1 Emerging medical technologies: high stakes science and the need for technology assessment

In the past century, advances in medical technology have yielded enormous improvements in human health. For example, our scientific understanding of the immune response and the resulting development of vaccines has vastly reduced the incidence of many infectious diseases. Smallpox has killed more people throughout history than perhaps any other infectious disease. Yet, in 1980, the World Health Organization announced that smallpox had been eradicated worldwide through a program of vaccination (Figure 1.1). Despite these advances, many medical technologies are available to only a small segment of the world's population that can afford them.

Today, emerging technologies have the potential to transform the future of healthcare, offering the potential to diagnose and prevent disease before it strikes, to treat disease in a targeted manner, and to utilize cells and genes for patient-specific therapies. For example, gene therapy offers the promise to cure fatal genetic diseases such as cystic fibrosis and to reprogram a patient's immune system to more effectively fight HIV/AIDS, the leading cause of death in sub-Saharan Africa. Sequencing the genome of *M. tuberculosis* has pointed to new molecular targets for more effective drugs to treat tuberculosis. Small silicon chips containing every gene in the human genome may soon be used to detect cancer at the earliest and most curable stages and to

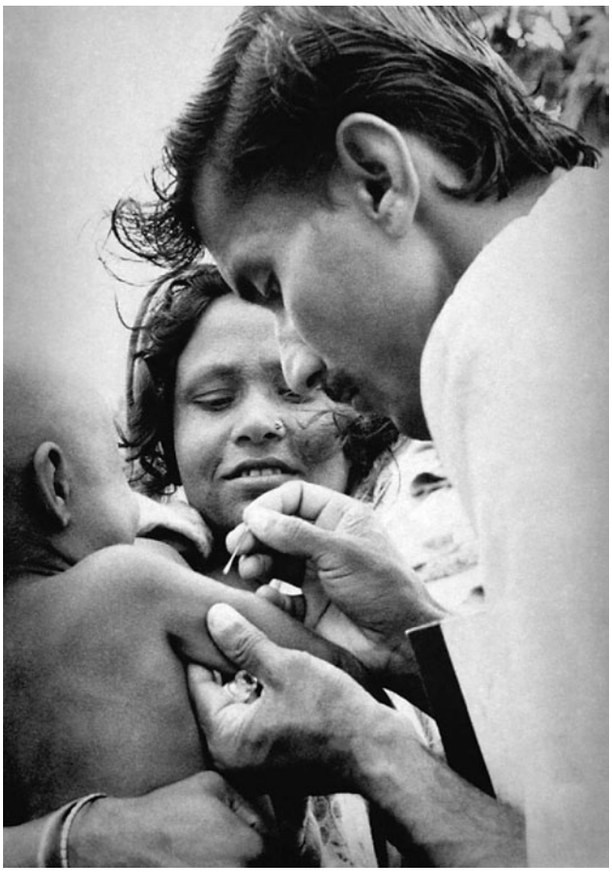

Figure 1.1. *The development of the smallpox vaccine and the subsequent eradication of the disease is an example of a powerful medical technology. CDC/ World Health Organization; Stanley O. Foster.*

individually tailor therapeutic agents for each patient. Tissue engineering holds the promise to create artificial organs, overcoming problems with the limited supply of donor organs. Novel, biologically active materials may be used to coat blood vessels within the heart to prevent heart attacks, one of the leading causes of death in the United States.

Medical technology
The use of novel technologies to develop new drugs, biologics, or medical devices designed to diagnose, treat or prevent disease.

Bioengineering
The application of engineering design to develop new medical technologies.

Biotechnology
The use of living systems to make or improve new products, frequently targeted toward improving human health.

What is needed to bring these new technologies from the research laboratory to your physician's office in a safe and affordable way? As a society, how should we invest our limited financial and human resources to develop new medical technologies? Can new technologies reduce global disparities in health or will they simply widen the gap in health status between developing and developed countries? In this textbook, we examine how bioengineers integrate advances in the physical, information and life sciences to develop new **medical technologies**. To be effective, new healthcare technologies must provide a better means of preventing, detecting or treating disease. At the same time, technologies must also be affordable to those who need them. The goal of bioengineering is to harness science to solve health problems in the face of such constraints. Our study of bioengineering for world health is organized to first understand both global health needs and resource limitations – as we will see, the healthcare problems and economic constraints vary dramatically throughout the world. With this beginning, we profile new technologies emerging from **biotechnology** and **bioengineering** which can significantly impact world health. Throughout the book, we present and apply tools to systematically evaluate these new medical technologies. The book is organized to address **four central questions**.

Four central questions addressed
(1) What are the major human health problems worldwide and how do these differ throughout the world?
(2) Who pays to solve problems in healthcare and how does this vary throughout the world?
(3) How can we use technology to solve world health problems?
(4) How do new technologies move from the laboratory to the bedside?

(1) What are the major health problems worldwide?

Global mortality data show a significant gap in health status between developed and **developing countries**. Leading causes of death in the developed world include cancer, ischemic heart disease, and stroke. In the developing world, infectious diseases like tuberculosis and malaria are far more prevalent owing to widespread poverty, poor infrastructure, and a lack of healthcare resources. A child born today in one of the least developed countries is more than 1000 times more likely to die of measles, an easily preventable and curable disease, than one born in an industrialized country. Worldwide, more than 31 million adults and 2.0 million children are living with HIV/AIDS, most in developing countries. Over the next decade, noncommunicable diseases such as diabetes and heart disease are expected to overtake infectious diseases and malnutrition as leading causes of death in developing countries. The fraction of the global burden of disease linked to lifestyle and behavior choices, currently 20–25%, is expected to increase throughout the world – for example, by 2020 tobacco is expected to kill more people than any single disease, even HIV/AIDS [2]. Understanding how health needs differ throughout the world and how these needs are projected to change in the coming years is the first

UN Millenium Development Goals

Some 80% of the world's population live in **developing countries**. In 2000, 189 countries committed to a broad set of goals to meet the needs of the world's poorest citizens. The goals include the following.

Eradicate extreme poverty and hunger

- Halve the proportion of people whose income is less than one dollar a day by 2015.
- Halve the proportion of people who suffer from hunger by 2015.

Achieve universal primary education

- Eliminate gender disparity in primary and secondary education in all levels of education by 2015.

Reduce child mortality

- Reduce the under-five mortality rate by two thirds by 2015.

Improve maternal health

- Reduce the maternal mortality ratio by 75% by 2015.

Combat HIV/AIDS, malaria and other diseases

- Halt and begin to reverse the spread of HIV/AIDS by 2015.
- Halt and begin to reverse the incidence of malaria and other major diseases by 2015.

Ensure environmental sustainability

- Halve the proportion of people without sustainable access to safe drinking water and sanitation by 2015.

Develop a global partnership for development

The Millenium Country Profiles (http://unstats.un.org/unsd/mi/mi.asp) provide a source of data to compare economic and health status of countries and to monitor progress toward these goals [1].

Table 1.1. *Average health care expenditures per capita of selected WHO nations [3].*

Country	Avg. Health Care Expenditure per capita, 2001 (US$)
Liberia	$1
India	$24
China	$49
Colombia	$105
Mexico	$370
Portugal	$982
Israel	$1641
Switzerland	$3779
United States	$4887

step to enable the development of new technologies to address these needs.

(2) Who pays to solve problems in healthcare?

Despite recent advances, many medical technologies are available only to a small segment of the world's population. As a result, standards of medical care differ radically between the developed and developing world. Average annual healthcare expenditures in high income countries are more than $1800 per person, compared to only $16 per person in the world's least developed countries (Table 1.1). Even in high income countries, the cost of new medical technologies is of great concern. Over the past two decades, healthcare spending has risen dramatically in the United States and throughout the industrialized world, and this rise is expected to continue through the next decade. In the USA, healthcare costs now account for one seventh of the nation's expenditures. The increasing use of new, expensive technologies, an aging population, and increased administrative costs all contribute to the overall rise in healthcare spending. As we will see later, increasing health expenditures does not always improve health status. As health spending grows beyond a minimum value, there is a decreasing rate of return on investment, with fewer years of life gained per dollar invested [4]. In order to achieve the promise of new technologies worldwide,

Major areas of bioengineering

Tissue engineering and regenerative medicine
The use of engineering design principles to regenerate natural tissues and create new tissues using biological cells and three dimensional scaffolds of biomaterials.

Molecular and cellular engineering
Engineering approaches to modify properties of molecules and cells to solve biotechnological and medical problems.

Computational bioengineering
Use of computational tools to analyze large biological data sets such as in genomics or proteomics; computational models to predict structure and behavior of large biological molecules and to guide design of new drugs.

Biomedical imaging
Design of imaging systems (e.g. ultrasound), image analysis tools, and contrast agents to record anatomic structure or physiologic function.

Biomaterials
The engineering design of materials compatible with biological organisms that can be used to make implants, prostheses, and surgical instruments that do not provoke immune rejection.

Drug delivery
Design of materials and systems to achieve controlled release of drugs in physiologic systems.

Biomechanics
The study of mechanical forces in living systems and the use of engineering design to create prosthetic devices and tools for rehabilitation.

Biosensors
Engineering design of systems to identify and quantify biological substances. Advances in microelectronics have aided in developing miniature, implantable biosensors.

Biosystems engineering
Modeling complex, interacting networks of biological systems within cells and organisms to understand physiology and disease and suggest therapeutic strategies to modify behavior.

our society must develop and evaluate technologies in a cost-conscious manner.

(3) How can bioengineering solve global health problems?

Technology development begins with scientific knowledge; in health issues this often means an understanding of a disease and its effects on the body. **Bioengineers** build on this scientific knowledge to create new technologies that solve healthcare problems. Magnetic resonance imaging, radiation therapy, and vaccines are all examples of health-related technologies that have become widespread within the past century. The heart–lung bypass machine, pacemakers and other technologies have revolutionized the treatment of heart disease, reducing cardiovascular mortality by half over the past 50 years. In this book, we will consider how new technologies can be used to diagnose, treat, and ultimately prevent the three leading causes of death throughout the world: infectious disease, cancer, and heart disease.

As we will see later, the development of new healthcare technologies must take into account the societal and economic context in which they will be used and their potential status as a priority or a luxury at a given time. For example, development of a totally implantable artificial heart may provide a solution to the problem of end-stage heart failure in developed countries, but owing to differences in infrastructure and resources is unlikely to be a practical solution in many developing countries. To help illustrate these challenges, throughout this book, we will profile the experiences of several undergraduate students who carried out internships in sub-Saharan Africa as a part of a course in Bioengineering and World Health. Their experiences highlight both the opportunities and challenges of developing new technologies to improve world health.

(4) How do new technologies move from the laboratory bench to the patient's bedside?

New medical technologies developed in research laboratories must be subjected to a rigorous testing procedure to ensure that they are both safe and effective. In many cases, this involves carrying out experiments with human subjects. How can we ensure that these experiments are carried out in an ethical way? How can we balance the desire to bring promising new treatments to patients who need them as soon as possible against the risk of harming patients by allowing them access to therapies that haven't been sufficiently tested? As healthcare consumers we are often faced with conflicting media reports of the safety of new medical technologies. In order to make choices about our own healthcare, it is necessary to understand how medical research is funded and how new drugs and medical devices are regulated.

Learn more about breast cancer

Breast Cancer Facts and Figures 2005–2006. (Atlanta, GA: American Cancer Society, Inc.; 2005). [5]
http://www.cancer.org/downloads/STT/CAFF2005BrF.pdf

Answers to these four questions are complex and interrelated. We begin our journey to understand how bioengineering can be used to improve world health by examining a case study of the development of a new technology – the use of high dose chemotherapy and bone marrow transplant to treat advanced breast cancer. This case study illustrates the difficult personal and social issues that can arise as new technologies are developed and tested, and will introduce many of the issues that we will examine in more detail throughout the text. We conclude our case study with a look at how the process of healthcare technology assessment can be systematically used to address these complex and sensitive issues in a scientifically sound manner.

Case study: breast cancer and bone marrow transplant

Breast cancer is both a devastating and a common disease. If you are female and live in the United States, you have a one-in-eight (12.5%) chance of developing breast cancer sometime in your life [5]. When detected early, there are many effective treatments for breast cancer. However, few effective treatments exist for the disease in its later stages. Less than 20% of women are alive five years after the detection of Stage IV metastatic breast cancer, the most advanced form of the disease. In the 1980s a promising new therapy was developed for women with metastatic breast cancer: high dose chemotherapy followed by bone marrow transplant (HDCT+BMT).

Small, early clinical trials of this technique were very promising. The effectiveness of a new cancer treatment is initially measured by the fraction of patients who experience a complete or total response following treatment. In the 1980s, a number of small studies showed a substantial increase in the number of patients with metastatic breast cancer who responded to this new therapy compared to historical experience for patients treated with standard chemotherapy. Although these results were exciting, they were viewed with caution until the patients could be followed for a longer period of time. Many patients who initially respond to therapy may relapse; thus long term

Beyond Traditional Borders: Reports from Student Interns

Kim Bennett accompanied Dr. Ellie Click across Malawi conducting intensive training at hospitals as part of a pilot project for the use of bloodspot PCR for infant HIV diagnosis.

Dave Dallas and **Tessa Elliott** assisted in the design and implementation of World Food Program food distribution system at a pediatric AIDS clinic in Mbabane.

Lindsay Zwiener and **Rachel Solnick** pilot-tested software that generates pictorial medication guides, which were developed as their Bioengineering & World Health course projects. They assessed whether these guides help caregivers in Botswana in the proper dosing and timing of anti-retroviral (ARV) medications, promoting adherence to ARV therapy.

Christina Lagos and **Sophie Kim** rolled out their Bioengineering & World Health course project in the SOS Village in Maseru. The project was an after-school activities club to promote interest in science and health education with a focus on HIV/AIDS. They also implemented a Reach Out and Read program at a pediatric AIDS clinic.

The course in Bioengineering & World Health was developed and offered at The University of Texas at Austin and at Rice University. Through a new initiative called Beyond Traditional Borders, made possible by a grant to Rice University from the Howard Hughes Medical Institute through the Undergraduate Science Education Program, students at Rice University can travel to Africa for a summer and implement the projects they developed as part of this course. The inaugural class of interns kept a blog describing their experiences. Throughout the book, we include excerpts from the blog to provide a student's view of how bioengineering can improve world health.

You can find more student blogs at:
www.owlsbeyondborders.rice.edu

Departure: June 8th, 2007
Christina Lesotho

Coming from a close family, I have been doing a lot of explaining about my goals and purpose for this trip and doing my best to calm the fears of my family. I know that they simply want me to be safe and are concerned about me while I am gone, and I am used to the ways of overprotective Greek relatives. In the end, I think I have convinced them that this will be the experience of a lifetime and that I have been looking forward to something like this since I began college.

I was getting ready to record something in my personal journal last night and found that the last sentence I wrote the last time I made an entry had to do with Africa. From my last weeks in Washington, D.C., working on health policy in Africa, I expressed a desire to go and experience the challenges and situations first hand. "I want to go to Africa . . . why not me?", that is what I had written as I wondered why it always seemed so far-fetched or impossible that I would one day be able to visit. And now it's quickly approaching, and I feel so fortunate and excited for this opportunity.

I am prepared for some of the best and worst emotions I have ever experienced and am ready to fully immerse myself in the work I am about to do in Lesotho. I feel almost guilty for having somehow cheated during this pre-departure period . . . I have been looking at tons of Google images of Maseru, Lesotho, and the surrounding area, and I feel like I have some sort of unfair advantage as I travel. When I was younger and did not use or have access to the Internet as much, traveling to a new place was always so much more of a mystery and I always envisioned my destination so differently than it turned out to be. I know that a bunch of Google images and travel sites will not do Lesotho justice, but I still feel like I have done away with at least a bit of the mystery of travel. Maybe I won't do that next time.

I am looking forward to spending the next few days in Johannesburg with a family-friend who grew up there. I will be there until the 12th when I will be meeting up with Sophie at the airport to head to Maseru.

It will be nice to leave the hot and humid start of summer here in Florida and find the cold beginnings of winter in southern Africa!

survival rates are often used as a better metric to determine the effectiveness of a new cancer therapy. The three year survival rate measures the number of patients still alive three years after beginning cancer therapy. In the early 1990s, a small study indicated that women with high risk breast cancer treated with HDCT+BMT had a 72% three year survival rate, dramatically higher than the historical experience for women treated with standard dose chemotherapy, which was only 38–52% [6].

These studies offered new hope to women who faced high risk or metastatic breast cancer. HDCT+BMT is a grueling treatment that has been described by Dr. Jerome Groopman as "an experience beyond our ordinary imaginings – the ordeal of chemotherapy taken to a near-lethal extreme [7]." In desperation, more than 41 000 American women with advanced breast cancer endured HDCT+BMT in the 1990s, even though there was little clinical evidence to show that it was superior to standard therapy [8]. The story of what happened as this technology was developed and tested illustrates how political pressures can overwhelm science, leading to substantially increased medical costs and dramatically reduced quality of life for patients.

Breast cancer in the USA

After skin cancer, breast cancer is the most common cancer among women, and accounts for almost one of every three cancers diagnosed in women in the United States [5]. In 2005, more than 40,000 American women are expected to die of breast cancer; only lung cancer causes more cancer deaths in women. An estimated 211,240 new cases of breast cancer occurred in the USA in 2005, and there are over 2.3 million women living in the USA who have been diagnosed with breast cancer.

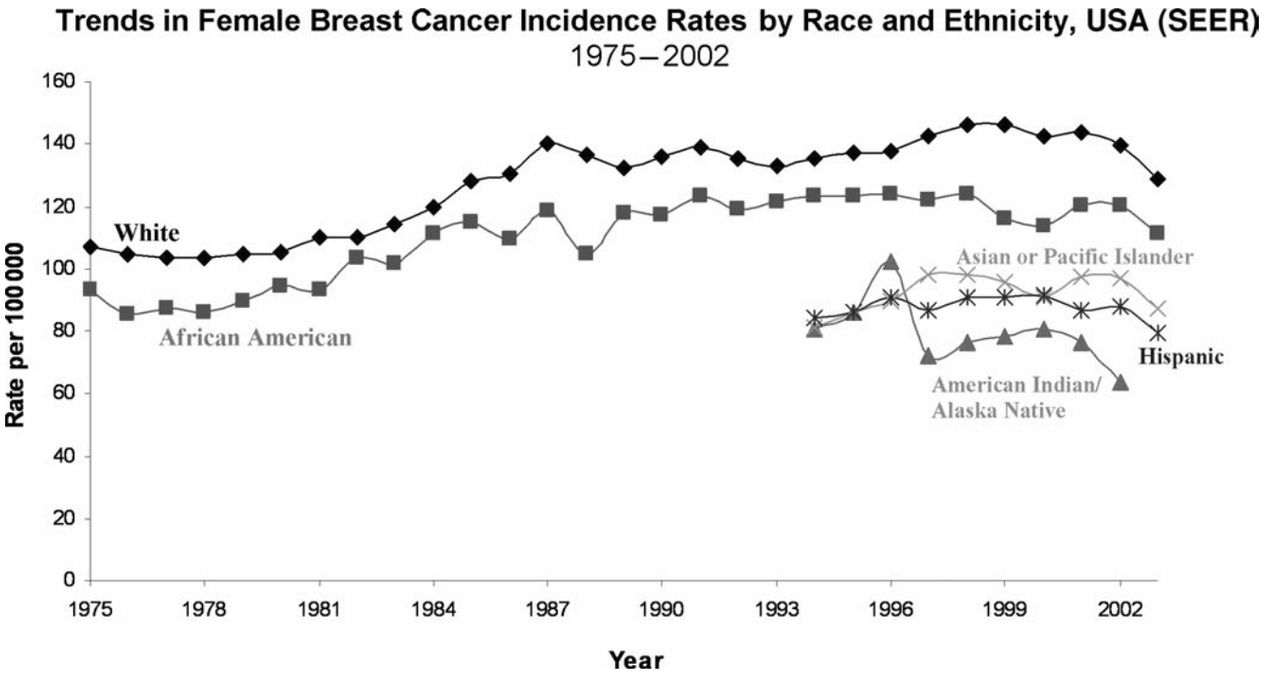

Figure 1.2. *Female breast cancer incidence rates by race and ethnicity in the United States as reported by SEER [9]. The rates are age adjusted to the 2000 USA standard population.*

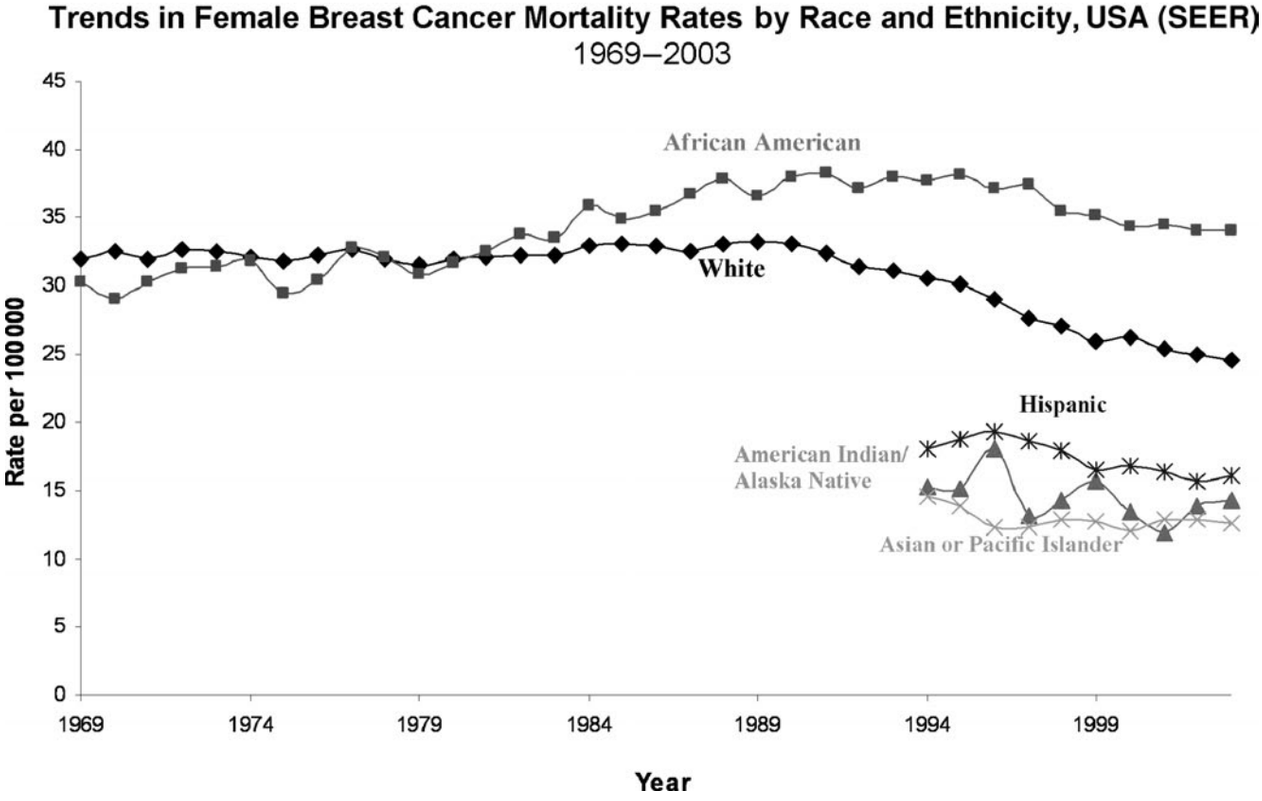

Figure 1.3. *Female breast cancer death rates by race and ethnicity in the United States as reported by SEER [10]. The rates are adjusted to the 2000 USA standard population.*

Female breast cancer incidence rates have risen in the USA from 1973 to 1998, as reported by the NCI Surveillance, Epidemiology and End Results (SEER) Program (Figure 1.2). Incidence rates have increased owing to a combination of changes in reproductive patterns (delayed childbearing, having fewer children) and better early detection with mammography. Female breast cancer death rates in the USA during the same period have decreased (Figure 1.3), primarily owing to better early detection of more treatable cancers and to improvements in breast cancer treatments.

Figure 1.4 shows an illustration of the female breast. After childbirth, milk is produced in glandular tissue in the breast, leading to milk ducts [11]. This glandular tissue is where most breast cancers develop. When cancer cells are confined to these ducts, and have not spread to surrounding fatty tissue, the disease is called Stage 0, and is completely curable with surgical excision. Lesions which have spread to the surrounding fatty tissue but

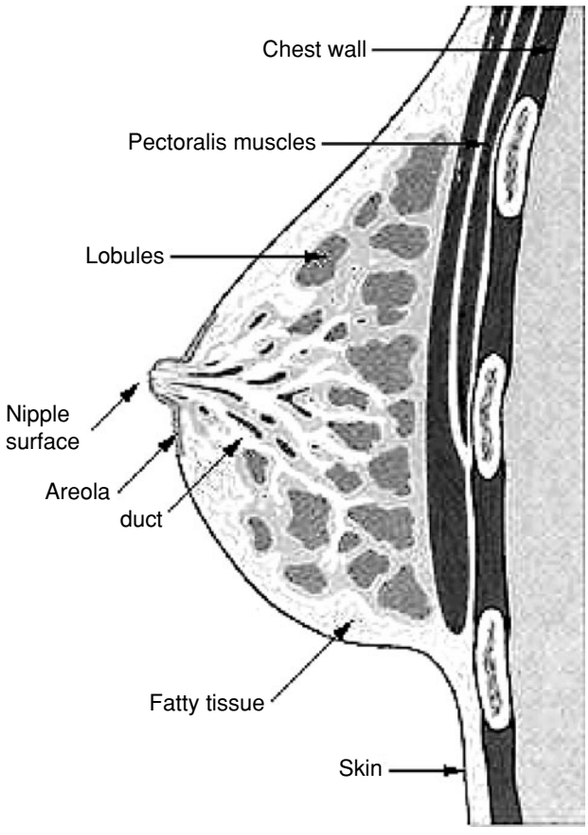

Figure 1.4. *The human female breast. Source: SEER Training Modules, Breast Cancer. US National Cancer Institute. 2009. http://training.seer.cancer.gov/*

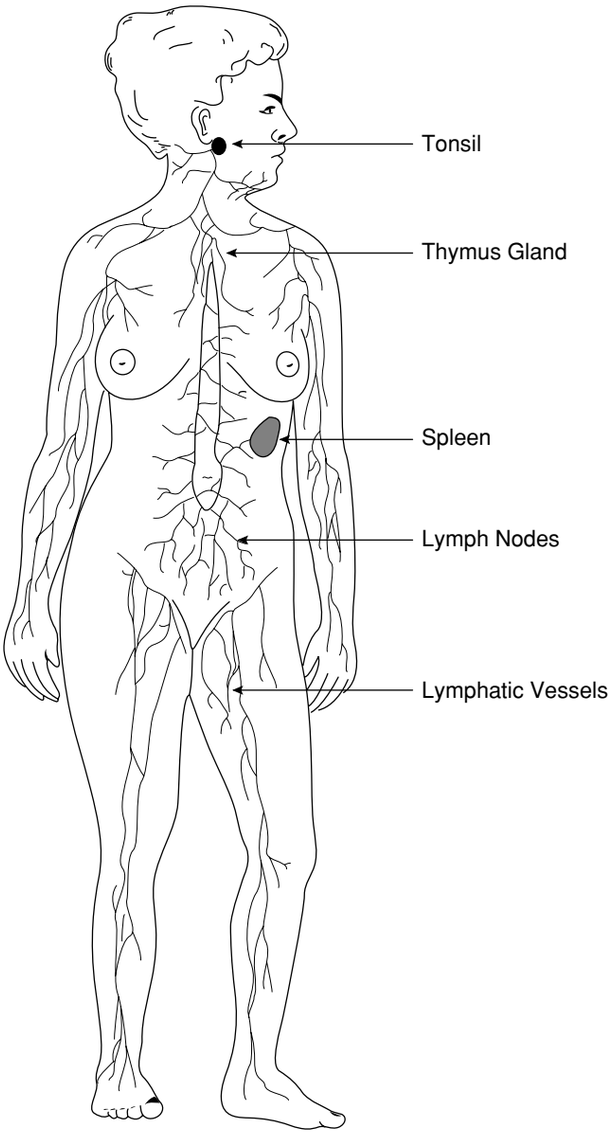

Figure 1.5. *Lymphatic system. Source: SEER Training Modules, Lymphoma. US National Cancer Institute. 2009. http://training.seer.cancer.gov/*

are less than 2 cm in diameter are referred to as Stage I lesions, and also have excellent prognosis, with a 100% five year survival rate [12]. A series of lymphatic vessels, leading to lymph nodes under the armpit (axillary lymph nodes), drain breast tissue (Figure 1.5) [11]. Breast cancer cells can migrate from the initial lesion and enter these lymphatic vessels, providing a way for breast cancer cells to spread to other distant organ sites (metastasize). If the cancer has spread to one–three lymph nodes close to the breast but not to distant sites, it is referred to as a Stage II lesion, and the five year survival rate is in

Table 1.2. *Breast cancer staging [12].*

Stage	Definition	5 yr survival
Stage 0	Cancer cells are located within a duct and have not invaded the surrounding fatty breast tissue	100%
Stage I	The tumor is 2 cm or less in diameter and has not spread to lymph nodes or distant sites.	100%
Stage II	The cancer has spread to 1–3 lymph nodes close to the breast but not to distant sites	81–92%
Stage III (High risk)	The cancer has spread to 4–9 lymph nodes close to the breast but not to distant sites	54–67%
Stage IV (Metastatic)	Cancer has spread to distant organs such as bone, liver or lung or to lymph nodes far from the breast.	20%

the range 81–92%. Stage III breast cancers involve more than four nodes, and because the five year survival rates are so low (54–67%) are referred to as "high-risk breast cancers." In metastatic breast cancer (Stage IV), the disease has spread from the lymphatics to other organ sites far from the breast, such as the brain. The five year survival rate for metastatic breast cancer is only 20%. The stages of breast cancer and the prognosis for each stage are summarized in Table 1.2 [12].

Treatments for breast cancer

There are many treatments for breast cancer. Treatment for most early cancers involves some form of surgery to remove the cancer cells. If the lesion is small, only a portion of tissue may be removed (lumpectomy), or the entire breast may be removed (mastectomy). Larger tumors may be treated using chemotherapy. In some cases, chemotherapy may be used to shrink larger tumors so that they can be removed surgically; in others it may be used following surgery to reduce risk of recurrence. In chemotherapy, drugs which are toxic to cancer cells are given intravenously or by mouth. These drugs travel through the bloodstream, reaching cancer cells throughout the body. Chemotherapeutic drugs interfere with ability of cells to divide; many cancer cells cannot repair damage caused by chemotherapy drugs so they die.

Rapidly dividing normal cells may also be affected by chemotherapy drugs, but they can repair this damage. Because chemotherapy drugs affect rapidly dividing normal cells, they give rise to many undesirable side effects. The cells which line the gastrointestinal tract divide rapidly; thus chemotherapy can lead to nausea, vomiting, mouth sores and loss of appetite. Cells in the hair follicles divide rapidly and chemotherapy can lead to hair loss. Rapidly dividing cells in the bone marrow which produce oxygen carrying red blood cells, infection fighting white blood cells, and platelets important in blood clotting are also affected by chemotherapy drugs. Chemotherapy patients are thus at high risk for infection, bleeding and fatigue. While these side effects are temporary, chemotherapy can also produce permanent side effects such as premature menopause and infertility.

High dose chemotherapy

Because chemotherapy can damage both cancer cells and rapidly dividing, but crucial, normal cells, cancer treatment must strike a balance between completely destroying all cancer cells while causing minimal damage to normal cells. In the 1980s a number of dose comparison studies of chemotherapy to treat metastatic breast cancer showed that a higher dosage of chemotherapy was associated with a higher response rate. Scientists and clinicians hypothesized that metastatic breast cancer could be treated more effectively with higher doses of chemotherapy. Unfortunately, such high doses completely destroy the bone marrow, leaving patients with no way to continue to produce the cells of the blood system and the immune system, which are necessary for life.

Our blood consists of four components: plasma, red blood cells, white blood cells, and platelets. Plasma carries nutrients and hormones throughout the body. Red blood cells deliver oxygen throughout the body, while white blood cells are necessary to fight infections. Platelets are necessary for blood clotting following injury. Throughout our lives, our blood cells are continually renewed within the bone marrow. The source