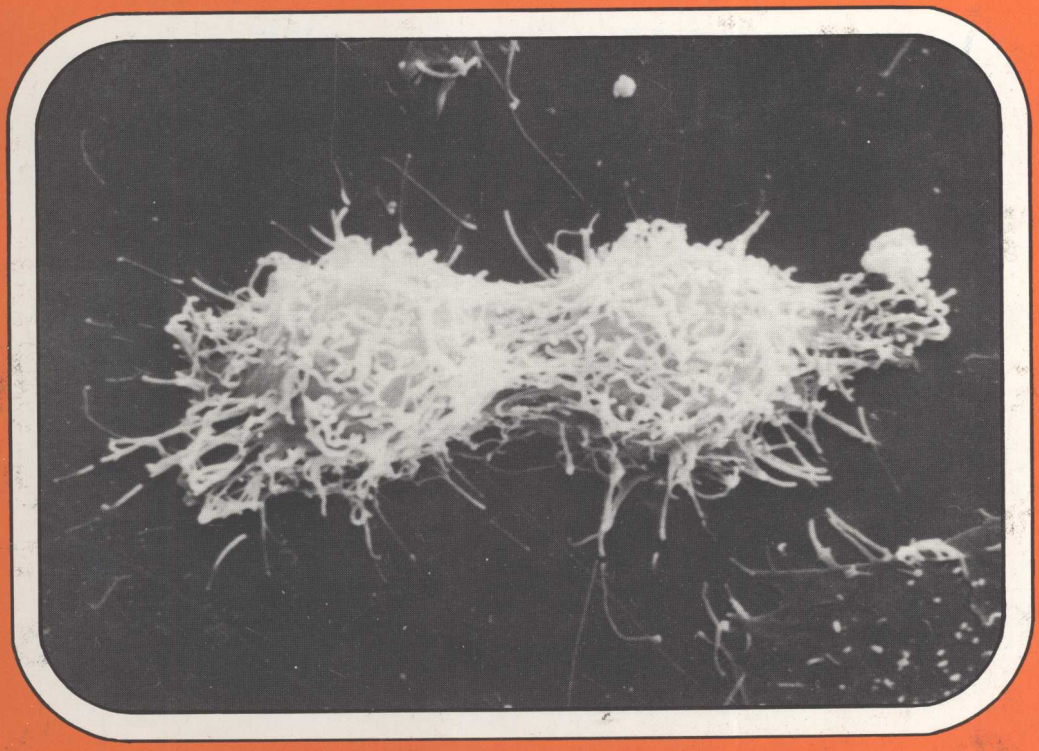
CANCER

A Biological and Clinical Introduction

Second Edition



Steven B. Oppenheimer

CANCER

A Biological and Clinical Introduction

Second Edition

Steven B. Oppenheimer
California State University, Northridge

Jones and Bartlett Publishers, Inc.
Boston/Portola Valley

Medicine, to produce health, has to examine disease.

Plutarch
Lives, Demetrius

To the American Cancer Society and dedicated students and faculty who have brought us programs in the biology of cancer, *and* to the National Cancer Institute and National Science Foundation for research support.

Cover photo: Scanning electron micrograph of dividing cells. From G. Shih and R. Kessel. 1982. *Living Images.* Jones and Bartlett Publishers, Inc.

Editorial offices: Jones and Bartlett Publishers, Inc., 30 Granada Court, Portola Valley, CA 94025

Sales and customer service offices: Jones and Bartlett Publishers, Inc., 20 Park Plaza, Boston, MA 02116

Library of Congress Cataloging in Publication Data
Oppenheimer, Steven B., 1944–
Cancer, a biological and clinical introduction.

Includes bibliographies and index.
1. Cancer. I. Title. [DNLM: 1. Neoplasms.
QZ 200 064c]
RC261.064 1984 616.99'407 85-18182
ISBN 0-86720-062-6

Design/Production: Unicorn Production Services
Printer/Binder: Alpine Press

Printed in the United States of America
10 9 8 7 6 5 4 3 2

Preface to the Second Edition

Rapid advances in certain aspects of cancer biology, in particular, the study of oncogenes, have made it necessary to update the first edition of this book one or two years earlier than originally planned. A great deal of enthusiasm from teachers and students who have used the book in the past two years has given me the interest to prepare this revision.

The book has been updated, a new chapter on oncogenes has been added, and most of the figures have been redrawn. Furthermore, the text has been revised and clarified, a task guided by David Freifelder, and read by Rachel Freifelder, both of whom deserve my thanks.

The instructor and students will note that many concepts and facts appear numerous times in the book, frequently duplicating what has been presented before. This pedagogical device has been considered advisable in view of the complexity of the topic and the variability in backgrounds of the students.

I appreciate the enthusiasm of Arthur Bartlett, who agreed to include the book in the Jones and Bartlett publishing program, and the administration of Allyn and Bacon who allowed the transfer of copyright in order that the second edition could be published rapidly.

Steven B. Oppenheimer
August, 1985

Preface to the First Edition

In recent years, courses in the biology of cancer have found a place in the curricula of numerous undergraduate institutions and health-related, professional programs. Having been associated with such a course, sponsored by the American Cancer Society, I have become keenly aware of the need for a text in this area that treats both cellular aspects of cancer and the clinical aspects of the disease in an organized, clear, and coherent manner. It is hoped that this text will provide a balanced treatment of the entire cancer problem that is stimulating and clearly presented for undergraduates, nurses, and other health professionals.

The text begins with the cellular aspects of cancer and concludes with the clinical and organismal aspects of the disease. What causes cancer? What causes cancer to spread? What are the characteristics of cancer cells? Can our body defenses attack cancer cells? What are the similarities and differences between different tumors? What is the intriguing relationship between cancer cells and embryo cells? Is cancer inherited? Is cancer infectious? How is it diagnosed? How is it treated? What are some new experimental methods of cancer treatment?

These are some of the questions that are examined in this text. Not all of the answers to these sorts of questions are at hand but some are. It is hoped that this text will provide the reader with some of the answers and with an understanding of the ways in which investigators approach the study of cancer. Also, I hope that sharing my own enthusiasm for the subject matter will excite the curiosity and interest of students so that some may eventually contribute to the body of knowledge concerning one of the most dreaded diseases.

I wish to thank Michael Edidin, Heinrich Ursprung, Malcolm Steinberg, Saul Roseman, Stephen Roth, and Robert DeHaan, who served as the nucleus of individuals at Johns Hopkins who helped provide me with the foundations needed to write this text. I would

also like to express my gratitude to the National Cancer Institute, the American Cancer Society, and the National Science Foundation for supporting my research efforts and my program in cancer biology at Northridge.

Special thanks is given to Joseph Burns, Editor, Allyn and Bacon, who skillfully steered this book through all of the phases of its development. He has not been just an editor but has actively participated in molding content and style. I thank Gary Folven, Managing Editor, who has helped me over the years by providing an excellent atmosphere in which to work. I thank Judith Gimple and Sarah Doyle of Bywater Production Services for a meticulous job and the entire staff at Allyn and Bacon for their enthusiastic assistance.

I would like to thank all my colleagues who have kindly provided photos and permission to use illustrations of their work in this book. I am particularly indebted to the American Cancer Society, Robert Dyson, David Epel, Harvey Gilbert, Garth Nicolson, Nuclear Associates, R. E. Saxton, K. Tanaka, Victor Vacquier, and Varian Associates for providing collections of superb micrographs and charts.

I would like to make special mention and express my gratitude to the many fine reviewers who have helped guide me in the writing of this book: Peter B. Armstrong, University of California, Davis; Lois M. Bergquist, Los Angeles Valley College; Joel S. Greenberger, Harvard Medical School; Charles M. Haskell, Wadsworth Cancer Center; George Lefevre; California State University, Northridge; George M. Malacinski, Indiana University; Robert G. McKinnell; University of Minnesota; Richard Schwarz, University of California, Berkeley; John R. Seffrin; Indiana University; Rachel Spector, Boston College; Michelle Stuart, Rush Presbyterian-St. Luke's Hospital; Robert A. Weinberg, Massachusetts Institute of Technology; and Melanie Wolf, Houston, Texas. I have taken much of the advice of these reviewers. Any errors, however, are my own. Finally, I wish to thank my wife Carolyn for excellent typing and suggestions and a superb sense of humor.

Steven B. Oppenheimer
1982

Contents

1

Introduction

Diseases such as plague, smallpox, polio, and diphtheria were once major scourges of the world. However, in the past few decades, with the introduction of antibiotics and vaccines, the incidence and seriousness of infectious diseases has become minor. Now, the diseases that usually affect older individuals, namely, heart disease, stroke, and cancer, which account for 37.8, 20.4, and 9.6 percent, respectively, of all deaths in the United States, are the major causes of death; and a major effort is in progress to combat these diseases. Heart disease and stroke are usually progressive and not totally curable; however, many cancers have become curable to some extent (Tables 1-1, 1-2). After reading this book, students should feel generally optimistic that the incidence of death by cancer will continue to fall in the future. Although the current statistics of cancer incidence and mortality appear grim, numerous specific cancers, such as acute leukemia in children, which once was considered incurable, today is curable in an increasing number of cases.

The relation between survival rates and death rates, and the expectation for changes in these values, has in the past primarily reflected new treatments. However, these values do not really indicate what can be expected in the future, because they do not indicate possible changes caused by reducing the incidence of cancer. For example; one of the major cancer killers, lung cancer, is seldom diagnosed early enough to effect a cure, and indeed death rates from

TABLE 1-1 Progress against cancer

Period	Fraction alive after 5 years
1930s	Less than 1 in 5
1950s	Less than 1 in 4
1970s	1 in 3

TABLE 1-2 5-year survival rates for certain cancers

Site	Condition of tumor at time of detection	
	Localized	Spread
Bladder	72%	14%
Breast	85	47
Colon-rectum	71	26
Larynx	79	32
Lung	33	4
Oral	67	25
Prostate	70	35
Uterus-cervix	78	37

lung cancer are increasing (Tables 1-3, 1-4). However, lung cancer is largely preventable. Eighty percent of the roughly 100,000 new lung cancer patients detected annually are smokers, and many of the other patients are workers in high-risk occupations, such as those dealing with specific carcinogenic substances like asbestos. Lung cancer deaths in the United States are about a third of the total number of deaths from all other kinds of cancers combined. Elimination of smoking may in time reduce cancer death rates by 50 percent! Smoking is also believed to be a major cause of numerous other types of cancers, and these too would be reduced by the elimination (or at least substantial reduction) of smoking.

It seems unlikely that smoking will be eliminated in the near future. However, a decline in lung cancer deaths could result from the introduction of cigarettes with reduced amounts of tar and nicotine. A recent study by the American Cancer Society, carried out over a 12-year period with one million individuals, has indicated that the rate of death by lung cancer in users of low-tar and low-nicotine cigarettes was 26 percent lower than that among smokers of standard cigarettes. (This is not to say that these cigarettes are safe, because the death rate due to lung cancer among these smokers is still six times greater than that of the general population.) Thus, progress in reducing lung cancer deaths in the short run must rely in part on the tobacco companies marketing less hazardous cigarettes.

THE PROBLEM OF EARLY DIAGNOSIS

A major reason for the high death rate with some types of cancer is the fact that they are detected fairly late. For example, lung cancer

TABLE 1-3 Summary of cancer death rates, 1930-1976

Men	Women
Substantial decrease	
Stomach (6-fold)	Uterus (4-fold) Stomach (7-fold)
About the same	
Colon-rectum Prostate Pancreas Esophagus Leukemia Bladder	Breast Colon-rectum Ovary Lung Pancreas Leukemia
Substantial increase	
Lung (18-fold)	Lung (4-fold)

TABLE 1-4 25-year trends in cancer death rates per 100,000 population, 1950-1952 to 1975-1977.

Sex	*Sites*	*1950–52*	*1975–77*	*Percent changes*	*Comments*
Male	All Sites	131.1	102.3	+ 23.8	Steady increase mainly due to lung cancer.
Female	All Sites	118.9	107.9	− 9.3	Slight decrease.
Male	Bladder	5.1	4.9	*	Slight fluctuations; overall no change.
Female	Bladder	2.2	1.4	− 35.1	Some fluctuations; noticeable decrease.
Male	Breast	0.3	0.3	*	Constant rate.
Female	Breast	22.0	23.2	+ 0.6	Slight fluctuations; overall no change.
Male	Colon & rectum	19.4	19.0	− 2.1	Slight fluctuations; overall no change.
Female	Colon & rectum	18.9	14.9	− 19.5	Slight fluctuations; noticeable decrease.
Male	Esophagus	3.6	4.3	+ 19.0	Some fluctuations; slight increase.
Female	Esophagus	.9	1.2	*	Slight fluctuations; overall no change in females.
Male	Kidney	2.8	3.7	+ 32.1	Steady slight increase.
Female	Kidney	1.6	1.8	*	Slight fluctuations; overall no change.
Male	Leukemia	6.5	6.9	+ 6.2	Early increase, later leveling off.
Female	Leukemia	4.6	4.1	− 8.7	Slight early increase, later leveling off and decrease.
Male	Lung	18.3	56.7	+210.6	Steady increase in both sexes due to cigarette
Female	Lung	3.9	14.0	+263.3	smoking.
Male	Oral	4.7	4.8	*	Slight fluctuations; overall no change in both sexes.
Female	Oral	1.2	1.6	*	
Female	Ovary	7.0	7.3	+ 4.3	Steady increase, later leveling off.
Male	Pancreas	6.5	8.4	+ 29.2	Steady increase in both sexes, then leveling off.
Female	Pancreas	4.2	5.2	+ 23.8	Reasons unknown.
Male	Prostate	13.3	13.9	+ 5.3	Fluctuations all through period; overall no change.
Male	Skin	2.3	2.8	*	Slight fluctuations; overall no change in both sexes.
Female	Skin	1.5	1.6	*	
Male	Stomach	17.6	6.8	− 61.2	Steady decrease in both sexes; reasons unknown.
Female	Stomach	9.3	3.2	− 65.6	
Female	Uterus	18.2	7.4	− 59.3	Steady decrease.

* Percent changes not listed because they are not meaningful.

Source: *Cancer Facts and Figures*. New York: American Cancer Society, 1980.

is usually not diagnosed until the tumor is about 1 cm in diameter, and such a tumor already contains about one billion cells. It has been estimated that many lung cancers require ten years to reach this size, and during this time the cells may have spread to other parts of the body. As shown in Table 1-2 the prognosis (the chances for cure) for a cancer that has spread is much poorer than that for one that has been diagnosed before spreading has occurred. Improved diagnostic techniques that enable a much smaller tumor to be detected should reduce the death rate. Development of such techniques is a feature of the research effort against cancer.

A major success story in decreasing cancer deaths by early diagnosis is that of cancer of the cervix (Tables 1-3, 1-4). The lower death rate due to cervical cancer is almost exclusively a result of the widespread use of the Pap test. In this test a smear of vaginal cells is taken and examined by microscopy. Abnormal cells can be observed, and often precancerous conditions can be identified and treated before spreading occurs.

We face a complex interplay of various factors when discussing cancer death rates and cures. Not only must one be concerned with diagnostic techniques and methods of treatment, but also with public attitudes, habits (for example, to smoke or not), and awareness. Specialists in public health have recognized for some time that improvements in any of these areas will greatly reduce cancer death rates and that education of the public must be given highest priority. Throughout this text, we will see these features of the cancer problem. It goes without saying that combating cancer also requires knowledge of the causes of cancer, as we now understand them. The causes of cancer will be a major part of this book and will be discussed in some detail. However, it is valuable to have a preliminary look at some general aspects of factors that appear to be involved in causing cancer. These are presented briefly in the next section.

CAUSES OF CANCER

From studies of humans and other vertebrates a variety of factors have been implicated in causing cancer. These factors include environmental agents (chemicals, ionizing radiation, ultraviolet radiation), the genetic constitution of the individual, gross chromosomal abnormalities, hormonal dysfunctions, and viruses.

Cancer is a disease in which cells grow in an uncontrolled way. Most cells in the body are neither growing nor dividing, and those that do are strictly controlled. However, cancer cells are not subject to the mechanisms of growth control present in most normal cells, and hence they multiply. As a result of their continual division and spreading, cancer cells eventually interfere with one or more vital functions and cause death. Anything that can interfere with the normal control of cell division may lead to cancer. For more than 200 years it has been recognized that long-term exposure to certain substances increases the probability of cancer. In fact, from accumulated statistics it is now estimated that perhaps 90 percent of all human cancers are caused by exposure to environmental agents. As we will see, these

factors include not only manufactured substances but also sunlight and naturally occurring agents in our diets. Substances and agents that cause cancer are called carcinogens.

Chemical studies of many carcinogens have shown that most of these substances act either directly or indirectly on cellular DNA and thereby alter genetic information. In fact, most compounds that cause cancer have also been shown to cause mutations in DNA. For this reason, in the next chapter we will examine the structure of DNA and the mechanism of production of mutations.

Nuclear radiation is an important cause of cancer. This had been suspected for many years but was made clear by determining cancer rates among survivors of the atom bomb blasts in Japan. The rates of many types of leukemia among the exposed population are correlated closely with the radiation exposure. Study of the effects of radiation on a variety of cells (bacteria, animal cells, plant cells) has shown that the primary damage caused by radiation is again to the DNA, both breakage of the molecules and alteration of its informational content.

An important feature of cancer is that frequently a tumor does not develop until a very long time after exposure to a carcinogenic agent, perhaps 20 years. This observation has led to the belief that cancer does not result from a single molecular change in a cell but may require several distinct alterations, each of which may occur at very different times. This hypothesis was made more certain by studies with particular classes of cancer-causing agents that cannot cause cancer by themselves. These classes, called initiators and promoters, have the property that tissue must be exposed to one agent of each class and that exposure need not be simultaneous. In fact, all that is needed is that the initiator be applied first. Exposure to the promoter can occur years after exposure to the initiator. The hypothesis, which will be examined in Chapter 6 is that the first step (initiation) involves a permanent change, such as a mutation, while the second step (promotion) involves some sort of stimulus that causes the initiated cells to divide. The existence of these two classes of substances, specific combinations of which are required for cancer induction, sometimes makes identification of substances that cause cancer quite difficult. For example, a test for the activity of a carcinogen may give a negative result if the appropriate initiator is unknown and thus not used in the test.

The genetic makeup of an individual is definitely important in the development of some cancers. For example, bilateral retinoblastoma, a cancer that develops in the eyes of children, is clearly inherited. An individual receiving the bilateral retinoblastoma gene from a parent will develop the cancer. However, most cancers and precancerous conditions do not appear to be inherited, at least not directly. The predisposition to develop cancer or certain types of cancers may have a genetic basis; however, if so, it is much more complicated than for bilateral retinoblastoma. For example, lung cancer is much more prevalent in smokers who have a close relative with lung cancer than in smokers who do not have such a family history. Such a correlation suggests a predisposition with a genetic basis, but still the actual carcinogens from tobacco smoke are the agents that cause the cancer