double those in Whites (45). However, this striking disparity is masked when Alaska Natives are combined with other American Indian populations (Table 2.4). Although men have higher colorectal cancer incidence compared to women (Table 2.3), the lifetime probability of developing the disease is similar due to longer life expectancy in women (Table 2.2).

Colorectal cancer incidence rates have been decreasing since 1985 for both sexes, with the exception of a slight, unexplained increase from 1996 to 1998 (Figure 2.3). Declines prior to 2000 are equally attributed to changes in risk factors and the introduction of screening, whereas the more rapid recent declines are thought to largely reflect widespread uptake of screening colonoscopy, which can detect and remove precancerous colorectal polyps before they progress to cancer (46). Colorectal cancer mortality rates have been declining in men since 1980 and in women since 1997 (Figure 2.4); in both sexes combined, rates (per 100,000) declined from 29.2 in 1970 to 14.0 in 2015 (45).

The risk of colorectal cancer increases with age; however, decreasing incidence rates in ages 55 and older, among whom about 80% of cases are diagnosed, mask increasing rates in ages 20 to 54 (47). In addition to age, there are many modifiable and nonmodifiable factors associated with increased risk. While about 30% of colorectal cancers are related to familial factors (e.g., a family history of the disease), only 5% are attributable to well-characterized genetic mutations, such as Lynch syndrome (48). A personal history of diabetes or chronic inflammatory bowel disease is also associated with increased risk (49,50). Potentially modifiable factors include excess body weight, physical inactivity (colon only), excess alcohol consumption, a diet high in red or processed meat, and low calcium consumption (51). Beginning at age 50, men and women who are at average risk for developing colorectal cancer should begin screening.

When colorectal cancer is diagnosed at localized stage, when the disease has not spread beyond the colorectum, the 5-year survival is 90%; however, only 39% of colorectal cancers are diagnosed at this stage (9). For patients whose cancer has spread regionally to involve adjacent organs or lymph nodes, the 5-year survival drops to 71%. For persons with distant metastases, 5-year survival is 14%. Five-year relative survival for all stages combined is higher for rectal cancer than for colon (69% vs. 65%, respectively; Table 2.5), reflecting a slightly higher proportion of rectal cancer patients diagnosed at a localized stage (43% vs. 38%, respectively).

Liver and Intrahepatic Bile Duct Cancer
In 2018, an estimated 42,220 newly diagnosed cases of liver and intrahepatic bile duct (liver) cancer and 30,200 liver cancer deaths are expected in the United States (18). Liver cancer is about three times more common in men than in women (Table 2.3). Incidence generally increases with advancing age except in Blacks, among whom age-specific incidence peaks at ages 60 to 64 years (52). In contrast to racial patterns for the most common cancers, liver cancer incidence and mortality rates in Asians/Pacific Islanders and Hispanics are more than double those in Whites (Table 2.4).
About three-quarters of liver cancers in the United States are hepatocellular carcinomas (52). The major causes of liver cancer are chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) (53), especially in developing countries. Certain other risk factors, such as inflammation of the intrahepatic bile ducts with liver flukes, are also more common in developing countries, particularly in parts of Asia. In the United States, 7% of liver cancers are associated with chronic HBV infection and 24% are due to chronic HCV infection, with substantial portions also attributable to excess body weight (34%), cigarette smoking (23%), and excess alcohol consumption (22%) (28). Although liver cancer incidence in the United States is low compared to East and Southeast Asia, which have the highest regional rates (54), it is the fastest rising cause of cancer death (55). Trends in the United States are largely driven by higher prevalence of chronic HCV infection among those born between 1945 and 1965, although other adverse trends in liver cancer risk factors, such as the obesity epidemic, have also likely contributed (56,57). However, incidence rates are increasing by 1% to 2% annually in men and women younger than age 40, which may be a bellwether of future trends (Figure 2.6).

Five-year relative survival for liver cancer was only 19% for patients diagnosed during 2007 to 2013 (Table 2.3). Survival for localized stage disease has doubled since the early 1990s, reflecting advances in surgical and transplant techniques, but remains generally low (43%) (9,55). Because a substantial proportion of liver cancers are due to potentially modifiable risk factors, broad and equitable application of prevention mechanisms for the major causes of the disease is vitally important. A vaccine that protects against HBV has been available since 1982, and state laws mandating hepatitis B vaccination for middle school children have contributed to achieving high immunization coverage among adolescents (58). However, vaccination coverage among adults and certain population subsets (e.g., healthcare personnel) remains below public health targets (59). HBV treatment, while not curative, has been shown in some instances to reduce the risk of developing liver cancer among those who are chronically infected (60,61). While there is no vaccine available for HCV, curative treatments for the infection are available. Several expert organizations have published recommendations for preventive measures for reducing HBV and HCV transmission (e.g., universal precautions for healthcare workers). The Centers for Disease Control and Prevention recommends that routine HCV testing be offered to individuals at high risk for infection, and recommends one-time testing for those born between 1945 and 1965 (62); however, the proportion of adults in this cohort who have received such testing remains low, about 14% in 2015 (63).


**Esophageal Cancer**

An estimated 17,290 newly diagnosed cases and 15,850 deaths due to esophageal cancer are expected in the United States in 2018 (18). Incidence rates in men are more than fourfold those in women (Table 2.3). Cancers of the esophagus typically have two distinct histologic types, squamous cell carcinoma and adenocarcinoma, the occurrence of which varies greatly by race and ethnicity. Rates of esophageal adenocarcinoma are higher among Whites than Blacks, while the inverse is true for squamous cell carcinoma. Squamous cell carcinoma occurs in the upper third of the esophagus and is caused mainly by cigarette smoking and alcohol consumption, which increase risk both independently and synergistically (64). Adenocarcinoma generally occurs in the lower third of the esophagus and has risk factors that include obesity, gastroesophageal reflux disease (GERD), and Barrett esophagus, which is a preneoplasmic condition involving chronic inflammation and dysplasia (64).

Incidence rates for esophageal cancer overall began declining in 2004 in both men and women (Figure 2.3), although trends differ by histologic type. Historically, squamous cell carcinoma was the most common histologic type. However, declines in esophageal squamous cell carcinoma rates since at least 1975 in Whites and since the late 1980s in Blacks, coupled with rising rates of esophageal adenocarcinoma, have led to a crossover in the histologic types in Whites and converging rates in Blacks (Figure 2.7). Trends in esophageal squamous cell carcinoma, particularly in recent years, are in part driven by decreases in smoking prevalence. Reasons for the higher rates of and steeper increase in esophageal adenocarcinoma among White men compared to Black men are not fully understood, but might be related to a higher prevalence of *Helicobacter pylori* infection in Blacks, which may be protective against adenocarcinoma of the esophagus (65,66). The increase in adenocarcinoma of the esophagus may also be related to the increase in obesity and GERD in the United States.
Survival from esophageal cancer is low and does not differ by histologic type (67). In the United States, the 5-year survival rate was 21% during the period 2007 to 2013, up from 5% for patients diagnosed during 1975 to 1977 (Table 2.5).

Pancreatic Cancer

An estimated 55,440 newly diagnosed cases and 44,330 deaths due to pancreatic cancer are expected in the United States in 2018 (18). The median age of diagnosis is 70, and the majority of cases occur between ages 65 and 79 (9). Pancreatic cancer incidence rates are higher among Blacks compared to Whites in the United States (Table 2.4).

Trends in pancreatic cancer incidence rates differ by race and sex. Rates in White men declined from 1975 through the mid-1990s, but increased by 1% per year thereafter (9). Rates in White women have generally been stable or increasing since at least 1975, and are currently rising at a similar pace to White men. In contrast, incidence rates among Blacks have steadily declined by 0.3% per year in men and have been stable in women since at least 1975. Pancreatic cancer death rates are slowly rising in White men, but stable in White women and declining in Blacks. Tobacco smoking increases the risk of pancreatic cancer (44), and incidence rates are more than twice as high for cigarette smokers than for nonsmokers. Risk also increases with excess body weight, chronic pancreatitis, diabetes, cirrhosis, and certain inherited genetic conditions, such as Lynch syndrome and BRCA1 or BRCA2 mutations (68,69). Excess alcohol consumption may also increase risk.

Pancreatic cancer is highly lethal, and survival rates are among the lowest of any cancer. For all stages combined, the 5-year survival rate is about 9% (Table 2.5). More than half of cases (52%) are diagnosed at a distant stage, but even for the 10% of patients diagnosed with local disease, 5-year survival is only 32% (9). There is no screening test for the early detection of pancreatic cancer, and early stages of the disease are usually asymptomatic. Treatment with surgery, radiation, and/or chemotherapy may extend survival or relieve symptoms in many patients, but seldom produce a cure. Combined, these challenges make pancreatic cancer an important medical and public health problem.
KEY POINTS

- Cancer is a complex group of hundreds of diseases, with variations in occurrence by cancer type, age, sex, race/ethnicity, SES, geographic location, and time.
- The entire United States is covered by population-based cancer registry through the SEER program of the National Cancer Institute or the National Program of Cancer Registries of the Centers for Disease Control and Prevention.
- Mortality data based on information from death certificates have been collected for most of the United States since 1930.
- Incidence is the number of new cancer cases or deaths, respectively, in a specified population over a defined time period and is commonly expressed as counts per 100,000 people per year.
- Prevalence measures the proportion of people living with a history of cancer at a certain point in time.
- The relative cancer survival rate reflects the proportion of people alive at a specified period after diagnosis, usually 5 years, compared to that of a population of equivalent age, sex, and race without cancer.
- The risk of developing cancer is influenced by age, race, sex, SES, geographic location, and calendar year.
- An estimated 1,735,350 new cancer cases and 609,640 deaths due to cancer are expected in the United States in 2018.
- The probability of developing a lifetime is about 40% for men and 38% for women.
- Survival rates for all cancers combined have increased substantially, from 50%, during 1975 to 1977, to 69%, during 2007 to 2013.
- The three most commonly diagnosed cancers in the United States in 2017 were prostate, lung and bronchus, and colon and rectum in males and breast, lung and bronchus, and colon and rectum in females.
- Lung cancer accounts for the most cancer-related deaths in both men and women.

REFERENCES

3. SEER*Stat Database: NAACCR Incidence Data – CiNA Analytic File, 1995–2014, Public Use (which includes data from CDC’s National Program of Cancer Registries (NPCR), CCCR’s Provincial and Territorial Registries, and the NCI’s Surveillance, Epidemiology and End Results (SEER) Registries), certified by the North American Association of Central Cancer Registries (NAACCR) as meeting high-quality incidence data standards for the specified time periods, submitted December 2016.
Principles of Radiation Therapy in Cancer

Virginia Osborn, Pavnesh Kumar, and Yoshiya Yamada

Ever since the discovery of x-rays by Wilhelm Röntgen in 1895, radiation has been closely tied to medical applications, and it has been known to have significant biologic effects from the very beginning of the radiologic era. Antoine-Henri Becquerel, who discovered that uranium compounds emitted radiation in 1896, was the first to record the biologic effect of radiation, when he inadvertently left a vial of radium in his vest pocket, noting skin erythema 2 weeks later. This later turned into a skin ulcer, which took several weeks to heal. Pierre Curie repeated the experiment in 1901 by deliberately causing a radiation burn on his forearm. An Austrian surgeon, Leopold Freund, demonstrated in 1896 to the Vienna Medical Society that radiation could cause a hairy mole to disappear (1).

From these beginnings, radiation therapy has evolved into an important modality for treating benign and malignant illness. For cancers in every organ system in the body, radiation therapy has been shown either to contribute to the cure or serve as the primary curative therapy. Improvements in computer and imaging technology have expanded the role of radiation therapy, allowing for the effective noninvasive management of tumors without the morbidity commonly associated with surgical or chemotherapeutic strategies. Radiation therapy may offer curative options for patients who may not be able to tolerate radical surgery. Radiation therapy is not limited by the anatomic or functional constraints of surgical resection and thus is able to treat cancer in a regional paradigm, often reducing morbidity and functional loss or deformity associated with radical resections. Because radiation effects are typically locoregional, patients can also be spared the generalized toxicity associated with cytotoxic chemotherapy. Radiation therapy is not dependent upon the circulatory system to reach the target tissue. Hence toxicity is limited to the tissues to which radiation is administered, but the benefits of radiation are also limited to the area to which radiation is given. Radiation therapy is also an integral part of combined modality therapy with systemic therapy and/or surgery. Nearly two-thirds of all cancer patients will receive radiation therapy at some point during their illness, and over one million patients are treated with radiation therapy in the United States annually (2). As the incidence of cancer increases with an increasingly aging population, it is expected that even more patients will benefit from radiation therapy. Furthermore as technology has advanced and the interest in precision medicine and immunotherapy has increased, the role of radiation therapy appears more relevant than ever (3). Currently there are about 5,000 radiation oncologists in the United States.

RADIATION PHYSICS

Radiation therapy can be broadly defined as the use of ionizing radiation for the treatment of neoplasms. The most commonly utilized form of radiation is photon radiation, commonly known as x-rays (artificially produced) or gamma rays (emitted from naturally decaying isotopes). Photons are packets of energy that can interact with the atoms that make up the DNA of a cell, causing disruption of chemical bonds and DNA strand breaks, which ultimately leads to irreparable damage (4). Cells unable to repair this damage may not successfully complete mitosis, resulting in the death of both mother and daughter cells. Many cells will also undergo apoptotic death, when the cell detects DNA damage, without completing mitosis (5).

Radiation dose (gray or Gy) is commonly defined as joules per kilogram (energy per unit mass) where 1 Gy equals 1 joule/kg (6). Since radiation is ionizing energy, radiation therapy does not induce heat or other manifestations of energy transfer that can be felt by patients. Thus patients feel no pain during radiation administration. Because radiation effects are stochastic, it may cause similar effects on healthy normal cells. In order to reduce the side effects of radiation therapy, radiation oncologists attempt to concentrate the radiation in tumors and minimize the amount of radiation absorbed by surrounding normal tissues.

THE THERAPEUTIC RATIO

Tumor control probability and normal tissue complication probability are usually dose dependent. Efforts to minimize radiation dose to normal tissue result in lower normal tissue complication probabilities, while increasing dose to the tumor should increase tumor control probabilities. Hence a basic mantra of radiation oncology is to increase the gap between toxicity and tumor control probability curves (see Figure 7.1), commonly referred to as the therapeutic ratio.

One strategy to minimize radiation toxicity is to use the appropriate photon energy. Most radiation beams are
Figure 7.1: The therapeutic ratio. The aim of successful treatment is to increase the tumor control probability (red) while reducing the treatment complication curve (blue). Increasing the dose delivered to the tumor will typically increase the probability of cure, but will also increase the likelihood of toxicity. By reducing the amount of radiation given to normal tissues and/or the volume of normal tissue exposed to radiation, toxicity can be reduced (shifting the complication curve to the right of the tumor control curve). Because of the sigmoid nature of these curves, a moderate increase in dose (X to Y) can often result in a much higher probability of complications with only a modest gain in tumor control probability.

Another method of improving the therapeutic ratio is to shape radiation fields to match the three-dimensional shape of the target volume, thereby limiting the exposure of normal tissues to high doses of radiation (6). The shape of the radiation beam can also be manipulated by placing thick lead or cerrobend blocks into the head of the linac to block out radiation except to the tumor. Modern linacs utilize a device known as the multileaf collimator (see Figure 7.2), which has multiple individually motorized leaves of thick tungsten 3 to 10 mm wide. These leaves can be pushed in or out of the radiation field to approximate the tumor outline and similarly block radiation from areas where it is not necessary or desired. Most tumors have complex shapes, and will present different outlines when viewed from different angles. When multiple beams of shaped radiation fields intersect in the tumor, the result is a cloud of radiation where the high dose volume is similar to the actual three-dimensional characteristics of the tumor. By conforming the high-dose region to just the tumor, higher doses of radiation can be delivered while the surrounding tissues are relatively spared, thus limiting the toxicity of treatment and improving the therapeutic ratio.

An important innovation has been the use of intensity modulation. By using fast computers, radiation doses can be changed or modulated within different regions of each radiation field. Hence the radiation not only conforms to the three-dimensional outline of the tumor, but can be modulated to reduce dose to areas of the field that might approach a dose sensitive normal structure that might be just in front or behind the field, or account for a change in the tumor outline, which may not be appreciable from different angles. This technique, called intensity modulated radiation therapy (IMRT), has allowed steep dose gradients around tumors, as high as 10% per millimeter (6). Figure 7.3 illustrates how spinal cord doses are minimized relative to the tumor. More recently, volumetric modulated arc therapy (VMAT) has also been developed in which radiation is delivered as the treatment beam moves in a continuous arc around the patient, allowing for further conformality and efficiency in treatment delivery.

Uncertainty of where the radiation actually goes in relation to the intended target has always been a problem in radiation therapy. In traditional radiation therapy, patients undergo a procedure called simulation to radiographically identify the center of the target. During simulation, either two-dimensional (standard x-ray) or three-dimensional imaging (CT, MRI, PET, or a combination) is utilized to identify the target center in relation to the patient’s anatomy. Small skin marks are made to allow the patient to be triangulated relative to the treatment machine to allow for daily administration of radiation. When patients are treated in this manner a number of uncertainties must be accounted for...
not needing treatment can be otherwise spared from radiation exposure. MRI, PET, and more recently perfusion imaging have been incorporated into the process of treatment planning to more accurately identify the volume at risk, as well as better visualization of normal tissues to be avoided.

**STEREOTACTIC BODY RADIATION THERAPY**

Thanks to improvements in precision of both dose delivery and anatomic localization, radiation oncologists have increasingly been able to offer abbreviated courses of high-dose radiation for certain tumors. This technique has been termed stereotactic body radiation therapy (SBRT), stereotactic ablative body radiation therapy (SABR), or simply hypofractionation. The initial application of this concept was at least 50 years ago, when Leksell pioneered use of ablative doses of radiation to small tumors in the brain, which came to be known as stereotactic radiosurgery (9). Now, single-fraction ablative treatments can be safely delivered to metastases in the spine, and courses of up to five fractions are frequently used with curative intent for lung cancer, prostate cancer, bone sarcoma, melanoma, and in certain cases, for metastases.

**ELECTRON BEAM THERAPY**

In addition to photons, modern high-energy linacs provide electron beams of varying energies, which can be utilized for the treatment of superficial or subcutaneous tumors. Electrons possess much more mass than photons, and the associated kinetic energy is lost upon passing through and interacting with tissue. As a result, tumors within around 6 cm of the patient’s surface can be irradiated with little dose to underlying normal structures, in contrast with x-rays, which continue to penetrate all the way through the patient. Figure 7.4 demonstrates this sharp dose fall-off. Because unlike photons electrons do not exhibit skin-sparing, they are particularly useful if tumor involves the skin. Due to low penetrating power of electrons, surrounding normal structures can be shielded using external or internal shields made up of lead or tungsten, which can also help in delineating irregular field borders (10). Electron beam radiation therapy can be used for treatment of (a) skin and lip cancers, (b) chest wall and neck irradiation, (c) upper respiratory and digestive tract lesions, and (d) higher dose boost treatment to lymph nodes, scars, and residual disease.

**SUPERFICIAL X-RAY THERAPY**

Superficial x-rays have lower energies, in the kilovoltage range. Because of low penetrating power, the maximum dose deposition occurs near the surface, and thus the primary application is in treatment of skin cancers like basal cell carcinoma. Kilovoltage x-ray beams are grouped by their respective energy ranges: (a) Grenz rays (10–20 kVp), (b) contact therapy (up to 50 kVp), (c) superficial therapy (50–150 kVp), and (d) orthovoltage therapy (150–500 kVp) (11).

**PROTON BEAMS**

Charged particles, such as proton beam radiation therapy, are another type of ionizing radiation garnering more
and more interest. As noted earlier with electrons, if such charged particles have mass and kinetic energy, they are also subject to the physics of kinetic energy. One very useful aspect unique to charged particles is the Bragg peak effect (see Figure 7.5), in which accelerated particles such as protons deliver their inherent energy within a very narrow depth spectrum in tissue (3). Protons in effect have almost no “exit” dose, while photons are attenuated as they interact with atoms within tissue, but are likely to “exit” out of the back of the tumor. The kinetic energy of particle beams also results in higher amounts of energy deposition per linear distance, or linear energy transfer (LET) (4). This depends upon the energy of the beam. For practical purposes, the conversion of proton beam doses to photon beam doses is expressed in cobalt gray equivalents by multiplying the proton beam doses by a factor of 1.1. However, other charged particles such as carbon ions have a much higher LET than photons, and are more likely to inflict damage along the track the particle travels.

**BRACHYTHERAPY**

As opposed to treating tumors with the radiation source distant from the tumor, brachytherapy (placing radioactive sources inside of tumors) is another way to deliver very high-dose radiation and limit normal tissue doses. In brachytherapy, the dose falls off at an inverse to the square of the distance. Thus, the radiation dose quickly falls even a short distance from the implanted source. A commonly used isotope is iodine 125, which emits very weak gamma rays (29 KeV). The dose of radiation absorbed by the tissues immediately surrounding the source (within 1 cm) is very high. Hence if iodine 125 sources are placed strategically within a tumor, a very high dose can be given without exposing neighboring organs to much radiation (12).

**RADIOBIOLOGY**

An understanding of radiobiology (how radiation affects different tissues) can also help improve the therapeutic ratio. The effects of radiation therapy on tissues is dependent upon the inherent radiosensitivity of the tissue or organ in question, the dose of radiation given, and the volume of tissue irradiated (1). The dose per fraction (treatment) is also an important determinant of toxicity. In general, a higher dose per fraction has a greater biologic impact, both for normal tissue as well as tumor. Thus if larger doses of radiation are administered per fraction, the same probability of tumor control can be achieved with a lower total cumulative dose in comparison with a treatment schedule utilizing a small dose of radiation per fraction, which would require a higher total dose to achieve the same level of tumor control (13). A smaller dose per fraction may be desirable when it is important to spare radiosensitive organs, which may be near the target volume, or when a large volume of tissue needs to be treated. Since the total time required to deliver the prescribed radiation also has biologic effects, the dose rate, or how quickly radiation is given is also important (14). This is especially significant in brachytherapy. The total dose prescribed may be reduced when using isotopes with a higher dose rate, in comparison with an implant utilizing lower dose rate sources.

Time is thought to be critical because it may affect how well a cell can recover from radiation damage. A cell that has more time to repair damage is less sensitive to radiation effects. Thus it is often noted that tissues that have a high rate of turnover, such as the bone marrow, are very sensitive to radiation. Time also allows the irradiated tissue to repopulate or replace cells lost to radiation. Because different phases of the cell cycle have different sensitivities to...
radiation, allowing time for reassortment can also make tissues more radiosensitive. Other factors, such as the oxygenation status of the tissue may also be important. Hypoxic tissues are less sensitive to radiation therapy, and so allowing time to permit reoxygenation to increase the oxygen tension within the tumor is also thought to increase the effects of radiation. Thus, most radiation schedules give radiation in multiple treatments or fractions, to allow opportunity for normal tissues to repair radiation effects, and repopulate. It also allows for reassortment of tumor cells into more radiosensitive phases of the cell cycle and reoxygenation of hypoxic tumors to increase the radiation effect (1).

There is great interest in the use of chemicals to increase the effect of radiation (radiosensitizers, such as many chemotherapeutic agents that also target DNA) or protect normal tissues from the effects of radiation (radioprotectors such as amifostine) (15). The cell cycle appears to be regulated by a variety of protein kinases that are under the control of complex pathways of signal transduction pathways. These may also be manipulated to increase the sensitivity of tumors to radiation (16).

It has also become increasingly clear that the immune system can be harnessed in cancer treatment, and that radiation can play an important role in the process. Immune checkpoint inhibitors (e.g., nivolumab, an anti-PD-1 antibody) can inhibit the tumor cells’ ability to evade the patient’s natural cellular-mediated immunity. The full role of radiation therapy in this process is still under investigation. However the idea of abscopal effects, in which local radiation therapy can cause tumor regression in unirradiated areas, remains tantalizing (3).

Although dose is a significant contributor to the effects of radiation on normal tissue, another important factor to consider is the volume of irradiated tissue. In general, when a significant volume of an organ has been irradiated, the risk of radiation effects is higher. Whole organ irradiation carries a much higher risk of organ failure compared to partial organ irradiation. Hence a higher dose or larger volume is more likely to result in radiation toxicity. For example, whole brain radiation is typically much more morbid than stereotactic radiosurgery, which focuses a high dose of radiation to a very small volume (17).

Radiation effects have been traditionally classified as early or late effects (18). Early effects are generally seen during the course of treatment or within 6 weeks of radiation therapy. Early effects are usually manifested in tissues that are quite sensitive to radiation, such as the skin or oral mucosa, which are highly proliferative. Fortunately, most early or acute effects of radiation are temporary. Late effects are considered those that appear months to years after radiation, and are more likely in tissues with low proliferative potential, such as connective tissue (fibrosis) or neural tissue (neuropathy). Although the mechanisms involved are not completely well understood, the late effects of radiation therapy, such as fibrosis, are often irreversible. Microvascular damage (endothelial thickening to the point that red blood cells are not able to pass through) has been thought to play an important role in late toxicity, causing hypoxic stress and cellular death. Endothelial thickening can take months to years to manifest. Loss of cells due to apoptosis after radiation-induced DNA damage also is likely to play a role. At high doses (>8 Gy) per fraction there are likely greater effects on the endothelial lining mediated by the ceramide pathway, and could help explain the significantly higher risk of late radiation effects seen with higher doses per fraction (19).

Another difficult late effect of radiation therapy is the risk of radiation-induced secondary cancers. For example, radiation therapy represented the first curative treatment for Hodgkin disease, but requires regional radiation therapy of the lymph nodes. When breast tissue was included in these fields to treat mediastinal lymph nodes, the risk of subsequent breast cancer was found to be more than 10 times greater than that in women who had never had such treatment (15 times greater in women who were irradiated between the ages of 20 and 30) (20). Overall, the risk of second cancers is approximately 2% higher over a patient’s lifetime, but exposure to radiation at a younger age or to a large volume of normal tissue carries a higher risk (21).

PATIENT MANAGEMENT AND DECISION MAKING

A radiation oncologist must weigh many factors when approaching the treatment of a patient. Radiation effects are dependent upon the inherent radiosensitivity and the volume of irradiated tissue, the dose of radiation delivered, and the dose fraction schedule employed for treatment, and must be considered when weighing the risks and benefits of such therapy. This requires a careful evaluation of the patient, paying particular attention to the potential toxicities of therapy weighed against the probabilities of benefit.

A common approach is to assess both patient factors and tumor factors associated with the case. Patient factors include the patient’s ability to tolerate treatment, such as Karnofsky Performance Status (KPS) (22), organ function, nutrition, or bone marrow reserve. Patient symptoms and signs are also considered. The prognosis is important to assess. Prior treatment must also be considered. When evaluating tumor factors, histology, the extent of disease, location of the disease and adjacent normal structures, as well as potentially involved areas of the body must be factored in. A tissue diagnosis of a disease for which radiation can potentially be useful is also critical.

An important decision point is to assess whether the intent of treatment is palliative or curative. In potentially curable disease, a higher level of toxicity is generally acceptable. However, with advances in systemic therapy, patients with incurable cancers may enjoy longer and longer survivals, and may warrant a more aggressive approach to controlling gross disease. Also, as patients live longer, quality of life is still an important issue. Aggressive treatment may add or detract to a patient’s long-term quality of life, depending upon the situation. Hence it is important for radiation oncologists to assess each patient thoroughly in order to recommend appropriate therapy.

SUMMARY

Cancer treatment is becoming increasingly complicated and a multidisciplinary approach to treatment is often indicated. For example, radiation therapy can have adverse effects on wound healing (23), and if the patient is to undergo surgery after radiation, radiation treatment should be planning in
such a way as to minimize the effects on the surgical bed. Chemotherapy can also potentiate the effects of radiation on both normal tissue and tumor (24). As a result, determination of the optimal treatment approach often results from evaluation of a patient from surgical, medical oncology, as well as radiation oncology perspectives, and with the help of input from other allied specialties such as pathology, radiology, neurology, and physiatry.

**KEY POINTS**

- Radiation therapy can be broadly defined as the use of ionizing radiation for the treatment of neoplasms.
- Radiotherapy is not limited by the anatomic or functional constraints of surgical resection and thus is able to treat cancer in a regional paradigm, often reducing morbidity and functional loss or deformity associated with radical resections.
- Improvements in computer and imaging technology have expanded the role of radiotherapy, allowing for the effective noninvasive management of tumors without the morbidity commonly associated with surgical or chemotherapeutic strategies.
- The most commonly utilized form of radiation is photon radiation, commonly known as x-rays (artificially produced) or gamma rays (emitted from naturally decaying isotopes).
- Radiation dose (Gray or Gy) is commonly defined as joules per kilogram (energy per unit mass) where 1 Gy equals 1 joule/kg.
- A technique called intensity modulated radiotherapy (IMRT), has allowed steep dose gradients around tumors, as high as 10% per millimeter.
- As opposed to treating tumors with the radiation source distant from the tumor, brachytherapy (placing radioactive sources inside of tumors) is another way to deliver very high dose radiation and limit normal tissue doses.
- The effects of radiation therapy on tissues is dependent upon the inherent radiosensitivity of the tissue or organ in question, the dose of radiation given and the volume of tissue irradiated.
- Microvascular damage (endothelial thickening to the point that red blood cells are not able to pass through) has thought to play an important role in the late toxicity, causing hypoxic stress and cell death.

**REFERENCES**