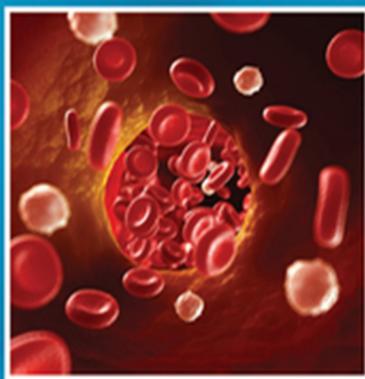


Edited by
Gary S. Stein | Kimberly P. Luebbbers

CANCER

Prevention, Early Detection,
Treatment and Recovery

Second Edition



WILEY Blackwell

CANCER



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Prevention, Early Detection, Treatment and Recovery

SECOND EDITION

Edited by

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Kimberly P. Luebbers

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PREFACE

Cancer is a leading cause of death globally. The social and economic burdens are profound. Making a difference in cancer prevention, early detection, treatment, and survivorship is not an option but a requirement and obligation. This responsibility is shared by cancer scientists, physicians, and a broad spectrum of healthcare professionals as well as by cancer advocates, educators, thought leaders, and lawmakers who are committed to making cancer preventable and treatable. Every life lost to cancer is a powerful motivation to accelerate progress toward bringing cancer under control. We are moving forward with confidence that more than half of the people who encounter cancer are cured. Reinforcing progress, an increasing number of people are living with cancer, undergoing long-term treatments, and experiencing quality lives.

Collaborative, multidisciplinary partnerships of dedicated scientists and physician-investigators are providing unique opportunities to reduce the burden of cancer. There is increasing capacity and capability to abbreviate the translation of discoveries in laboratories to advances in cancer prevention, early detection, treatment with clinical trials, and survivorship. There is recognition for the necessity to rectify disparities that result from restrictive healthcare access in many rural and urban communities. Initiatives to expand treatment options and opportunities for cancer patients irrespective of social or economic limitations must be a priority. An investment that enhances capabilities in cancer prevention, early detection, targeted treatment, and survivorship should be obligatory. The return on the investment will be immediate, progressively increase, and make a sustainable difference in quality of life.

“Cancer: Prevention, Early Detection, Treatment and Recover” was developed to provide a patient-centric book that synthesizes current understanding of the biology and treatment of cancer. We have responded to the importance of readily accessible explanations that accurately, directly, and comprehensively explain the biomedical parameters of cancer. We were guided by the necessity for facts, perspectives, and resources to enable cancer patients and caregivers to responsibly access options for “informed” and “comfortable” decisions.

This book provides a unique and valued resource, presenting an overview of cancer with emphasis on navigating the emerging “roadmap” from cancer prevention to early detection, treatment, and recovery. There are comprehensive books focused on the mechanistic and clinical facets of cancer. “Cancer: Prevention, Early Detection, Treatment and Recovery” authoritatively outlines the challenges

and opportunities associated with cancer biology, cancer research, and the spectrum of clinical considerations that are central to “experiencing cancer” as well as to studying, investigating, and treating cancer.

“Cancer: Prevention, Early Detection, Treatment and Recovery” is dedicated to Dr. Arthur B. Pardee, who has been instrumental in establishing the foundation for progress in the prevention and treatment of cancer. Arthur Pardee has, for many years, been making visionary and far reaching discoveries in cancer-compromised biological control that translate molecular and cellular changes during the onset and progression of cancer to novel strategies for cancer diagnosis and therapy. His contributions include the mechanistic understanding for control of gene expression, regulation of the cell cycle, and the coordinate control of genes that are responsible for physiological responsiveness and compromises associated with cancer onset and progression. Until his death on February 24, 2019, Arthur Pardee’s discoveries consistently accelerated progress toward making cancer preventable and treatable. He will continue to be an inspirational role model for scientists and physician investigators throughout the international cancer research community.

Gary S. Stein

Kimberly P. Luebbbers

I

CANCER AND THE CANCER
EXPERIENCE

CANCER AND THE CANCER EXPERIENCE

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ENCOUNTERING CANCER

The impact and consequences of cancer are immense and far-reaching. Everyone is vulnerable. Many of us have experienced cancer and most of us have been close to someone encountering this challenging disease. The cumulative toll is extensive. The data is compelling. Cancer is the leading cause of death in many states as well as globally. The social and economic (financial) burdens are profound.

A cancer diagnosis is frightening, confusing, and generally unexpected, evoking thoughts and feelings that are unfamiliar and unsettling. The patient has concerns that come without warning or preparation. The patient may experience a roller coaster of signs, symptoms, and emotions that are difficult to understand and tame. Cancer often changes the lives of patients, families, and friends, derailing goals, wishes, hopes, and dreams. Plans must be put on hold and decisions are required without experience to draw on. Priorities instantly change. Survival becomes a reality with many perplexing unanswered/unanswerable questions.

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CHALLENGES, OPPORTUNITIES AND COMMITMENTS

Despite the complex causes for cancer, the uncertainties associated with cancer risk and the requirements for unique strategies to advance cancer diagnosis and treatment, we can and should be optimistic that significant advances are being made toward reducing the burden of cancer. Making a difference in cancer prevention, early detection, treatment, and survivorship is not an option but a requirement and obligation. This responsibility is shared by dedicated scientists, physicians, a broad spectrum of healthcare professionals, cancer advocates, educators, thought leaders, and law makers who are committed to making cancer a preventable and treatable disease. And, while there is so much to be learned and so much to be accomplished we are making tremendous advances in understanding the biology and treatment of cancer – knowledge that can be captured to move toward putting cancer behind us as a life threatening disease. Numbers speak. While every life lost to cancer is powerful motivation to accelerate progress toward bringing cancer under control we are moving forward with confidence that more than half of the people who encounter cancer are cured. Reinforcing progress, an increasing number of people are living with cancer undergoing long-term treatments and experiencing (compatible with) quality lives.

WHAT IS CANCER?

Pursuit of the causes for cancer and discovery of strategies for treatment have been elusive. Cancer defies conventional definitions for a disease with unique, sometimes ambiguous and frequently challenging biology and pathology. The complexities of changes in cells, tissues, and organs that do not respond to traditional therapies are often unfamiliar and unpredictable. The elusiveness of cancer is an enigma to dedicated scientists at the forefront of studying cancer in the laboratory and to physicians who are committed to maximizing effectiveness of treatment for cancer patients. Sustained effectiveness for the treatment of cancer and the recurrence of disease have been and continue to be difficult problems. Cancer can be refractory to drugs, develop resistance, and acquire capabilities to circumvent therapeutic targets.

While there are many gaps in our knowledge about cancer (biology and pathology) there is emerging appreciation for the absence of a single cause. This is in striking contrast to polio, which is caused by an identifiable infectious agent and prevented by a specific vaccine. The lack of a shared treatment responsiveness for all tumors can be frustrating. However, it is widely recognized that the dominant unifying features of cancer are compromised control of cell proliferation with decline in specialized cell functions and abrogated (relinquished) competency for the responsiveness to environmental regulatory signals. Cancer cells generally exhibit unrestricted proliferation that may not be compensated by cell loss.

The onset as well as progression of cancer is associated with changes that include but are not restricted to: enhanced cell mobility and motility providing capability for metastasis, the development of secondary malignant growth at a distance from the primary tumor; decline in the patient's capability to enlist the immune system to recognize and reject tumor cells; a shift from aerobic (oxidative phosphorylation) to anaerobic (glycolysis) metabolism; recapitulated expression of fetal proteins in tumor cells; and, competency for tumor cells to populate and multiply in vital organs interfering with essential functions. Many of the modifications exhibited by tumor cells provide biomarkers, biochemical indicators for the presence of cancer and full effectiveness of cancer therapy. Others are *targets* for the identification and design of pharmaceuticals to treat cancer.

Acceptance of the absence for a single cause of cancer has been long coming. During the past century there have been an evolving series of infectious agents and environmental factors that have been held accountable for cancer. Genetic predisposition and recently epigenetic control, non-DNA-encoded cellular regulatory information that is retained and distributed to progeny cells during cell division, have been implicated as accountable for cancer. Viruses that include HPV, EBV, and HIV have been directly linked to cancer. Inflammation is associated with the onset and progression of tumors. And, a long list of cancer causing chemicals designated *carcinogens* has been identified. Compelling evidence has linked smoking, alcohol consumption, ultraviolet exposure, and obesity with cancer risk. Rather than assigning blame to a single cause for cancer, prevailing evidence that is widely understood and accepted supports a multifactorial basis for cancer with the realization that synergy between risk factors can exacerbate and accelerate cancer onset, progression, and recurrence of disease. The incidence of cancer increases with age, attributable to accumulation of acquired genome mutations, compromised capability to repair damaged DNA/chromosomes, genes, and compromised metabolic control.

Objective, scientifically based documentation for cancer risk has been leveraged through public awareness, effective advocacy and support from law makers into policies, recommendations and legislative mandates to reduce exposure to factors and practices that contribute to cancer. Regulations, guidelines, and persuasive public opinion is implementing cancer prevention, the benefits for quality of life are increasingly understood and accepted. The economic impact (consequences) is recognized and appreciated. Cancer prevention is becoming understood and accepted as a shared responsibility. With enhanced capabilities for treating cancer, emphasis on survivorship is becoming increasingly important.

CANCER AND THE PATIENT

The emotional impact of cancer cannot be captured in words. With so many unfamiliar considerations and perplexing decisions, it is difficult to navigate the cancer experience with confidence. What should I do? Who should I turn to? How can I

have assurance my decisions are appropriate? There is so much information, most authoritative and some questionable. There are so many options. There are numerous opinions, most highly responsible but not all consistent. And it can be difficult to distinguish between authoritative and anecdotal reports and recommendations.

Confirmation of a Cancer Diagnosis

A cancer diagnosis may result from cancer screening; a mammogram, a colonoscopy, or a prostate cancer test. A routine physical examination or evaluation of a suspicious symptom can be the basis for diagnosing cancer. Regardless of the competency and experience of the diagnosing physician and the capabilities of the medical practice or health center where the diagnosis is made, the patient should not hesitate to seek a *second opinion* for multiple reasons. Obtaining a *second* or *third opinion* does not preclude treatment by the physician who provides the initial diagnosis. Confirmation of a diagnosis provides assurance that the full spectrum of diagnostic options are utilized or considered and that a comprehensive evaluation of treatment plans is performed. A second opinion should not be a challenge to confidence in the treating physician. Rather, a contributory diagnosis provides a valuable perspective and reassurances for decision-making by the patient and the doctor. Criteria for tumor diagnosis and staging are evolving and options for treatment are rapidly emerging. Seeking recommendations from experts is vitally important.

Specialized diagnostic procedures that can be informative for decision-making may be available at centers that specialize in treating certain tumors. With rapidly accruing developments in treatment options, not only rare tumors but also the prevalent types of cancer, it is advantageous to secure a comprehensive assessment of the treatment possibilities as well as an understanding of the strengths and limitations of the options. Decisions may be between medical, surgical, or radiation therapy or a combination of these treatments. Consultation to obtain multiple perspectives is becoming increasingly important for informed decision-making with an understanding of the strengths and limitations of options that are available.

Treatment Options

Medical treatments include conventional *cytotoxic chemotherapy* that is directed to selectively kill rapidly dividing cancer cells with doses, treatment regimens, and combinations of drugs that are designed to maximize specificity and minimize non-specific, *off-target* affects. Precision medicine is emerging with the objective to target the unique defect of a specific tumor and requires molecular diagnostic evaluation involving analysis of the tumor genome. Another emerging dimension to medical oncology is immunotherapy where the tumor is specifically targeted or the patient's immune system is rendered competent to reject the tumor by providing cues that the tumor is *non-self*.

Surgical options are expanding. Minimal invasive surgical procedures are being developed that are highly effective and reduce recovery time for the patient. With complex surgical cases a consideration is the experience of the surgeon with the specific procedure.

Radiation treatments are advancing rapidly with more focus on *treatment fields* to prevent/reduce tissue and organ complications. Specific modalities of radiation therapy can be beneficial for certain tumors and be advantageous for contained or disseminated (metastasized) cancers. There are advances in treatment plans that combine medical, surgical, and radiation therapy, both sequential and combined.

To treat or not to treat is an important decision for DCIS and prostate cancer. There is growing concern that these tumors may be excessively treated and guidelines are being developed for *active surveillance*, where the lesions are frequently reevaluated. The objective is to avoid unnecessary medical, surgical, or radiation intervention where consequences can include treatment/procedure-related complications including the risk for secondary cancers.

Where to Obtain Treatment?

It is important to engage the most knowledgeable and experienced physicians to establish and confirm a cancer diagnosis and contribute to development of a treatment plan. Academic cancer centers provide the most comprehensive opportunities for state-of-the-art cancer diagnosis and treatment. Multidisciplinary team approaches are utilized for diagnosis and decision-making. The most advanced capabilities, instrumentation and expertise are available for characterizing tumors and evaluating patients. Clinical trials are available to provide the most up-to-date options for tumor detection and therapy. Research at cancer centers translates laboratory discovery to novel options for treating cancer.

Community-based cancer centers offer cancer patients quality care and are affiliated with academic cancer centers, working collaboratively to provide patients with the advantage of treatment near home with access to academic cancer centers for specialized diagnoses or therapy. Community-based physicians who are affiliated with academic cancer centers have the ability to draw on the expertise and experience of the centers as well as participate in clinical trials. For highly specialized medical, surgical, or radiation therapy it may be advantageous to obtain treatment where unique capabilities are available.

Patient and Family-Centered Care

There is growing appreciation for the importance of family and friends for the well-being of the patient. It is recognized that involvement of family and friends should be a priority from the initial visit. Engagement of people close to the patient can expand availability of care givers. Unquestionably, involvement of family and friends makes a decisive difference in the quality of life for a cancer patient.

Assistance with care and emotional reinforcement are decisive factors. Understanding the cancer patient, the disease, and treatments enables families and friends to be maximally supportive with an accurate understanding of the challenges confronting the patients. Beyond the treatment, involvement of family and friends continues to be important for survivorship and should not be dismissed.

Shared Decision-Making

The options for treatment decisions and strategies for survivorship are extensive and complex. Turning the clock back, physicians provided treatment plans to patients and generally there was minimal dialog beyond clarification of expectations of patient compliance and the anticipated outcomes. Now there is emphasis on shared decision-making with discussions between the patient and physician on cancer detection, treatment options, recovery, and surviving cancer as a treatable disease. Cancer prevention is another area where there is a spectrum of choices and these can best be evaluated by considering consequences of options by physician–patient discussion. Engaging the patient and physician in shared decision-making provides the patient with in-depth understanding that will impact on patient compliance. The dialog will allow the physician to understand the thoughts and feelings of the patient.

PATHWAYS TO DISCOVERY

Building on Discoveries of the Aberrant Biology of Tumor Cells

Broad-based engagement of scientists and physician/investigators has provided an understanding of cancer biology that can translate to clinical applications. Initially, the focus was on a cause and emphasis was on a cellular change. There is now recognition for genetic, epigenetic, and environmental contributions to cancer risk, initiation, and progression. There is compelling documentation for multiple cancer-related alterations in control of cell proliferation and chromosome structure and function that are associated with altered metabolic control and compromised capabilities for responsiveness to regulatory signals and execution of activities required by specialized cells. Particularly significant is acceptance that cancer derails essential cellular processes. Cross-talk between parameters of control is altered and compensatory mechanisms are invoked during the onset and progression of cancer that are mechanistically informative and clinically relevant. There is increasing emphasis on multiple dimensions of regulation and integration of activities. There are emerging *success stories* where genetic, epigenetic, metabolic, cellular, and biochemical properties of cancer cells are informative for cancer diagnosis, decisions and options for treatment, monitoring therapeutic responsiveness, and monitoring relapse. Monitoring the structural and functional properties of cancer cells enhances the effectiveness of conventional chemotherapy,

radiation therapy, immunotherapy, and cancer stem-cell-based interventions. With the development of genome-based medicine where aberrant genes and altered gene expression support refined diagnosis and targeted therapy it is increasingly important to consider cellular changes that occur with cancer and are responsive to treatment.

Embracing the *Value Added* from Collaboration

The complexity of cancer research, diagnosis, and treatment requires collaborative team approaches. Effectiveness in cancer investigation and patient care necessitates partnerships where complementary perspectives, expertise, and experience optimize capabilities.

Collaboration accelerates mechanistic, behavioral, clinical, and translational cancer research. Multidisciplinary approaches reinforce creativity and innovation as well as enhance the transition from discovery to clinical applications. Collaboration supports development of novel laboratory-based and behavioral strategies, data acquisition and analysis as well as integration of complex data sets including sophisticated informatics. Research initiatives that incorporate scientists and physician/investigators support pursuit of fundamental mechanisms within the context of clinical applications. Collaborative research is the longstanding approach in the pharmaceutical and biotechnology industries. Cancer centers, to accommodate expectations from the National Cancer Institute emphasize and incentivize multidisciplinary, inter-programmatic and inter-institutional collaboration. And educational institutions are supporting collaborative contributions for academic advancement.

Collaboration increases the effectiveness of clinical care with increasing development of disease-site-specific multidisciplinary clinics. To expedite diagnosis and development of a treatment plan with comprehensive clinical input, during the initial visit the patient is evaluated by a medical oncologist, surgical oncologist, and radiation oncologist and there is participation of a radiologist and pathologist. In addition to follow-up evaluations for immediate initiation of treatment, the patient is generally spared the anxiety associated with a series of sequential visits.

Developmental and Age-Dependent Considerations

There are striking age-dependent cancer treatment considerations that are becoming increasingly evident. Pediatric oncology is an expanding field and there is accruing understanding for drug selection, dose, and treatment regimens that are effective and compatible with patient tolerance and responses that change with advancing age. With pediatric patients there is growing evaluation of minimal chemotherapy doses that achieve maximal responses to protect young children from lifelong vulnerability to treatment-related complications. There are similar treatment and dose considerations for radiation treatment of pediatric and geriatric

cancer patients. The changes in treatment responsiveness and dose tolerances that occur with the transition from pediatric to adolescence are important clinical considerations. Further understanding the optimal approaches for treating adolescent cancer patients will be important.

EMPHASIS ON CANCER PREVENTION AND SURVIVORSHIP

The advances in cancer diagnosis and therapy have been significant. Success stories include testicular cancer, breast cancer, skin cancer, GI (gastrointestinal) tumors, and leukemias. Equally important, there is an increasing emphasis on cancer prevention and survivorship that can advance progress toward making cancer preventable and treatable. Progress in cancer prevention reflects the combined effectiveness of education on the importance of healthy living, emphasizing diet and exercise and tobacco control. Policies and legislation that mandate warnings on tobacco products and prohibit the sale of tobacco and alcohol to minors and prohibiting smoking in many public areas has been influential. Identification of carcinogens that impact on cancer risk has had a positive effect, including scrutiny of inclusion in food products.

Early detection has been a driving force in alleviating the cancer burden. There has been development and refinement of technologies and assays for cancer screening with strong support of physicians, healthcare insurers, educators, law makers, and healthcare advocacy organizations. Breast cancer, prostate cancer, skin cancer, and recently lung cancer screening programs have made a difference in reducing the incidence of advanced stage cancer diagnoses. Acceptance of the importance for cancer screening is gaining momentum and will be an increasingly positive force for detecting cancer at a stage where response to treatment is effective. With an emerging pipeline of targeted drugs and immunotherapy, early detection is paving the way for cancer to be treated as a chronic and controllable illness. Living a high-quality life with cancer is an increasingly prevalent reality.

As a consequence of advances in cancer detection and treatment, survivorship is becoming increasingly important. Survivorship begins with a cancer diagnosis, continues through active surveillance or treatment, and continues thereafter to limit the risk of recurrence (relapse) and to support a productive and meaningful life.

Survivorship is not always intuitive. Guidance for strategies to live with and/or go beyond a cancer experience is available from multiple sources. Treating physicians, social workers, cancer support groups, and cancer advocacy organizations have programs that *reach out* to cancer patients and families to assist with adjustments in perspective and activities that are valuable for survivorship with maximal capabilities and minimal limitations. There is increasing emphasis on capturing opportunities for growing from a cancer experience – acquiring appreciation and understanding for priorities that should not (can) be taken for granted.

LESSONS LEARNED AND ENCOURAGING PROSPECTS

A century of dedicated commitment to exploring the deviant behavior of cancer cells, the pursuit of the elusive cause of cancer, and the development of innovative strategies to eliminate or neutralize unrestricted proliferation of tumors has yielded valuable understanding for the biology and treatment of cancer. The recent advocacy by Vice President Joe Biden for the Cancer Moonshot will support initiatives that translate discovery to transformative clinical applications with immediate, far-reaching, and long-lasting impact. Drawing on breakthroughs in understanding cancer and advances in cancer therapy and learning from approaches that encountered obstacles, we are poised to accelerate progress toward making cancer a preventable and treatable disease.

