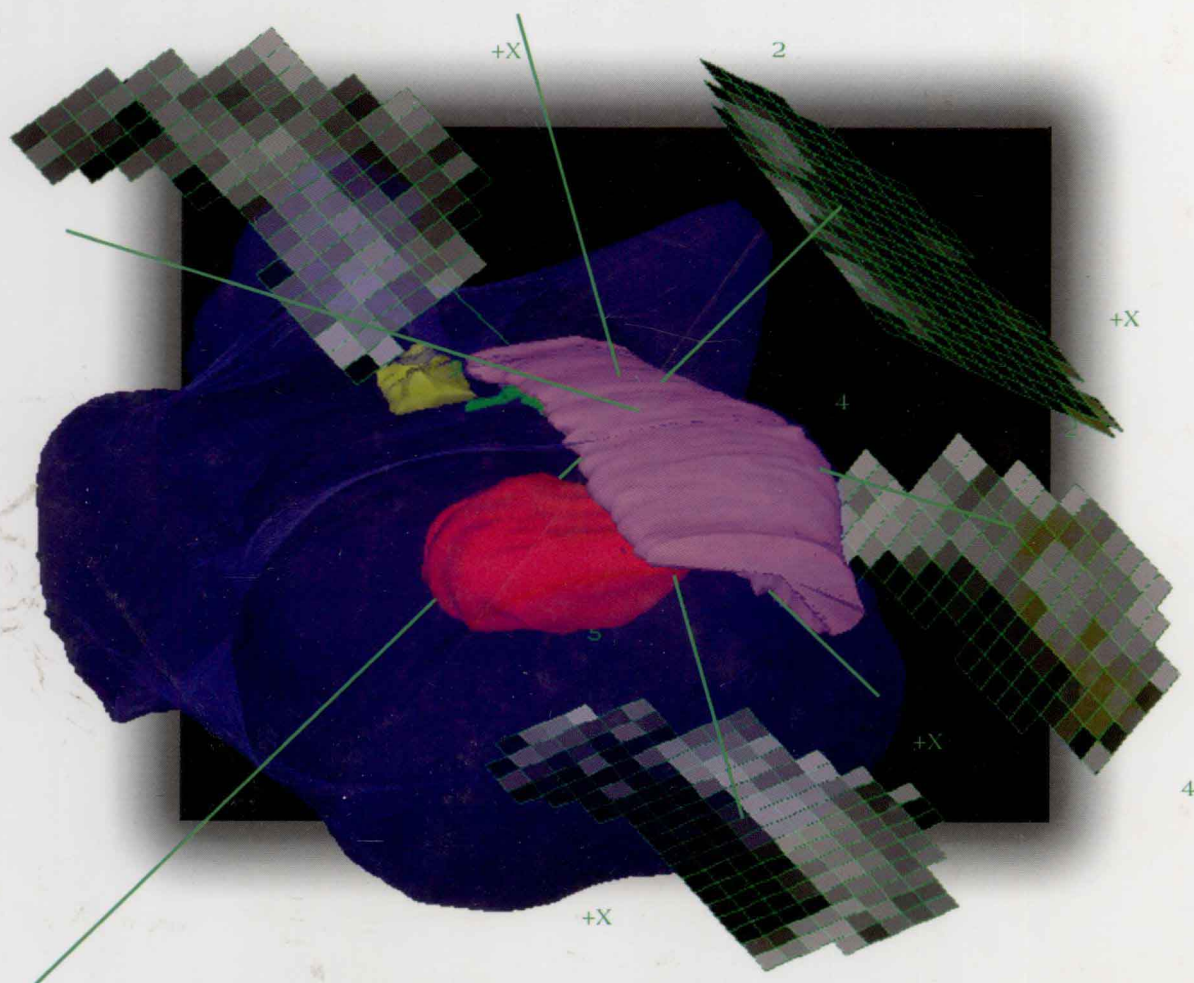


BREAST CANCER

Second Edition



**Winchester • Winchester
Hudis • Norton**

BREAST CANCER

Second Edition

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BREAST CANCER

Second Edition

Atlas of **Clinical Oncology**

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To our families, for their understanding and support, and to your patients,
who endure the challenges presented by this disease.

Preface

The organization of this book reflects the stepwise evaluation and treatment of the patient with breast cancer. It emphasizes the importance of early detection, but highlights the increasing emphasis on risk assessment and reduction. The treatment of breast cancer has evolved from radical mastectomy for all patients to a tailored approach with the selective use of multiple treatment modalities in accordance with the patient's risk of recurrence.

Despite shifting efforts to identify high-risk patients and address risk with preemptive strategies, there remains a worldwide educational challenge to adopt early-detection guidelines for screening. Although there is continuing progress in implementing mortality-reducing screening mammography, as reflected by the increased prevalence of preinvasive breast cancer and by falling breast cancer mortality, the full spectrum of disease is still a challenge to the medical community. The high prevalence of breast cancer continues to drive improvements in prevention, detection, diagnostic evaluation, disease characterization, multimodal therapy, and quality-of-life issues. Providing equal access to these improvements remains a challenge.

One of the most important advances in the understanding of breast cancer has been the identification of genetic mutations, which provides the opportunity to intervene with chemopreventive strategies or surgical procedures to dramatically reduce the risk of cancer. Diagnostic imaging continues to provide increased precision and resolution, resulting in an enhanced ability to preserve tissue and identify otherwise unrecognized disease. Minimally invasive surgery, including sentinel node biopsy, has progressed to a point where the role of the standard axillary dissection has become increasingly limited. The selection of breast conservation patients continues to be refined by improved diagnostic imaging and emerging patterns defined by molecular profiles.

Adjuvant systemic therapy has also become significantly more precise with the improved clarity in the mol-

ecular characterization of tumors. New and improved categories of antiestrogen therapies have emerged, along with numerous highly effective chemotherapy regimens, including trastuzumab therapy. Proven as a highly effective drug in the metastatic setting, trastuzumab has recently emerged as one of the most significant advances in the adjuvant therapy of breast cancer, providing dramatic reductions in recurrence and mortality rates for suitable patients. Such advances underscore the importance of understanding breast cancer on the molecular level in order to develop improved therapies. Molecular markers now provide more than prognostic value and have become critical determinants in the selection of adjuvant therapy.

Improved therapies for breast cancer have lessened the physical and psychological burdens of the disease. Immediate reconstruction, microvascular surgery, and tissue expanders have also significantly improved cosmetic outcome. Tissue damage has become less common with minimally invasive surgery and the targeted delivery of radiation therapy. Proactive and preemptive prevention and treatment of lymphedema have helped to control the physical and mental consequences of the more radical treatments that remain necessary for a subset of patients.

It is the goal of this book to identify significant improvements in breast cancer prevention, diagnosis, and treatment and to help accelerate the dispersion of this knowledge to an ever-broadening spectrum of scientists and physicians who are dedicated to the prevention and treatment of one of the most common afflictions to strike women. We wish to thank our distinguished authors for their timely and expert contributions to this effort.

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Contents

	Preface	xi
	Contributors	xiii
1	History of Breast Cancer	1
	William L. Donegan	
2	Anatomy of the Breast, Axilla, and Thoracic Wall	15
	Helen Krontiras, Kirby I. Bland	
3	The Evolving Concept of the Breast Cancer	31
	Stephen B. Edge	
4	Epidemiology of Breast Cancer	47
	Victor G. Vogel	
5	Genetics, Natural History, and DNA-Based Genetic Counseling in Hereditary Breast Cancer	61
	Henry T. Lynch, Jane F. Lynch	
6	Molecular Basis of Breast Cancer	83
	Jacqueline Sara Jeruss	
7	Breast Cancer Risk Assessment and Management	96
	Banu Arun, Henry Kuerer	
8	Role of Screening in Breast Cancer Mortality Reduction	107
	Stephen F. Sener, Robert A. Smith	
9	Diagnostic Breast Imaging	116
	Daniel B. Kopans	
10	Sonography of Breast Cancer	137
	Bruno D. Fornage	
11	Magnetic Resonance Imaging	162
	Mitchell Schnall	
12	Diagnostic Techniques	176
	Richard Fine	

13	Pathology of Invasive Breast Cancer	198
	Aysegul A. Sahin	
14	Staging and Histologic Grading	217
	David P. Winchester	
15	Ductal Carcinoma In Situ	226
	Melvin J. Silverstein, Heather R. MacDonald, Helen C. Mabry, S. Brenda Moorthy	
16	Oncoplastic Surgery of the Breast	248
	Neal Handel, Melvin J. Silverstein	
17	Evaluation and Surgical Management of Stage I and II Breast Cancer	272
	David J. Winchester, Timothy Kennedy	
18	Locally Advanced Breast Cancer	287
	Lisa A. Newman	
19	Axillary Staging and Therapeutics	302
	Jacobo Nurko, John Ralph Broadwater, Michael J. Edwards	
20	Adjuvant Chemotherapy	312
	Bryan T. Hennessy, Vicente Valero	
21	Endocrine Therapy of Early and Advanced Breast Cancer	331
	Aman U. Buzdar	
22	Radiation Therapy in Early and Advanced Breast Cancer	353
	Sabin B. Motwani, Eric A. Strom	
23	Evolution in Breast Reconstruction	380
	Geoffrey C. Fenner, Thomas A. Mustoe	
24	Unusual Breast Histology	405
	David R. Brenin, Kristen A. Atkins	
25	Multifocal, Multicentric, and Bilateral Breast Cancer	420
	Malcolm R. Kell, Monica Morrow	
26	Breast Cancer in the Previously Augmented Breast	432
	Colleen McCarthy, Andrea Pusic, Hiram S. Cody III, Babak Mehrara	
27	Breast Cancer in the Irradiated Breast	446
	William D. Bloomer, Michael A. LaCombe	
28	Novel Radiation Therapy Techniques	454
	Reshma Jagsi, Lori Pierce	

29	Pregnancy and Breast Cancer	473
	Emer O. Hanrahan, Richard L. Theriault	
30	Hormone Therapy and Breast Cancer	487
	Toncred Marya Styblo, Catherine A. Madorin, William C. Wood	
31	Male Breast Cancer	497
	William L. Donegan, Philip N. Redlich	
32	Management of Locoregional Recurrences	511
	Stefan Aebi, Irene Wapnir	
33	Breast Cancer and Multiethnic/Multiracial Populations	524
	Lisa A. Newman	
34	Image-Guided Ablation for Breast Cancer	540
	Tara L. Huston, Rache M. Simmons	
35	Lymphedema	551
	Joseph L. Feldman, David J. Winchester	
36	Surveillance Strategies for Breast Cancer Survivors	575
	Laura P. McGartland, William J. Grandishar	
37	A Patient's Perspective	583
	Ruth Silverman	
	Index	589

History of Breast Cancer

WILLIAM L. DONEGAN

The story of breast cancer is told in the acts and artifacts of the human struggle against disease. It is an epic tale that follows the concepts of illness from the work of evil spirits or of offended gods to the results of identifiable physical causes, and the healing arts from mysticism to the tools of modern science. The following is a brief history of breast cancer in the Western world.

PREHISTORY AND THE ANCIENT WORLD

Prior to recorded history, life was undoubtedly short, and as cancer is predominantly a disease of maturity one suspects that cancer was a poor competitor among causes of mortality. The study of primitive peoples indicates that for the ill, rituals, potions, and recipes at the hands of magicians, witch doctors, and folk healers were the usual recourses. In ancient Babylon (2100–689 BC) it was common practice to place the ailing in public places for the recommendations of passersby, but professional healers were also recognized. The Code of Hammurabi, inscribed on a pillar in Babylon, indicated that healers were paid fees for their services and were penalized for surgical deaths with amputation of their hands.¹

Before the third millennium BC, physicians had learned the futility of treating certain tumors of the breast. Among the eight extant Egyptian medical papyri, *The Edwin Smith Surgical Papyrus* is believed to contain the first reference to breast cancer (Figure 1–1). This surgical text, penned in hieratic script, is the incomplete and fragmented copy of an original document that probably dates back to the pyramid age of Egypt (3000–2500 BC) and was pos-

sibly written by Imhotep, the physician-architect who practiced medicine and designed the step pyramid in Egypt in the 30th century BC.² It provides the earliest references to suturing of wounds and to cauterization with fire drills. More pertinently, it includes the diagnosis and treatment of eight cases of ailments of the “breast,” meaning of the bones and soft tissues



Figure 1–1. Column VIII of *The Edwin Smith Surgical Papyrus*, a copy of the first document believed to describe cancer of the breast, circa 3000 BC. Used with permission from The Classics of Surgery Library.²

of the anterior thorax, all in men and most due to injuries. One of the five cases relating to soft tissues (Case 45) describes “bulging tumors” in the breast. The author writes that if the tumors have spread over the breast, are cool to the touch, and are bulging, there is no treatment. Whether this case was a rare cancer of the male breast is conjectural, but in stark contrast to the physician’s active recommendations for the other cases, he recognized this one as sinister; and his conviction that no treatment would help appears to have been based on established practice.

GREEK AND ROMAN PERIOD (460 BC–475 AD)

Ancient Greece was pervaded by a rich mythology based on a belief in close associations between humans and gods. Historians speculate that the god of medicine, Aesculapius, may have had origin in a physician who lived around the time of the siege of Troy (≈ 1300 BC) and to whom were attributed miracles of healing. In the *Iliad*, Homer mentioned Aesculapius’ two sons as “good physicians” who had come to join the siege.³ On the seal of the American College of Surgeons, Aesculapius is pictured seated, holding his staff entwined with a serpent, the symbol of life and wisdom. Early Greeks sought cures by sleeping in the abaton at the temples of Aesculapius and enjoying the associated baths and recreations, forerunners of modern health spas. Votive offerings in the form of breasts found at such sites offer evidence that some came hoping for cure of breast disease (Figure 1–2).

Greek medicine and surgery became the most sophisticated of its time. In the course of his conquests, Alexander the Great of Macedonia (356–323 BC) founded the city of Alexandria on the Nile delta in 332 BC, and a famous medical school arose there around 300 BC. The library at Alexandria was the largest of its time, housing more than 700,000 scrolls. Many prominent Greek and Roman physicians studied, taught, and practiced in Alexandria. The study of anatomy was based on dissection of human bodies and surgery flourished; vascular ligatures were used.

Physicians of the Hellenistic period provide vivid accounts of breast cancer. The Greek term “karkinoma” was used to describe malignant

growths and “scirrhus” to describe particularly hard, solid tumors. “Cacoethes” referred to an early or a probable malignancy. A “hidden” cancer was one not ulcerating the skin. In an anecdote, Herodotus (484–425 BC), historian of the wars between Greece and Persia, claimed that Democedes, a Persian physician living in Greece, cured the wife of Persian King Darius of a breast tumor that had ulcerated and spread.

Hippocrates (460–375 BC), whose legacy, the *Corpus Hippocraticum*, may have been the work of more than one person, was the most prominent of Greek physicians. He maintained that every disease was distinctive and arose from natural causes, not from gods or spirits.⁴ He also believed in the power of nature to heal and in a humoral origin of disease. In his view, a balance of the four bodily fluids, blood, phlegm, yellow bile, and black bile (later linked to sanguine, phlegmatic, choleric, and melancholy dispositions by Galen) was necessary for good health. Hippocrates described cases of breast cancer in detail. One of his case histories was of a woman of Abdera who had a carcinoma of the breast with bloody discharge from her nipple. Attaching a beneficial effect to the bleeding, he noted that when the discharge stopped, she died. Similarly, Hippocrates associated cessation of menstrual bleeding with breast cancer and sought to restore menstruation in young sufferers. His detailed description of the inexorable course of advancing breast cancer rings true today. He said that

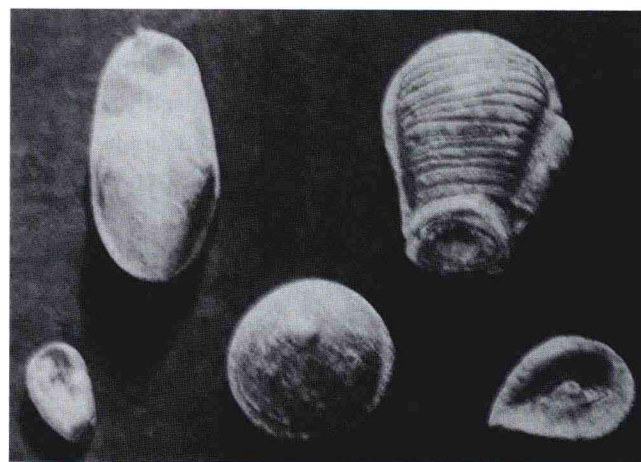


Figure 1–2. Votive offerings from an Etruscan temple include a vagina, a uterus, an ear, an eye, and a breast (lower central). Reproduced with permission from Lyons AS and Petrucelli RJ.⁶

hard tumors appear in the breast, become increasingly firm, contain no pus, and spread to other parts of the body. As the disease progresses, the patient develops bitter taste, refuses food, develops pain that shoots from the breast to the neck and shoulder blades, complains of thirst, and becomes emaciated. From this point death was certain. He advised no treatment for hidden breast cancers because treatment was futile and shortened the patient's life.

In the ascendant Roman Empire, physicians were guided largely by Greek medicine. Around 30 AD, the Roman physician Aulus Cornelius Celsus (42 BC–37 AD) noted that the breasts of women were frequent sites of cancer. Celsus described breast cancer in his manuscript, *De Medicina*, and defined four stages. The first was cacoethes, followed by carcinoma without skin ulceration, carcinoma with ulceration, and, finally, "thymium," an advanced exophytic and sometimes bleeding lesion, the appearance of which suggested to him the flowers of thyme. Celsus recommended excision for the cacoethes but no treatment for other stages. In situations of uncertainty, the tumor was treated first with caustics, and if the symptoms improved, it was a cacoethes; if they worsened, it was a carcinoma. Some masses for which treatment was successful might have been fibroadenomas, phylloides tumors, or even tuberculosis.

Leonides, a surgeon of the Alexandrian school, described surgical removal of breast cancers during this time.⁴ Leonides said that with the patient supine he cut into the sound part of the breast and used a technique of alternately cutting and cauterizing with hot irons to control bleeding. The resection was carried through normal tissues wide of the tumor and customized to the extent of involvement. The operation was concluded with a general cauterization to destroy any residual disease. Poultices were then applied to the wound to promote healing. He explained that excision was used selectively for tumors in the upper part of the breast of limited extent, and he specifically advised against surgery if the whole breast was hardened or if the tumor was fixed to the chest wall. Leonides was perhaps the first to record that breast cancers spread to the axilla. Complete and thorough excision of breast malignancies has been a cardinal principle of surgery since the time of Leonides.

The teachings of the Greek physician, Galen of Pergamum (129–200 BC), on the subject of breast cancer reached far beyond his time. Born of a wealthy and educated family in Asia Minor, he traveled and studied widely. Galen became surgeon to gladiators in Pergamum and finally practiced in Rome, attending the emperor Marcus Aurelius. His vast experience, clinical acumen, investigative approach to knowledge, and prolific, authoritative writings (400 treatises) gained Galen enormous respect. For the next 1,500 years, Galen's teachings guided medical practice, and his animal dissections provided the bases for human anatomy and physiology.

Galen revered Hippocrates and adopted his humoral theory of disease. In Galen's view, breast cancer was a systemic disease caused by an excess of black bile in the blood (ie, melancholia). Black bile was formed in the liver from blood elements and absorbed in the spleen; malfunction of either of these organs caused an excess of black bile, which thickened the blood, and where black bile accumulated, carcinoma developed as hard, non-tender tumors that ulcerated if the bile was particularly acrid. Like Hippocrates, he noted that carcinomas were predisposed to accumulate in the breasts of women who had ceased to menstruate, a recurring theme and doubtless a reference to the frequency of cancer in postmenopausal women. This observation supported Galen's belief that menstruation, and the practice of bleeding, served to clear the body of excess black bile. He likened the dilated veins that radiated from carcinomas to the legs of a crab; as a result, the crab became a symbol for cancer. Leonides had also likened cancers to crabs, but rather because the tenacious adherence to surrounding tissues mimicked the crab's pinchers. For early cancers, Galen recommended purging, bleeding, diet, and topicals. Ulcerating cancers were treated with caustics or cleansed and treated with zinc oxide.

In operating for breast cancer, Galen's approach was less modern than that of Leonides before him. Galen condemned the use of ligatures, and although he was aware of the dangers of excessive blood loss, he preferred to let the blood run unchecked and to express the dark, dilated veins in order to rid them of the morbid black bile. The cancer was removed at