Cancer: Basic Science and Clinical Aspects

Craig A. Almeida and Sheila A. Barry

Department of Biology, Stonehill College, Easton, Massachusetts, USA
Cancer
I am indebted to Kevin, my parents, brothers, and sisters for their unconditional love, support, and understanding, especially through the process of writing this book.

Craig A. Almeida

This book could not have been made possible without the continuing love and support of my husband Richard and children Janine and Craig, all of whom were eternally patient and encouraging of this effort.

Sheila A. Barry

This book is accompanied by a companion website:
www.wiley.com/go/almeida/cancer
Cancer: Basic Science and Clinical Aspects

Craig A. Almeida and Sheila A. Barry

Department of Biology, Stonehill College, Easton, Massachusetts, USA
Contents

Preface ix
Acknowledgements xi

1 The basics of cancer 1
   Cancer is a complex entity 1
   Cancer through the ages 6
   Modern day cancer research and treatment 11
   Prevalence and mortality varies with each cancer 15
   Risk factors have been identified 18
   Will cancer be conquered within our lifetime? 23

2 Cells: The fundamental unit of life 26
   Seven hierarchal levels of organization 27
   Four types of macromolecular polymers 32
   Cell structure and function 45
   Relationship between structure and function is important 48

3 The human genome and protein function 51
   The composition and function of the human genome 51
   Having a diploid genome has its advantages 56
   Proteins carry out diverse functions 60

4 Cell cycle, oncogenes, and tumor suppressor genes 67
   Cell division in germ-line and somatic tissues 68
   Consequences of germ-line and somatic tissue mutations 74
   Cell division, differentiation, and maturation occur to
   form functional tissues 74
   Cell division is under the regulation of the cell cycle 76
   Loss of cell cycle control results in uncontrolled cell growth 91

5 Tumor formation, growth, and metastasis 94
   Tissue changes that occur in response to stimuli 94
   Feeding tumor growth by angiogenesis 100
   Characteristics of benign and malignant tumors 103
   Events that occur during the process of metastasis 105
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Cancer screening, detection and diagnostic procedures and tests</td>
<td>115-117</td>
</tr>
<tr>
<td></td>
<td>Factors that determine the accuracy of a diagnostic test or procedure</td>
<td>116</td>
</tr>
<tr>
<td></td>
<td>Common screening tests</td>
<td>117</td>
</tr>
<tr>
<td></td>
<td>Diagnostic procedures for the confirmation of a disease</td>
<td>119</td>
</tr>
<tr>
<td></td>
<td>Tumor grade and stage factor into the type of treatment regimen and prognosis</td>
<td>131</td>
</tr>
<tr>
<td>7</td>
<td>Cancer treatment modalities</td>
<td>135-163</td>
</tr>
<tr>
<td></td>
<td>Surgery: the oldest and most commonly used treatment method</td>
<td>136</td>
</tr>
<tr>
<td></td>
<td>Radiation kills by causing extensive DNA damage</td>
<td>139</td>
</tr>
<tr>
<td></td>
<td>Cytotoxic effects of chemotherapeutic drugs</td>
<td>145</td>
</tr>
<tr>
<td></td>
<td>Side effects and risks from the use of cytotoxic drugs</td>
<td>150</td>
</tr>
<tr>
<td></td>
<td>Hormonal deprivation treatment: used for estrogen- and androgen-dependent cancers</td>
<td>153</td>
</tr>
<tr>
<td></td>
<td>Can cancer growth be controlled by inhibiting angiogenesis?</td>
<td>158</td>
</tr>
<tr>
<td></td>
<td>Additional enzymes targeted for inhibition</td>
<td>161</td>
</tr>
<tr>
<td></td>
<td>Biological therapy stimulates the body’s ability to fight cancer</td>
<td>163</td>
</tr>
<tr>
<td>8</td>
<td>Breast cancer</td>
<td>165-187</td>
</tr>
<tr>
<td></td>
<td>Breast cancer statistics</td>
<td>166</td>
</tr>
<tr>
<td></td>
<td>Women’s breast tissue: unique in structure and function</td>
<td>167</td>
</tr>
<tr>
<td></td>
<td>Causes of breast cancer</td>
<td>169</td>
</tr>
<tr>
<td></td>
<td>Regular examinations of the breast are important for early diagnosis</td>
<td>173</td>
</tr>
<tr>
<td></td>
<td>What follows a positive diagnosis?</td>
<td>179</td>
</tr>
<tr>
<td></td>
<td>Treatment options are unique for each individual</td>
<td>182</td>
</tr>
<tr>
<td></td>
<td>Much has been accomplished, more needs to be done</td>
<td>187</td>
</tr>
<tr>
<td>9</td>
<td>Ovarian cancer</td>
<td>189-203</td>
</tr>
<tr>
<td></td>
<td>Ovarian cancer statistics</td>
<td>189</td>
</tr>
<tr>
<td></td>
<td>Structure and function of ovaries</td>
<td>190</td>
</tr>
<tr>
<td></td>
<td>There are three tissue categories of ovarian cancer</td>
<td>191</td>
</tr>
<tr>
<td></td>
<td>Symptoms of ovarian cancer are vague and often missed</td>
<td>192</td>
</tr>
<tr>
<td></td>
<td>Certain factors have been associated with a higher risk</td>
<td>193</td>
</tr>
<tr>
<td></td>
<td>Diagnostic tools are available but not always used or recommended</td>
<td>197</td>
</tr>
<tr>
<td></td>
<td>Additional procedures are necessary to confirm suspicious results or if there is metastasis</td>
<td>199</td>
</tr>
<tr>
<td></td>
<td>The FIGO system may be used to stage ovarian cancer</td>
<td>200</td>
</tr>
<tr>
<td></td>
<td>Treatment options for ovarian cancer</td>
<td>200</td>
</tr>
<tr>
<td></td>
<td>Steps are taken to prevent recurrence but do not always work when the cancer is advanced</td>
<td>203</td>
</tr>
<tr>
<td></td>
<td>Much needs to be done in the future</td>
<td>203</td>
</tr>
<tr>
<td>10</td>
<td>Cervical cancer</td>
<td>206-207</td>
</tr>
<tr>
<td></td>
<td>Cervical cancer statistics</td>
<td>206</td>
</tr>
<tr>
<td></td>
<td>Structure and function of the cervix</td>
<td>207</td>
</tr>
</tbody>
</table>
Symptoms of cervical cancer 208
Pelvic examinations and Pap tests enable early detection 208
Risk factors for cervical cancer 214
The HPV test is a vital diagnostic tool 215
Additional tests are necessary to examine the cervix 216
Treatment depends on the stage 218
A vaccine will prevent many cases of cervical cancer 221

11 Prostate cancer 224
Prostate cancer statistics 224
Function of the prostate gland 225
Certain factors influence the development of prostate cancer 226
Symptoms of an enlarged prostate 228
Screening and diagnostic tests for prostate cancer 228
There are traditional and unique treatment options available 237
Prostate cancer mortality rates have decreased 245
Much attention is being given to the number one cancer affecting men 245

12 Testicular cancer 247
Testicular cancer statistics 247
Structure and function of testicles 248
There are three types of testicular tumors 249
Risk factors for the disease 250
Symptoms of testicular cancer 252
Testicular self-examination (TSE) is recommended 253
Blood and imaging tests are used to determine diagnosis and possible metastasis 255
Testicular cancer treatment results in a high cure rate 256
Causes and treatments are being studied 260

13 Skin cancer 262
Skin cancer statistics 262
Structure and function of the skin 263
Three types of skin cancer 266
Risk factors for developing skin cancer 267
Methods used to screen for skin cancer 275
Surgery and chemotherapy are standard treatments for metastatic skin cancer 284
What happens after skin cancer treatment 289
Limited UV radiation exposure is the number one form of prevention 289

14 Lung cancer 293
Lung cancer statistics 294
Lungs are the site of the exchange of gases 294
Risk factors associated with the development of lung cancer 294
CONTENTS

Lack of distinctive symptoms makes early diagnosis difficult 299
Lung cancer is often diagnosed at an advanced stage 303
There are two main categories of lung cancer 306
Three traditional therapies are used in lung cancer treatment 307
Is there discrimination in cancer research funding? 310

15 Colorectal cancer 312
Colon and rectum are the last two sections of the gastrointestinal tract 313
Risk factors for colorectal cancer 317
Screening tests 319
Treatment options 329
Targeted therapies 334
Screening tests performed after the course of treatment 336

16 Leukemia and lymphoma 338
Leukemia statistics 338
Leukemia is a cancer of the blood cells 339
The exact cause of leukemia is unknown 340
Early symptoms of leukemia 340
Laboratory studies are necessary to determine the diagnosis 341
There are many types of leukemia 343
Nonchemotherapeutic treatment options have significantly improved survival rates 351
Lymphoma is a malignancy of the lymphatic system 355
Hodgkin’s vs. non-Hodgkin’s lymphoma 355
Certain risk factors are associated with an increased incidence of lymphoma 357
Diagnosing lymphoma involves biopsies and imaging tests 358
Lymphomas must be classified to determine appropriate treatment 358
Treatment options depend on the type of lymphoma, stage, and extent of metastasis 359

Glossary 361
Index 389

Companion website www.wiley.com/go/almeida/cancer
We have authored a textbook on cancer that is unique in its coverage in a number of respects. This book stands out from others because it is written for both nonscience and science majors. The coverage spans the spectrum from the molecular, cellular, and genetic through to the applied aspects of the disease. The book has been structured so that it will be an appropriate text for use by an instructor regardless of the depth to which he/she desires to cover any of the material. The amount of material is manageable within a single semester, and individual chapters can be excerpted for study on each of the major cancers.

We believe this book is appropriate for cancer courses offered to either science or nonscience majors at any level. A target audience with such a variant science background is accommodated by a series of introductory chapters that provide the molecular, cellular, and genetic information needed to comprehend the material of the subsequent chapters. A reader without a science background could study the chapter on breast cancer and learn the risk factors, symptoms, diagnostic testing, and treatment methods without being overwhelmed. If after reading about the risks associated with the BRCA1 and 2 genes, a student wants a better understanding of what a gene is, he or she could then refer back to the appropriate section of one of the introductory chapters. This cross-referencing ability is what we feel is the basis for the success of the text from the perspectives of both student and instructor. The introductory chapters can be used by lower or upper class science majors to review foundational information.

The chapters of the book are grouped into two sections. The first seven chapters contain introductory information that will be most helpful to the nonscientist while serving as a review for the scientist in training. The second section contains nine chapters, each focusing on a specific form of cancer in areas such as risk factors, diagnostic and treatment methods, and relevant current research. Each of the chapters includes review questions as marginal insertions at points through the text, key words/terms in bold in the text, boxed articles highlighting stories of an individual’s experience, and complex questions in the section “Expand your knowledge” for the student to answer with some additional reading.
We have taught an undergraduate biology of cancer course open to all majors since the fall of 2005. The organization of the book reflects the format that we have used successfully when teaching the course. Since this text is intended for use in either a non-science or science course, it addresses a wide range of issues associated with cancer. Depending on each course design, it could be either an elective or satisfy a requirement within a general education program or a natural science or allied health major. One of the major strengths of the book is that it can be used in any level undergraduate course. There are no specific prerequisites assumed; the information in the introductory chapters is sufficient to bring the non-scientist to the level needed to read and understand the later chapters. The ultimate intent of the book is to have appeal to students who are either at the beginning or intermediate stages of scientific inquiry into the study of cancer.
Acknowledgments

We would like to thank the many editors from Blackwell and John Wiley and Sons that have worked with us during the development of the text for their thoughtful and creative contributions: Nancy Whilton, Elizabeth Frank, Humbert Haze, Steve Weaver, Karen Chambers, Kelvin Matthews, and Pat Croucher. We are appreciative of the talents of Ali McNeill, the illustrator of many of the text’s figures. A special thanks is extended to Sandy Parker for her enthusiastic Blackwell introduction. We are indebted to those who critically read and provided valuable feedback on draft chapters: anonymous faculty reviewers; our colleagues, Greg Maniero, Jane De Luca, David Gilmore, Lucy Dillon, and Brenda Sweeney; and our students, Jacqueline Tenaglia, Kristen McCarthy, Lauren Bennett, Samantha April, and Tyler Herbert. We are so appreciative of the valuable assistance provided by our administrative assistant Romelle Berry. Two additional students are due a tremendous thank you: Melissa Martin for her thoughtful insight and superior editorial skills, and Sarah Wilson for her creative draft illustrations. It is quite likely that our fellow faculty and administrators at Stonehill College are unaware of how truly grateful we are for their constant encouragement and generous support throughout the development and writing of this book.

A special appreciation goes to all of the students who have taken our biology of cancer course, for their subtle and unknowing influences can be found in the organization, content and pedagogy of this book.
If the three worst words are, ‘You have cancer’, then the four worst are ‘Your cancer is back’.

Katie Couric, American newscaster and journalist

Very little strikes more fear into peoples’ hearts than being told they have cancer. Such a diagnosis can turn a person’s world upside down and conjure up thoughts of what lies ahead: pain, disfigurement, disability, nausea, hair loss, or even death. Recent years, however, have seen extraordinary advances in basic cancer research and in the development of more effective methods for the detection, diagnosis, and treatment of cancer. Consequently, while the phrase “You have cancer,” may be life-altering, it is not necessarily the devastating, life-threatening diagnosis of generations past.

CANCER IS A COMPLEX ENTITY

In the most basic sense, cancer is the abnormal, uncontrolled growth of previously normal cells. The transformation of a cell results from alterations to its DNA that accumulate over time. The change in the genetic information causes a cell to no longer carry out its functions properly. A

CHAPTER CONTENTS

- Cancer is a complex entity
- Cancer through the ages
- Modern day cancer research and treatment
- Prevalence and mortality varies with each cancer
- Risk factors have been identified
- Will cancer be conquered within our lifetime?
- Expand your knowledge
- Additional readings

The primary characteristic of cancer cells is their ability to rapidly divide, and the resulting accumulation of cancer cells is termed a tumor. As the tumor grows and if it does not invade the surrounding tissues, it is referred to as being benign (Figure 1.1a). If, however, the tumor has spread to nearby or distant tissues then it is classified as malignant (Figure 1.1b).

**Metastasis** is the breaking free of cancer cells from the original primary tumor and their migration to either local or distant locations in the body through the process of metastasis. The cancer cells may then establish malignant growth in a different type of tissue: a breast cancer can spread to bone tissue, for example.

There are many types of cancer

Cancer is not a single disease; there are over 100 identified types, all with different causes and symptoms. To distinguish one form from another the cancers are named according to the part of the body in which they originate. Some tumors are identified to reflect the type of tissues they arise from, with the suffix -oma, meaning tumor, added on. For example, myelos- is a Greek term for marrow. Thus, myeloma is a tumor of the bone.
marrow, whereas hepatoma is liver cancer \((\text{hepato-} = \text{liver})\), and melanoma is a cancer of melanocytes, cells found primarily in the skin that produce the pigment melanin. (Table 1.1)

**There are four predominant types of cancer**

The four major types of cancer are carcinomas, sarcomas, leukemias, and lymphomas. Approximately 90% of human cancers are carcinomas, which arise in the skin or epithelium (outer lining of cells) of the internal organs, glands, and body cavities. Tissues that commonly give rise to carcinomas are breast, colorectal, lung, prostate, and skin. Sarcomas are less common than carcinomas and involve the transformation of cells in connective tissue such as cartilage, bone, muscle, or fat. There are a variety of sarcoma subtypes and they can develop in any part of the body, but most often arise in the arms or legs. Liposarcoma is a malignant tumor of fat tissue \((\text{lipo-} = \text{fat})\) whereas a sarcoma that originates in the bone is called osteosarcoma \((\text{osteo-} = \text{bone})\).

Certain forms of cancer do not form solid tumors. For example, leukemias are cancers of the bone marrow, which leads to the overproduction and early release of immature leukocytes (white blood cells). Lymphomas are cancers of the lymphatic system. This system, which is a component of the body’s immune defense, consisting of lymph, lymph vessels, and lymph nodes, serves as a filtering system for the blood and tissues.

**Each cancer is unique**

While there are certain commonalities shared by cancers of a particular type, each may be unique to a single individual. This is because of different cellular mutations that are possible, and can depend on whether the disease is detected at an early or advanced stage. As a result, two women diagnosed with breast cancer may or may not receive the same treatment. The impact of the disease on the individual, as well as the final outcome of the disease, is unique in every case. Still, several types of cancers can have a similar set of symptoms, which may be shared with several other conditions, making screening, detection, and diagnosis a complex problem.

A tumor can impact the function of the tissue in which it resides or those in the surrounding areas. Tumors provide no useful function themselves and may be considered “parasites,” with every step of their advance being at the expense of healthy tissue (Figure 1.2). While most types of cancers form tumors, many do not form discrete masses. As previously stated, leukemia is a cancer of the blood that does not produce a tumor, but rather rapidly produces abnormal blood cells in the bone marrow at the expense of normal blood cells.
### Table 1.1 Tumor terminology

<table>
<thead>
<tr>
<th>Prefix</th>
<th>Cell type</th>
<th>Benign tumor</th>
<th>Malignant tumor</th>
<th>Tissue affected</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumors of epithelial cells:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adeno-</td>
<td>Gland</td>
<td>Adenoma</td>
<td>Adenocarcinoma</td>
<td>Breast, colon/rectum, lung, ovary, pancreas, prostate</td>
</tr>
<tr>
<td>Basal cell</td>
<td>Basal cell</td>
<td>Basal cell adenoma</td>
<td>Basal cell carcinoma</td>
<td>Skin</td>
</tr>
<tr>
<td>Squamous cell</td>
<td>Squamous cell</td>
<td>Keratoacanthoma</td>
<td>Squamous cell carcinoma</td>
<td>Esophagus, larynx, lung, oral cavity, pharynx, skin, cervix</td>
</tr>
<tr>
<td>Melano-</td>
<td>Pigmented cell</td>
<td>Mole</td>
<td>Melanoma</td>
<td>Skin</td>
</tr>
<tr>
<td><strong>Tumors of supporting tissue origin:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemangio-</td>
<td>Blood vessels</td>
<td>Hemangioma</td>
<td>Hemangiosarcoma</td>
<td>Blood vessels</td>
</tr>
<tr>
<td>Lipo-</td>
<td>Fat</td>
<td>Lipoma</td>
<td>Liposarcoma</td>
<td>Fat cells</td>
</tr>
<tr>
<td>Meningio-</td>
<td>Meninges</td>
<td>Meningioma</td>
<td>Meningiosarcoma</td>
<td>Brain</td>
</tr>
<tr>
<td>Myo-</td>
<td>Muscle</td>
<td>Myoma</td>
<td>Myosarcoma</td>
<td>Muscle</td>
</tr>
<tr>
<td>Osteo-</td>
<td>Bone</td>
<td>Osteoma</td>
<td>Osteosarcoma</td>
<td>Bone</td>
</tr>
<tr>
<td><strong>Cancers of blood and lymphatic origin:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lympho-</td>
<td>Lymphocyte</td>
<td>Lymphoma</td>
<td>Lymphoma</td>
<td>Lymphocytes</td>
</tr>
<tr>
<td>Myelo-</td>
<td>Bone marrow</td>
<td>Myeloma, Myelogenous leukemia</td>
<td>Granulocytes</td>
<td></td>
</tr>
</tbody>
</table>
The development of tumors

All tumors begin with mutations (changes) that accumulate in the DNA (genetic information) of a single cell causing it and its offspring to function abnormally. DNA alterations can be sporadic or inherited. **Sporadic mutations** occur spontaneously during the lifespan of a cell for a number of reasons: a consequence of a mistake made when a cell copies its DNA prior to dividing, the incorrect repair of a damaged DNA molecule, or chemical modification of the DNA, each of which interferes with expression of the genetic information. **Inherited mutations** are present in the DNA contributed by the sperm and/or egg at the moment of conception. To date, 90–95% of diagnosed cancers appear to be sporadic in nature and thus have no heredity basis. Whether the mutations that result in a cancer are sporadic or inherited, certain genes are altered that negatively affect the function of the cells.

Genetic influence on tumors

A link between a particular genetic mutation and one or more types of cancers is made by analyzing and comparing the DNA of malignant tissue samples obtained from patients and members of families with a high incidence of a particular cancer and comparing it to the DNA from healthy
individuals. For example, a study could be conducted in which the DNA isolated from tumor cells obtained from liver cancer patients is analyzed and determined to possess certain versions of genes whereas different versions of those same genes are present in the DNA of liver cells of healthy persons. An association could then be drawn between the “bad” versions of those genes and liver cancer.

This type of analysis has been crucial in identifying certain versions of genes associated with a predisposition for the development of particular forms of cancer. For example, studies have demonstrated that there is an elevated risk of breast or ovarian cancer associated with certain versions of the BRCA1 and/or BRCA2 genes (Chapter 8). Another example is retinoblastoma, a rare tumor of the eye typically found in infants and young children, which is associated with alterations within the Rb gene (Chapter 4).

CANCER THROUGH THE AGES

Although not specifically identified as such, cancer has been known for many centuries. In fact, there is evidence of tumors in the bones of five thousand year old mummies from Egypt and Peru. The disease itself was not very common, nor explored or understood, because in ancient times fatal infectious diseases resulted in shorter lifespans. Given that the vast majority of cancers are sporadic, there was less opportunity for the accumulation of the mutations necessary to transform normal cells into cancerous ones.

The word “cancer” was first introduced by Hippocrates (460–370 BC), the Greek physician and “father of medicine” (Figure 1.3). He coined the term carcinoma, from the Greek word *karcinos*, meaning “crab,” when describing tumors. This is because tumors often have a central cell mass with extensions radiating outward that mimic the shape of the shellfish (Figure 1.4).

Hippocrates believed that the body contained four “humors” or body fluids, and that each fluid was associated with a specific personality or temperament characteristic. “Blood” persons had a sanguine or optimistic personality with a passionate, joyous disposition. Someone with a dull or sluggish temperament would have “Phlegm.” Possessing “Yellow Bile” meant that one was quick to anger, while having “Black Bile” indicated a person was melancholic or depressed. In medieval times, it was believed that disease was a result of an imbalance of any of the four humors and physicians could restore health or harmony by purging, starving, vomiting, or bloodletting. In particular, an excess of black bile was thought to be the primary cause of cancer. This theory was accepted and taught for over 1300 years through the Middle Ages and championed by Claudius Galen (131–201 AD), a Greek physician and writer who described many diseases using this hypothesis (Figure 1.5). Both Hippocrates and Galen defined disease as a natural process, a theory that remained for centuries.
Figure 1.3 Hippocrates is history’s most famous physician.

Figure 1.4 A cancer cell that has extensions extending out from the central body of the cell. Source: National Cancer Institute Visuals Online; http://visualsonline.cancer.gov/
Figure 1.5 Claudius Galen is considered by some to be the second most important contributor to medicine, after Hippocrates, in ancient times.

Box 1.1

Bloodletting as a medical practice

Interestingly, bloodletting is a method used in modern medical practice. The FDA formally approved the use of leeches as medical devices in June 2004. The invertebrate bloodsuckers are most often used following reconstructive surgery for the reattachment of fingers and toes to remove the excess blood that accumulates from severely damaged blood vessels. Since pooled blood often inhibits the healing of wounded tissues, the leeches’ ability to extract it is beneficial and efficient. Hirudin is an effective anti-blood clotting agent present in the saliva of the leech that keeps the blood flowing, giving time for the vessels and tissues to heal. Although it seems as if leech therapy would be painful, it is not thanks to a mild anesthetic the leeches produce.
The use of autopsies is very significant to medical discoveries

Unfortunately, during the Middle Ages the dissection of cadavers was largely prohibited for religious reasons, or yielded little data when conducted at all, due to its primitive nature. The failure to recognize the benefits of studying cadavers, or the understandable ignorance of the times, arguably delayed the progress of medical science. As a result, one of medicine’s most informative research tools, dissection of cadavers, was largely ignored.

The English physician William Harvey (1578–1657) is credited with conducting the first examples of postmortem (after death) analysis (Figure 1.6). Although rare and certainly unscientific by modern standards, his “public dissections” are now known as autopsies. Giovanni Morgagni (1682–1771), an Italian physician, is considered the founder of pathological anatomy (Figure 1.7). In 1761, at the age of 79, he published a book describing nearly 700 autopsies that he had performed associating a patient’s cause of death to the pathological findings made postmortem. His work was a far cry from the theory of “humors” that had previously existed and laid the foundation for the serious study of cancer as a cause of morbidity (disease) and mortality (death).

Figure 1.6 William Harvey was the first, as a result of performing many autopsies, to demonstrate that the heart pumped the blood around the body through arteries and veins.
Early discovery of carcinogens

Also published in 1761 was a paper by John Hill, an English physician. In it he made the first causal link between substances in the environment and cancer when he described a relationship between tobacco snuff and nasal cancer. This brought about the awareness of carcinogens (chemical agents that have been demonstrated to cause cancer). In 1775, the English surgeon Sir Percivall Pott observed and noted a high rate of scrotal cancer among chimney sweepers. He postulated that it was caused by long-term exposure to the chemicals in the soot-soaked ropes worn as harnesses. His research led to studies that associated particular occupations with an increased risk of developing specific forms of cancer – the forerunner to the field of public health and cancer.

The use of microscopes demonstrated changes at a cellular level

The development of improved microscopes in the late nineteenth century allowed for more thorough examinations of cells and their activities than was previously possible. It was realized that cancer cells were different
in both appearance and behavior from normal cells within the same tissue or organ (Figure 1.8). Early twentieth century accomplishments in the development of cell culture (an \textit{in vitro} technique for studying the activity of cells in an \textit{organism} under simulated physiological conditions\textsuperscript{1.1}), new and improved diagnostic techniques, the discovery of chemical carcinogens, and the use of \textit{chemotherapy} (powerful anti-cancer drugs) all had significant impacts upon the understanding and treatment of cancer.

\textbf{MODERN DAY CANCER RESEARCH AND TREATMENT}

The radioactive element radium, isolated by Marie and Pierre Curie in 1898, was found to be effective in the treatment of tumors in 1903. While both healthy and cancerous cells are susceptible to the damage caused by X-rays, cancer cells are inherently less able to repair the damage and recover. Once safe dosage levels were determined, \textit{radiation therapy} became a standard form of treatment for many cancers.

\textbf{Public awareness of cancer}

As the access to scientific knowledge increased, so too did the public’s fear and misconceptions. In the early 1900s the word “cancer” was rarely spoken in public and it was omitted from obituaries, similar to how the use of the word AIDS was avoided in the 1980s and 1990s. Surprisingly, the first widely published discussion of cancer was a 1913 \textit{Ladies Home Journal} magazine article that asked “What Can We Do About Cancer?” and listed the disease’s principal warning signs. With its large circulation,
the magazine brought the word “cancer” to the forefront of public awareness and discussion. That same year in New York City, a group of ten physicians and five laypeople established the American Society for the Control of Cancer (ASCC). The group raised $10,000 that year, and published a pamphlet titled *The Facts About Cancer*. In 1945 the ASCC changed its name and to this day is known as the American Cancer Society (ACS). The following year, volunteer Mary Lasker and her colleagues raised over $4 million, an extraordinary amount at that time and even today, for the Society. Of that sum, $1 million was allocated to establish the Society’s cancer research program. In 1947 the ACS initiated its public education campaign concentrating on “The seven signs and symptoms of cancer,” utilizing the word “Caution” as a way to remember the first letter of each symptom:

- Change in bowel or bladder habits.
- A sore that does not heal.
- Unusual bleeding or discharge.
- Thickening or a lump in the breast or other parts of the body.
- Indigestion that is chronic or difficulty in swallowing.
- Obvious changes in a wart or mole.
- Nagging cough or hoarseness.

Although currently outdated due to its lack of specificity and discontinued in the 1980s, the campaign served to provide enormous awareness among people who, for the first time, were encouraged to be aware of and on the lookout for possible signs and symptoms of cancer.

**Unexpected discoveries result in some cures**

The first clinical use of a dramatic new form of cancer treatment – *chemotherapy* – occurred in the 1940s. Soldiers in World War I who were exposed to the chemical warfare agent known as mustard gas would develop painful blisters on their skin and eyes. If the gas was inhaled, their ability to breathe was severely compromised because the gas would destroy the mucous linings of their lungs. It was noted that those who survived an attack developed low white blood cell counts. This led researchers to question whether mustard gas or a derivative of it could be used to treat certain cancers that affect white blood cells.

Shortly after World War II, a clinical study determined that the injection (rather than inhalation) of the principal component of mustard gas caused the temporary remission of lymphoma, a type of white blood cell cancer.\(^1\)\(^2\) As is commonly done when a molecule demonstrates potential...
clinical effectiveness, a large number of chemical variants were synthesized in an attempt to lessen the highly reactive nature of the original mustard gas compound while retaining, and eventually improving upon, its desired function.

The synthesis and testing of literally hundreds of molecules in animal and human trials have led to several of them becoming conventional cancer treatment regimens. Serendipitous findings similar to those associated with mustard gas tend to occur often in scientific discoveries and are examples of some good coming from an unfortunate event.

Another milestone came in 1947 when Dr Sidney Farber of the Harvard Medical School treated children with acute leukemia, another form of white blood cell cancer, with the drug aminopterin. The drug blocked the synthesis of nucleotides, the building blocks of DNA. This effectively inhibited the division of the cancer cells because they were unable to replicate their DNA and the children entered into a cancer-free state of remission. Even though the remission period was only temporary, Dr Farber is credited with the first successful use of chemotherapy.

**Government funding was/is necessary**

The National Cancer Institute Act was passed by the US Congress in 1937, creating the National Cancer Institute (NCI), with the goal of conducting

---

**Box 1.2**

**The Legacy of Henrietta Lacks**

Henrietta Lacks died of cervical cancer in 1951 at the age of 31 at Johns Hopkins University Hospital in Baltimore, Maryland. She might have long been forgotten by all except her family and friends. Instead, she lives on in the form of highly malignant cells taken from the quarter-sized tumor that was removed from her cervix and that eventually invaded almost every organ of her body. Laboratories and research centers worldwide have been using these cells for many years. Given the code name HeLa, for the first two letters of her first and last names, these were the first human cells known to thrive and multiply outside of the body. Still alive and rapidly dividing to this day, HeLa cells have been used in the development of the polio vaccine, the search for causes of cancer and a cure for leukemia, the study of the growth of viruses, the mechanisms that control the expression of our genetic information, and the effects of drugs and radiation on cellular functions. Henrietta’s cells grow aggressively, producing an entirely new generation of cells every 24 hours. Unfortunately, at the time of her death and for years after, there was no system of "informed consent" in medical research, so it took many years for her family to discover the impact that she has had on science.
and promoting cancer research. In 1971, President Richard M. Nixon signed the National Cancer Act, legislation that provided federal funds for cancer research to fight the disease. This Act infused money and authority into the NCI in order to more effectively carry out the national effort to understand and fight cancer. Thus the phrase “War on Cancer” was born. After more than three decades the war remains ongoing, although great strides occur almost daily.

The field of oncology was born

One primary outcome of the research and focus on cancer has been the establishment of the field of oncology, the medical subspecialty dealing with the study and treatment of cancer. Previously, primarily family physicians treated people diagnosed with cancer and followed their care throughout their illnesses. If a woman developed the disease she might have been treated by her gynecologist, a doctor who specializes in female medical issues and who did not have extensive cancer training. The body of knowledge physicians had to work with was limited, to say the least. Only 51 physicians attended the first meeting of the American Society of Clinical Oncology in 1964. Today the organization comprises more than 25,000 members representing the principal oncology disciplines (medical, radiological, and surgical) as well as several subspecialties (geriatric oncology, pediatric oncology, gastrointestinal oncology, etc.). Government funding and private research spurred by charitable giving and the tireless support of groups such as the American Cancer Society, St Jude Children’s Research Hospital, and the Boston-based Jimmy Fund have helped to raise cancer awareness. Unfortunately, as aging baby boomers become increasingly cancer-prone, medical schools cannot train enough new oncologists to satisfy the need for them. A 2007 report by the Association of American Medical Colleges estimates that by 2020, visits to oncologists will increase by 48% while the projected number of oncologists is estimated to grow by only 14% over the same time period. It is hoped that medical schools will acknowledge this shortage and address the issue by taking an active role in recruiting a greater number of future oncologists.

Currently, there are a wide variety of methods to diagnose and treat cancer. The ones used are dependent upon the type of cancer and its current stage and location within the body. Genetic links to the disease are being discovered at a rapid pace, enabling physicians to identify those patients who have a predisposition for the development of specific cancers or will respond best to certain forms of treatment. It is hoped that this knowledge will encourage people to be more diligent in maintaining healthy lifestyles and be more consistent in following recommendations for regular screening tests. Some treatments will be personalized based on one’s genetic make-up and/or the specific genetic make-up of the tumor.
While not all treatment options offer a “cure,” they enable a large number of individuals to manage their disease and live fairly normal and full lives.

The field of oncology is evolving and expanding, with research articles being published almost weekly announcing links between certain versions of genes and the risk for the development of a particular form of cancer, methods to either reduce certain cancer risks or detect the disease at an earlier stage, and treatment options that are more effective and increase the chance for survival. Media reports are often based on a single study, and they are designed so as to have a “wow!” factor that will garner maximum public attention. As a result, one must be able to differentiate between a reputable study and a report that is not scientifically valid, and learn to distinguish hype from reality. All too frequently, today’s established protocols are challenged by tomorrow’s newest discoveries. For this reason, the integrity and accuracy of new research findings must withstand the test of time and be constantly questioned and reviewed.

PREVALENCE AND MORTALITY VARIES WITH EACH CANCER

Unfortunately, most of us know or will know someone who has been diagnosed with cancer. In 2008 an estimated 1.4 million Americans were newly diagnosed with cancer and approximately 565,000 died from the disease (Table 1.2). This ACS estimate does not include two forms of cancer. The first are those classified as carcinoma in situ (in the original site), which are more commonly known as benign tumors. They are confined and have not invaded surrounding tissues. An exception to this rule is carcinoma in situ of the urinary bladder which is reported because of its tendency to aggressively grow and progress to a malignant state. The second form consists of nonmelanomas or basal and squamous cell skin cancers, which are the most common forms of skin cancer with over one million new cases per year. Because these skin cancers rarely spread and are not life threatening, they are routinely removed and treated on an outpatient basis in nonhospital settings and, as such, are rarely reported to cancer registries.

Cancer rates are different for men and women

For men, the five most prevalent cancers, in decreasing order, are prostate, lung and bronchus, colorectal, urinary bladder, and skin melanoma. The most commonly diagnosed cancers in women are breast, lung and bronchus, colorectal, non-Hodgkin’s lymphoma, and skin melanoma. Lung and bronchus, colorectal, and pancreatic cancers are among the top five most fatal forms of the disease in both men and women. Ironically, the number one cancer killer for both men and women, lung and bronchus,
Table 1.2 Estimated new cancer cases and deaths by sex, USA, 2008*

<table>
<thead>
<tr>
<th>Estimated new cases</th>
<th>Estimated deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Both sexes</td>
</tr>
<tr>
<td>All sites</td>
<td>1,437,180</td>
</tr>
<tr>
<td>Oral cavity and pharynx</td>
<td>35,310</td>
</tr>
<tr>
<td>Tongue</td>
<td>10,140</td>
</tr>
<tr>
<td>Mouth</td>
<td>10,820</td>
</tr>
<tr>
<td>Pharynx</td>
<td>12,410</td>
</tr>
<tr>
<td>Other oral cavity</td>
<td>1,940</td>
</tr>
<tr>
<td>Digestive system</td>
<td>271,290</td>
</tr>
<tr>
<td>Esophagus</td>
<td>16,470</td>
</tr>
<tr>
<td>Stomach</td>
<td>21,500</td>
</tr>
<tr>
<td>Small intestine</td>
<td>6,110</td>
</tr>
<tr>
<td>Colon†</td>
<td>108,070</td>
</tr>
<tr>
<td>Rectum</td>
<td>40,740</td>
</tr>
<tr>
<td>Anus, anal canal, and anorectum</td>
<td>5,070</td>
</tr>
<tr>
<td>Liver and intrahepatic bile duct</td>
<td>21,370</td>
</tr>
<tr>
<td>Gallbladder and other biliary</td>
<td>9,520</td>
</tr>
<tr>
<td>Pancreas</td>
<td>37,680</td>
</tr>
<tr>
<td>Other digestive organs</td>
<td>4,760</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>232,270</td>
</tr>
<tr>
<td>Larynx</td>
<td>12,250</td>
</tr>
<tr>
<td>Lung and bronchus</td>
<td>215,020</td>
</tr>
<tr>
<td>Other respiratory organs</td>
<td>5,000</td>
</tr>
<tr>
<td>Bones and joints</td>
<td>2,380</td>
</tr>
<tr>
<td>Soft tissue (including heart)</td>
<td>10,390</td>
</tr>
<tr>
<td>Skin (excluding basal and squamous)</td>
<td>67,720</td>
</tr>
<tr>
<td>Melanoma</td>
<td>62,480</td>
</tr>
<tr>
<td>Other non-epithelial skin</td>
<td>5,240</td>
</tr>
<tr>
<td>Breast</td>
<td>184,450</td>
</tr>
<tr>
<td>Genital system</td>
<td>274,150</td>
</tr>
<tr>
<td>Uterine cervix</td>
<td>11,070</td>
</tr>
</tbody>
</table>