

2

Basic Terminology

Philip C. Nasca

The overall objective of this chapter is to provide an introduction to basic terminology that the first-time student may find useful when exploring articles and books related to cancer epidemiology. The chapter is designed to introduce the reader to a number of basic concepts that apply to benign and malignant neoplasms, tumor metastases, tumor staging, and grading classification schemes and to a number of approaches to standardizing the anatomic and morphological classification of cancers. It also defines basic terms used in cancer diagnosis and management. Finally, it briefly discusses ways in which diagnostic difficulties may affect epidemiological studies of various cancers.

Different terms are often used to describe the benign and malignant growths referred to in this book. *Neoplasm* literally means “new growth” and can be defined as an abnormal mass of tissue that is uncoordinated with the normal tissues of the affected organ. A neoplasm may persist even after the stimulus that produced the growth is removed.¹ This definition implies two important facts about neoplasms: First, neoplasms exhibit growth in excess of normal tissue regeneration, suggesting that they have somehow escaped the biologic restraints on growth that govern normal cellular replication and tissue growth. Second, the stimuli provoking neoplastic changes at the cellular level are often permanent and inherited by all cellular progeny. The occurrence of permanent and heritable changes at

30 FUNDAMENTALS OF CANCER EPIDEMIOLOGY

the cellular level that lead to uncontrolled cellular proliferation and tissue growth will be referred to throughout the text as *neoplastic transformation*. The term *tumor* is often commonly used interchangeably with the term *neoplasm*. (A comprehensive glossary of terms used in the field of cancer epidemiology is provided in Appendix A.)

Pathologic Features of Cancer

The normal architecture of an organ involves standard relationships between specific groups of cells, whereas in neoplastic growth the relationships between cells are significantly altered, as shown in Figure 2–1. In normal epithelial tissues, the layers of epithelial cells are arranged in a regular and ordered manner, and cells replicate at the rate necessary to replace lost cells and to maintain the normal structure and functions of the tissues. The most common forms of cancer occur in the epithelial tissues, which are separated from the underlying connective tissue, blood and lymphatic vessels, and nerves by a basement membrane. Neoplasms of epithelial origin tend to show structural differences when compared with the normal architecture of the tissue within which the tumor originated. In neoplastic growth, many more cells are produced than are needed to replace lost cells. The architecture of neoplastic tissue is not orderly, and many layers of epithelial cells are arranged in irregular patterns.²

Neoplastic cells are distinguished from normal cells by a loss of cellular differentiation. The term *degree of differentiation* refers to the extent to which the neoplastic cells continue to resemble, morphologically and functionally, the normal cells of the tissue within which the neoplasm develops. Neoplasms defined as well differentiated have cells that are morphologically similar to cells normally found in the tissue of origin and that maintain many of the functions of normal cells. In poorly differentiated neoplasms, the neoplastic cells have a primitive appearance and suffer a loss of normal functioning. The reduction in differentiation is an important characteristic of malignant neoplasms, and it is referred to as *anaplasia*.

A number of morphologic and functional changes at the cellular level indicate the presence of anaplasia. The cells and their nuclei show variation in size and shape, which is referred to as *pleomorphism*. Neoplastic cells may be either much larger than normal cells in the same tissue or uncharacteristically smaller and more primitive in appearance than normal cells. The nuclei of neoplastic cells may show variability in their shapes, have large amounts of dark-staining DNA, and take up an exceptionally large proportion of the total volume of the cell. While the ratio of nuclear to cytoplasmic material is on the order of 1:4 to 1:6 in normal cells, this ratio may approach 1:1 in neoplastic cells. These neoplastic cells may also show evidence of frequent cell divisions, indicating rapid cellular proliferation. Evidence for cellular proliferation might include the presence of large nucleoli and large numbers of mitoses.^{3(p243)}

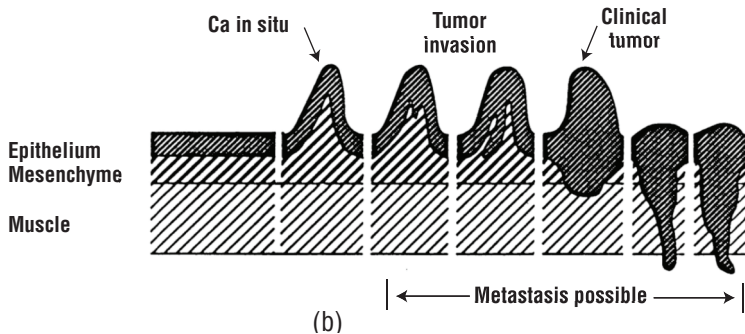
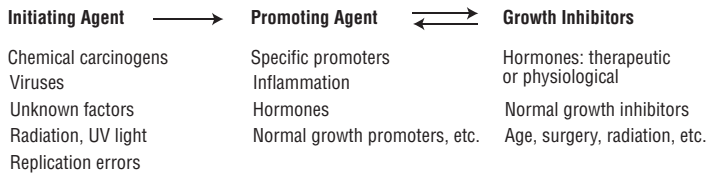
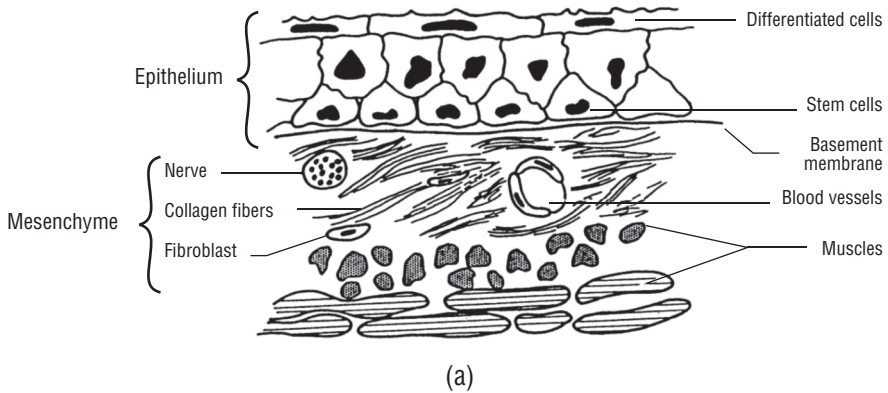


FIGURE 2-1 (a) A typical tissue showing epithelial and mesenchymal components and (b) factors influencing tumor development showing progression from a normal to an invasive tumor.

Source: From Franks, LM and NM Teich, *Introduction to the Cellular and Molecular Biology of Cancer*, 2nd ed. pp 2, 5, 1991. Reprinted with permission from Oxford University Press.

Microscopic studies of cancer cells also show gross changes in the cellular cytoskeleton. The cytoskeleton of normal cells is composed of actin fibers, which are arranged in an orderly cablelike fashion. These actin cables serve to provide structure to the cell and are connected to receptors on the cell surface, which in turn anchor the cell to the intracellular matrix. In cancer cells, these actin cables are either lost or become disorganized, and the cancer cells lose their adherence to the intracellular matrix.^{4(pp39-42)}

Benign and Malignant Neoplasms

Neoplasms are classified as either benign or malignant based on a number of important characteristics, which are summarized in Table 2–1. Benign neoplasms are usually well differentiated, whereas malignant neoplasms range from well differentiated to poorly differentiated. Systems of tumor grading have been developed by pathologists to describe the degree of differentiation observed in a particular epithelial tumor. Tumor grade as a measure of differentiation is clinically important as a measure of tumor progression and as a prognostic factor often related to the tumor's response to treatment, disease recurrence rates, and patient survival.

Rate of growth is also a critical distinguishing feature of benign and malignant neoplasms. Benign neoplasms tend to grow at a relatively slow pace and may take years to develop into a significant mass. Malignant tumors generally tend to grow faster, with growth rates inversely correlated with the degree of differentiation. Doubling time, the amount of time needed for the tumor to double in mass, is used as a measure of tumor growth. Benign tumors usually have long doubling times, whereas the doubling time for malignancies with high case-fatality rates can be quite short.

TABLE 2–1 Morphologic and Functional Differences between Benign and Malignant Tumors

<i>Characteristic</i>	<i>Benign tumors</i>	<i>Malignant tumors</i>
Structure	Structurally similar to tissue within which tumor originated	Architecture of tumor disorganized and not typical of tissue of origin
Differentiation	Well differentiated (anaplastic)	Poorly differentiated
Rate of growth	Slow rate of growth	Rapid rate of growth, with short doubling time
Mode of growth	Expansion (encapsulated)	Penetration and destruction of surrounding tissues
Metastases	No metastases	Metastases common through local tissue invasion and transport of malignant cells through the bloodstream or lymphatic system
Response to therapy	Rare for tumor to recur	Recurrent disease common after initial therapy
Prognosis	Usually excellent; inaccessible tumors can be fatal	More often fatal than benign tumors

Benign tumors, which are encapsulated by connective tissue, tend to remain confined within the tissue of origin. Malignant tumors may gain the ability to penetrate the basement membrane, a thin extracellular layer of mucopolysaccharides and proteins that separates the epithelial tissues from the underlying connective tissues, blood vessels, and lymphatics. This ability to penetrate the basement membrane leads to local invasion and destruction of adjacent tissues.

Metastasis

Penetration of the basement membrane also provides the tumor with access to local blood and lymphatic vessels, thus providing a route for the tumor to spread to other organs of the body. The process of systemic spread, referred to as *metastasis*, is another important distinguishing feature of malignant neoplasms. Metastasis can occur through a number of mechanisms, including by direct extension of the tumor into various natural body cavities, such as the peritoneal cavity, and, most commonly, by penetration of the nearby lymph nodes and blood vessels for transport to other vital organs.

Research has shown that most cancers contain subpopulations of cells of varying biologic characteristics. Cells may vary with respect to rate of growth, karyotype, pigment production, receptor content, degree of immunogenicity, and susceptibility to cytotoxic drugs.⁴ Subpopulations of cells probably exist at diagnosis, and these may have a greater potential to metastasize than other subpopulations of cells, possibly because they possess a greater ability to withstand exposure to chemotherapeutic agents. These metastatic cancer cells spread to other organs in the body via the circulatory and lymphatic systems by invading new blood vessels formed by tumor angiogenesis or by entering existing blood vessels or lymphatics. The metastatic cells enter and leave the circulatory system by excreting a number of substances that break down the vessel wall (Figure 2-2).⁵ The

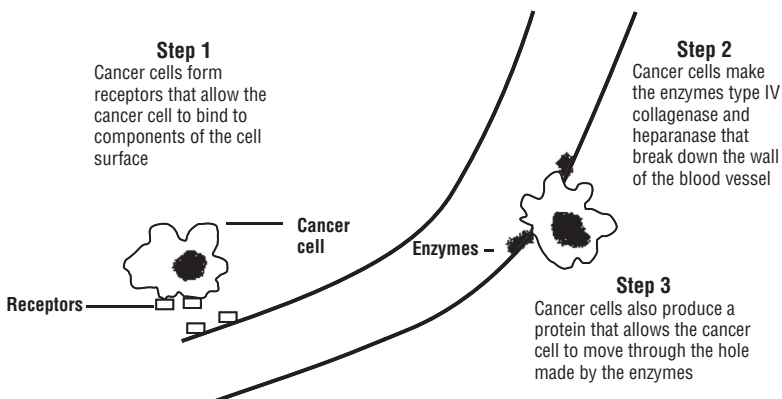


FIGURE 2-2 The migration of cancer cells through blood vessels.

34 FUNDAMENTALS OF CANCER EPIDEMIOLOGY

process of metastatic spread is a highly complicated biological process. A more detailed description of how metastases occur can be found in the article by Fidler.⁵

Angiogenesis

As early as 1971, Judah Folkman suggested that the growth potential of a primary tumor is dependent on the growth of new capillaries that feed the tumor, with this growth of new capillaries stimulated by a chemical signal from the tumor. If this hypothesis could be shown to be correct, then clinicians might be able to find chemotherapeutic agents that would inhibit new capillary production by blocking the action of these tumor-related chemical signals. The potential to block the metastatic spread of cancers through the blood vessels was also clearly evident. A wide array of indirect and direct evidence has accumulated that supports the angiogenesis hypothesis. A detailed review of this evidence can be found in a recent review.⁶ Randomized clinical trials have been initiated to determine the clinical effectiveness of various chemotherapeutic agents. These agents work through a variety of mechanisms, including the enhancement of apoptosis, inhibition of endothelial proliferation, the blocking of receptor signaling, and direct inhibition of various angiogenesis promoters. A summary of the phase I through phase III trials directed toward the testing of anti-angiogenesis agents is summarized in Table 2–2. The successful identification of effective anti-angiogenesis agents would be a great leap forward in the treatment of both primary and metastatic cancers.⁶

Cancer Diagnosis

A diagnosis of cancer is usually confirmed by obtaining a biopsy specimen or tumor sample by surgical excision, needle aspiration, or the collection of exfoliated cells from body fluids, among other methods. The specimen is then examined by a pathologist, who determines if the tissues are neoplastic, notes the behavior (benign or malignant) of the neoplasm, and notes the cell type. The pathologist will also determine the tumor grade (as a measure of degree of differentiation) and will examine any lymph nodes submitted by the clinician for evidence of cancer. The exact histology (or cell type) and tumor grade will help the clinician plan the proper course of therapy and establish a probable prognosis. In the pathology laboratory, the tumor specimen is fixed, sectioned, and stained as part of the preparation of slides for examination by the pathologist. The fixation process is designed to help preserve and stabilize the tissues. The protein structure of the specimen is cross-linked with specific fixatives, such as formalin, or

TABLE 2-2 Angiogenesis Inhibitors in Clinical Trials

<i>Drug</i>	<i>Sponsor</i>	<i>Mechanism</i>
<i>Phase I</i>		
COL-3	Collagenex, NCI	Synthetic MMP inhibitor; tetracycline derivative
Combretastatin	Oxigene	Apoptosis in proliferating endothelium
BMS-275291	Bristol-Myers Squibb	Synthetic MMP inhibitor
SU6668	Sugen	Blocks VEGF, FGF, & EGF receptor signaling
Endostatin	EntreMed	Inhibits endothelial proliferation
<i>Phase II</i>		
Squalamine	Megainin	Inhibits Na/H exchanger
PTK787/ZK22584	Novartis	Blocks VEGF receptor signaling
TNP-470	TAP Pharm.	Fumagillin analog; inhibits endothelial proliferation
Thalidomide	Celgene	Unknown
SU5416	Sugen	Blocks VEGF receptor signaling
Vitaxin	Ixsys	Antibody to integrin on endothelial surface
Interleukin-12	Genetics Inst.	Induces IFN-gamma and IP-10
CAI	NCI	Inhibits calcium influx
Anti-VEGF Ab	Genentech	Monoclonal antibody to VEGF
<i>Phase III</i>		
Marimastat	British Biotech	Synthetic MMP inhibitor
AG3340	Agouron	Synthetic MMP inhibitor
Neovastat	Aetema	Natural MMP inhibitor
Interferon-alfa	Commercially available	Inhibition of bFGF production
IM862	Cytran	Endothelial inhibitor

Source: Folkman J. Tumor angiogenesis. In: Bast RC, Kufe DW, Pollack RE, et al., eds. *Cancer Medicine*. 5th ed. London: BC Decker; 2000. Reprinted with permission.

36 FUNDAMENTALS OF CANCER EPIDEMIOLOGY

proteins are precipitated with alcohol-based chemicals, such as methacarn. The lipids and water are then removed from the tissue and the specimen is impregnated either with paraffin wax (for light microscopy) or resin (for ultrastructural studies).

If the specimen is to be viewed under a light microscope, a device called a *microtome* is used to cut thin sections of the tumor from the paraffin block. These thin sections are stained with acidic or basic dyes to highlight the nucleus, cytoplasm, and extracellular matrix, and they are then placed on slides for examination under the microscope. A device called a *cryostat* can be used to cut thin sections from a specimen that has been snap frozen with liquid nitrogen at -80°C . In addition to providing materials for initial diagnoses, paraffin blocks can be maintained for many years and have been used extensively in molecular-epidemiological studies. Recent innovations in gene amplification methods have led to studies of gene-environmental interactions that utilize DNA and RNA extracted from paraffin blocks.^{7,8}

Molecular Pathology

A number of useful molecular pathology techniques have emerged in recent years to aid the clinician in cancer diagnosis and management. For a detailed account of these techniques, the reader is referred to the excellent review by Chatterjee and Zetter.⁹ Some of these techniques are in the field of immunohistochemistry, some involve the measurement of total DNA content, and some are in the field of diagnostic molecular genetics.^{7,8}

Immunohistochemical techniques include a number of complicated laboratory techniques, including one in which antibodies are tagged with fluorescent molecules to bind with antigens expressed by various tumor cells. Innovations in immunohistochemistry have led to the development of more refined classification systems for tumors and a significant reduction in the proportion of tumors that are unclassified. Immunohistochemical techniques can also help sort out different cell types in tumors with mixed cellularity, help identify metastatic tumor cells in secondary sites, and occasionally help distinguish benign from malignant tumors. More recently, immunohistochemical classification of tumors has been used to develop markers to help establish prognoses. For example, recent studies have shown the multidrug resistance of tumors that overexpress p53 antigen; the overexpression is thought to reflect a point mutation in the tumor suppressor gene, a mutation that leads to inactivation of p53 protein.^{7,8}

Predictions of the course of a cancer can also be based on measurements of the DNA content within cancer cells. A commonly used prognostic marker is the number of chromosomes present in the cells. Cancer cells frequently show abnormal numbers of chromosomes, or ploidy.

The presence of ploidy indicates a poorly differentiated tumor and suggests a poor prognosis for the patient. In addition, cancer cells can be examined for the proportion of cells that have doubled their DNA in preparation for cell division. This measure, called the *S-phase fraction*, has been shown to correlate with increased tumor aggressiveness. Finally, a number of molecular techniques developed over the past 20 years can be used to examine cells obtained from the fluids or tissues of cancer patients for specific nucleotide sequences that indicate the presence of specific genes known to be associated with specific forms of cancer.⁷ (See Chapter 7 for a discussion of these techniques and their use in epidemiological research.)

A growing number of circulating tumor markers are useful in establishing the initial diagnosis of the cancer and in helping to predict a patient's prognosis. These markers are also useful for monitoring the course of the patient's disease or the tumor's response to therapy.⁸ Blood tests can be used to obtain baseline measures of certain biomarkers at the time of diagnosis and following treatment for the purpose of monitoring the patient for any recurrence of cancer. A significant increase in the value of one of these markers over the baseline value taken after initial treatment may signal the return of the disease. Table 2-3 contains a brief description of some of the biomarkers currently used by physicians to help manage the patient's disease in the optimal fashion. Some tests are performed at the time of initial diagnosis to help plan future treatments in the event that the cancer recurs. It is now standard practice for physicians to send a portion of a breast cancer biopsy specimen to a laboratory so that estrogen and progesterone receptor assays can be done.

These assays determine if the patient's breast cancer grows in response to the hormones estrogen and progesterone. The results play an important role in determining a suitable management plan for recurrent disease. If the breast cancer is estrogen receptor positive, then the patient may be treated with an estrogen antagonist, such as the drug tamoxifen. Estrogen and progesterone receptor status has also been used by epidemiologists to determine if breast cancers categorized as receptor positive or negative exhibit different epidemiological characteristics.¹⁰ (More is said about this approach in Chapter 10.)

It is also possible for a patient who is diagnosed with a cancer at one anatomic site to develop a second primary cancer at a different anatomic site many years later. Such multiple primary cancers sometimes involve paired organs, such as the ovary or breast. It is therefore necessary for the patient to undergo regular monitoring of the initially unaffected side. Women with breast cancer are usually given a mammographic and clinical examination of the initially unaffected breast at regular intervals to detect the development of new primary disease in the second breast or to detect metastatic spread from the original primary cancer.

38 FUNDAMENTALS OF CANCER EPIDEMIOLOGY**TABLE 2-3** Selected Cancer Biomarkers and Their Use in the Diagnosis and Characterization of Tumors

<i>Biomarkers</i>	<i>Cancers</i>	<i>Use</i>
PSA	Prostate	Screening, diagnostic, predict recurrence
CEA	Several cancers including colorectal, lung, breast, liver, pancreatic, thyroid, bladder	Determine recurrence, monitor treatment efficacy
CA 125	Ovarian	Diagnostic, monitor treatment, predict recurrence
BTA	Bladder	Diagnosis, predict recurrence
Calreticulin	Bladder	Diagnosis
Survivin	Bladder	Diagnosis, monitor treatment and predict recurrence
Antizyme	Prostate	Prognosis
Antizyme inhibitor	Prostate	Prognosis
Collagen XXIII	Prostate, breast, several others	Prognosis
MMP	Prostate, breast	Prognosis
MMP inhibitors	Prostate, breast	Prognosis
Her-2	Breast	Prognosis, response to therapy
Urokinase-type plasminogen activator	Breast	Recurrence
PAI-1, PAI-2		Recurrence
Cathepsin B and L	Breast	Recurrence
Cyclin D1	Ovarian	Prognosis, recurrence
ICTP	Ovarian	Prognosis, stage
β -2 microglobulin	Multiple myeloma and lymphoma	Prognosis
Caspase-3	Gastric carcinoma	Prognostic
EZH2	Prostate	Recurrence
Vimentin	Kidney	Prognosis
Myc and A1B1	Hepatocellular carcinoma	Prognosis
SELDI pattern	Ovarian cancer	Diagnosis, prognosis, stage

Sources: Chatterjee SK, Zetter BR. Cancer biomarkers: knowing the present and predicting the future. *Future Oncology*. 2005;1. *Practice of Oncology*. 5th ed. Philadelphia: JB Lippincott Co; 1997. Reprinted with permission.

A number of new research areas hold great promise for developing new tumor markers that can be used to screen asymptomatic individuals for common cancers, to better predict response to various cancer therapies, and to help tailor cancer therapies for individual patients.⁹ These new areas involve microarray and Serial Analysis of Gene Expression (SAGE) technology to search for differential gene expression, particularly overexpression of various genes such as BRCA1 and MDA435 in breast cancer cells.⁹ The new field of proteomics is also promising. This field of research uses two-dimensional electrophoresis and mass spectrometry to detect differentially expressed proteins in malignant and normal cells.⁹

Cancer Staging

A powerful predictor of recurrent disease and length of survival is the extent to which the patient's disease has become locally invasive, has spread to adjacent organs, or shows evidence of already having spread to distant organs, including bones, the liver, the lungs, and the central nervous system. The clinician will utilize the results of the clinical examination of the patient, observations obtained during surgical intervention, and the results of the pathologist's report to determine the extent of disease at the time of diagnosis. Determining the extent of disease is referred to as *cancer staging*. A number of special imaging tests may also be performed to discover if the cancer has spread into organs such as the liver or into a bone. The information gained is then used to categorize the patient's stage of disease at the time of diagnosis.

Tumor staging systems range from simple to sophisticated. The simpler systems include categories for in situ cancers (tumors limited to the first layer of epithelial cells), invasive cancers that are still restricted to the original primary site, invasive cancers that have spread to adjacent organs, and cancers that have already metastasized at the time of diagnosis. A more sophisticated and widely used system is the TNM system, where *T* stands for the size of the tumor, *N* stands for the extent of regional lymph node involvement, and *M* stands for evidence of metastases. The TNM system was developed jointly by the International Agency for Research on Cancer (IARC) and the American Joint Committee on Cancer (AJCC).¹¹ Data are extracted from the patient's record for each of the three variables and entered into an algorithm developed for each tumor type. The contributions of the three variables are combined to create a final stage for the tumor.

An example of the TNM staging process is presented in Exhibit 2-1, which shows the definitions that are applied to the individual staging components of tumor size, nodal involvement, and evidence of distant metastases for patients with primary cancers of the breast. The exhibit also

EXHIBIT 2-1
TNM STAGING FOR BREAST CARCINOMA

Primary Tumor (T)

TX	Primary tumor cannot be assessed
TO	No evidence of primary tumor
Tis	Carcinoma in situ: intraductal carcinoma, lobular carcinoma in situ, or Paget's disease of the nipple with no tumor
T1	Tumor 2 cm or less in greatest dimension
T1a	0.5 cm or less in greatest dimension
T1b	More than 0.5 cm, but not more than 1 cm in greatest dimension
T1c	More than 1 cm, but not more than 2 cm in greatest dimension
T2	More than 2 cm, but not more than 5 cm in greatest dimension
T3	Tumor more than 5 cm in greatest dimension
T4	Tumor of any size with direct extension to chest wall or skin
T4a	Extension to chest wall
T4b	Edema (including peau d'orange) or ulceration of the skin of breast or satellite skin nodules confined to same breast
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed (e.g., previously removed or not removed for pathologic study)
N0	No regional lymph node metastasis
N1	Metastasis to movable ipsilateral axillary lymph node(s)
N1a	Only micrometastasis, none larger than 0.2 cm
N1b	Metastasis to lymph node(s), any larger than 0.2 cm
N1bi	Metastasis in 1 to 3 lymph nodes, any more than 0.2 cm and all less than 2 cm in greatest dimension
N1bii	Metastasis to 4 or more lymph nodes, any more than 0.2 cm and all less than 2 cm in greatest dimension
N1biii	Extension of tumor beyond the capsule of a lymph node metastasis less than 2 cm in greatest dimension
N1biv	Metastasis to a lymph node 2 cm or more in greatest dimension
N2	Metastasis to ipsilateral axillary lymph nodes that are fixed to one another or to other structures
N3	Metastasis to ipsilateral internal mammary lymph node(s)

Distant Metastasis (M)

MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis (includes metastasis to ipsilateral supraclavicular lymph node(s))

EXHIBIT 2-1
TNM STAGING FOR BREAST CARCINOMA (Continued)

Stage Grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	Any N	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

Source: Greene FL, Page DL, Fleming ID, et al. *AJCC Cancer Staging Manual*, 6th edition (2002) published by Springer Publishing, New York.

shows how various combinations of these individual components are translated into a final stage at diagnosis.

Exhibit 2-2 presents an example of how a breast cancer patient's medical history is converted into an appropriate TNM stage.

In addition to general systems, such as the TNM, specialized systems have been developed for certain tumors. These include the Dukes System for staging cancers of the colon and rectum,¹² the Columbia system for breast cancers,¹³ and the International Federation of Gynecologists and Obstetricians (FIGO) system for staging tumors of the female reproductive organs.¹⁴ Tumors that are not locally invasive represent the most curable form of a malignancy and present ideal targets for early detection programs. A number of screening techniques for tumors have been developed, including cytological testing for early cancer of the uterine cervix and mammographic screening for early breast cancer. Early detection and prompt treatment of cancer of the uterine cervix is associated with a better than 90% five-year survival rate.^{15(p139)} Conversely, lesions that are not discovered early continue to grow, invade local tissues, and sometimes metastasize, and patients with undetected lesions have significantly decreased survival rates.

EXHIBIT 2-2**EXAMPLE OF HOW A BREAST CANCER PATIENT'S MEDICAL HISTORY IS CONVERTED INTO AN APPROPRIATE TNM STAGE****Case History**

A 52-year-old, postmenopausal, previously healthy woman visited her family physician after detecting a lump in her right breast. Upon questioning she stated she felt otherwise well. She denied having any pain or discharge from the nipple. On examination the physician noted a nontender, mobile, firm mass, approximately 3 cm in diameter, adjacent to the areola at "10 o'clock." In addition, two nontender and movable enlarged lymph nodes were palpated in the right axillary region. The left breast and axilla were normal on examination. Enlarged lymph nodes were not detected elsewhere, nor was the liver found to be enlarged. Physical examination was otherwise unremarkable and the patient appeared healthy. Subsequent mammography revealed a singular mass, 2.5 cm in greatest diameter, with irregular borders and microcalcifications. No abnormalities were detected in the left breast. Fine-needle biopsy of the mass showed infiltrating intraductal carcinoma. Nuclear bone scanning for metastases was negative, as was a CT scan of the chest and abdomen. Modified radical mastectomy with axillary lymph node dissection was performed. Adjuvant chemotherapy and radiotherapy was initiated. Histologic examination revealed moderately well-differentiated, infiltrating papillary ductal carcinoma. Blood vessel and lymphatic invasion was noted. Surgical margins were free of tumor cells. Metastatic tumor growth was found in three axillary lymph nodes. Tests for cancer cell hormone receptors were positive.

Staging by TNM Classification

I. Clinical-Diagnostic Classification. The tumor was palpated as being more than 2 cm but less than 5 cm in greatest diameter and was mobile, indicating no fixation to the underlying pectoral fascia and/or muscle (T2a). The enlarged lymph nodes were movable and nontender, suggesting tumor growth rather than inflammatory reaction (N1a). Clinical workup did not detect any distant metastases (M0). Thus the overall clinical-diagnostic TNM classification is T2aN1aM0, which represents Stage II disease.

II. Postsurgical Treatment-Pathological Classification. At operation the tumor was found to be 2.5 cm in maximum diameter and was not fixated to the pectoral fascia or muscle (T2a). The enlarged axillary lymph nodes were not fixated to one another or to the surrounding structures, but gross metastatic carcinoma was evident (N1b). No evidence of distant metastases was found (M0). Surgical margins were free of tumor growth (R0). The tumor was found to be moderately well-differentiated (G2). Thus the overall pathological TNM classification is T2aN1bM0R0G2, representing Stage II disease.

Classification of Neoplasms

Neoplasms are usually classified according to the type of tissue in which the tumor first develops and the anatomic site of the tumor within the body. Neoplasms that arise from the epithelial tissues are referred to as carcinomas, whereas neoplasms that arise from the connective tissues, such as bone, muscle, and fibrous tissues, are referred to as sarcomas. Tumors of epithelial origin constitute approximately 90% of all cancers, while sarcomas are relatively rare, representing only 2% of all cancers. In addition, approximately 8% of all cancers are classified as leukemias (malignancies of the hematopoietic system) or lymphomas (malignancies of the lymphatic system).^{1(p17)}

Histological classification may further specify the type of epithelial or connective tissue in terms of either function or morphology. A tumor originating in glandular tissue would be classified as an adenocarcinoma, implying a tumor of epithelial origin whose cells normally perform an excretory function. Classification of a tumor as a papillary carcinoma implies an epithelial tumor that exhibits fingerlike projections when viewed under the microscope. A connective tissue tumor that originates in bone would be classified as an osteogenic sarcoma.

The term for a neoplasm that has the appearance of originating from embryonic tissues is given the suffix *-blastoma*. Examples include *neuroblastoma* (for neural tumors) and *retinoblastoma* (for ocular tumors). The term for a type of tumor might include the name of the scientist who first reported the cancer in the medical literature. Examples include *Hodgkin's disease*, which refers to a tumor of the lymphatic system; *Wilms' tumor*, which refers to a childhood cancer; and *Kaposi's sarcoma*, the name of a cancer that has reached epidemic proportions in AIDS patients within the past decade.¹⁶

For instance, acute leukemias involving the lymphocytes can be subtyped as originating from either T or B lymphocytes. Further subtyping of the T- and B-cell acute lymphocytic leukemias can be accomplished by special laboratory tests that measure cell surface antigens.^{6(pp266-268)} Some enzymes and gene arrangements cancers exhibit a mixture of different cell types within the same tumor. Cancers of the central nervous system include a spectrum of tumors that develop in the astrocytes (supporting cells of the central nervous system), the ependymal cells (which line the ventricles of the brain and spinal cord), and cells that make up the meninges (the covering of the brain).¹⁷ Tumors of the brain and nervous system may be composed of a specific cell type or as a mixture of cells. Mixed cellularity also occurs in tumors of other anatomic sites, such as adenosquamous carcinomas of the vagina, which contain both glandular and squamous cell components.

44 FUNDAMENTALS OF CANCER EPIDEMIOLOGY

Neoplasms are also classified according to the primary anatomic site within the body where the tumor first appeared. Combining the histological and anatomic terminology, a breast tumor of the glandular epithelium with fingerlike projections might be described as a *papillary adenocarcinoma of the breast*. A number of disease coding systems have been utilized to incorporate various aspects of cancer classification. For several decades, cancer registries around the world have stored incidence data in computerized form using various versions of the International Classification of Disease (ICD) coding system.¹⁸ The ICD provides a detailed coding system based on the first or primary anatomic site of the tumor. The organ within which the cancer first developed is assigned a three-digit code ranging from 140 through 208 for malignant neoplasms, 210 through 229 for the benign neoplasms, and 230 through 239 for in situ tumors and tumors of uncertain or unspecified behavior. A cancer of the large intestine, for instance, would be assigned the code number 153 for anatomic site. A fourth digit is available to provide further specification of the tumor's location within the organ. A cancer originating within the ascending colon would be assigned the four-digit code 153.6.

As new versions of the ICD have been developed, registries have developed transmutation tables to allow researchers to equate older and newer codes for particular sites and thus extract computerized data for cancers of a particular anatomic site over several decades. Because the ICD codes for many cancers have not changed substantially from the 7th through the 9th revision, it is possible to conduct epidemiological analyses of long-term time trends for these cancers. However, there have been significant changes in the 10th revision of the classification system, which makes extension of these time trend analyses more difficult.¹⁹ In addition, ICD codes are used for identifying cause of death, and therefore cancer mortality data can be easily extracted from vital records systems for analysis and comparison with incidence data.

IARC has developed an International Classification of Diseases for Oncology (ICD-O), which provides codes to indicate the anatomic site of origin, the histological classification of the tumor, and the tumor behavior (benign, uncertain or unknown behavior, in situ neoplasms, malignant neoplasms of primary origin, and malignant neoplasms of secondary origin).²⁰ As an example, the anatomic site codes for cancers of the colon are shown in Table 2-4. A malignant adenocarcinoma of the ascending colon would be coded as C18.2 by anatomic site (Table 2-4) and M-8140/3 for histology. The digit 3 after the slash indicates that the behavior of this tumor is considered to be malignant and primary in origin. Data are generally stored in population-based cancer registries using the ICD and ICD-O coding systems.

TABLE 2-4 International Classification of Disease for Oncology, 2nd Revision, Codes for Cancers of the Colon

<i>Anatomic site</i>	<i>Site code</i>
Malignant neoplasm of the colon	C18.0
Cecum	C18.0
Appendix	C18.1
Ascending colon	C18.2
Hepatic flexure	C18.3
Transverse colon	C18.4
Splenic flexure	C18.5
Descending colon	C18.6
Sigmoid colon	C18.7
Overlapping lesions of the colon	C18.8
Colon, unspecified	C18.9

Source: World Health Organization, 1990. Reprinted with permission.

Case Identification Problems and Epidemiological Research

Epidemiological research studies that are designed to identify risk factors for a particular cancer need to aggregate data according to the primary site of the cancer rather than the secondary sites of metastases. Possible confusion between primary and secondary cancers varies according to anatomic site, and distinguishing true multiple primary cancers from metastatic cancers is often quite difficult. In North America and Europe, where primary liver cancers are rare but where the liver is a frequent site of metastases for other primary site cancers, separating the small number of primary liver cancers from those that represent metastatic spread is hard to do.

The degree of difficulty encountered when attempting to determine the primary anatomic site of a patient's cancer varies widely. Brain cancers, for example, can occur in physical locations in which any attempt to obtain a biopsy specimen is likely to cause harm to the patient. An epidemiologist who designs a case-control study of malignant central nervous system tumors might therefore elect to eliminate cases without histological confirmation. However, the decision to eliminate these cases, because their number is likely to be large, could result in selection bias. For example, extreme levels of a particular carcinogenic agent may be more strongly associated with advanced cancers than with early stage cancers. These high levels of exposure may increase the chances of developing cancers of the central nervous system and may also lead to more rapid tumor growth in those who do develop such cancers. Consequently, excluding advanced cancers could lead to an underestimate of the strength of the association between the carcinogen and cancers of the central nervous system. An alternative

46 FUNDAMENTALS OF CANCER EPIDEMIOLOGY

approach would be to have an expert neurologist review the clinical and radiological evidence as a basis for placing these clinically diagnosed tumors into several categories, such as “probably malignant,” “possibly malignant,” and “probably benign.” Separate analyses of standard risk factors could be conducted for the histologically confirmed cases and the various clinical groups defined previously. Similarity of findings in these subgroups would provide some assurance that a combined analysis of histologically confirmed and clinically diagnosed cases was warranted.

Difficulties also arise when the clinical course of the cancer tends to be silent and local or distant metastases have occurred in a large percentage of cases. As regards ovarian cancer, 54% of women younger than age 50 and 77% of women aged 50 and older are diagnosed with tumors that have already spread beyond the original primary site into adjacent or distant organs.¹⁵ In this instance, it is often difficult to determine the primary site of the cancer, and the epidemiologist may inadvertently include cases in which the primary cancer is not ovarian. A process similar to that used for central nervous system tumors can be utilized to manage this source of case heterogeneity.²¹

A related problem faces the epidemiologist who is interested in not only identifying risk factors for a specific primary site of cancer but also analyzing separately the histological subtypes that exist for that primary site. For a number of cancers, the determination of a specific cell type is relatively straightforward, and the investigator is probably justified in accepting the histological diagnoses reported by the individual hospital pathologists. However, there are other cancers, such as central nervous system tumors, ovarian cancers, and lymphomas, in which histological classification is more problematic. For epidemiological case-control studies, the investigator usually selects potential cases from the tumor registry or hospital discharge lists based on the ICD or ICD-O codes. However, the histological subtype of these tumors may be difficult to determine, and there is often disagreement among pathologists concerning proper classification. It is not uncommon for the epidemiologists to obtain representative pathologic slides from the hospital in which the diagnosis occurred for each cancer case identified from the cancer registry or hospital discharge files. These slides are then reviewed by an expert pathologist or panel of pathologists, who classify the histological subtypes of the tumors using special classification systems developed for these cancers. This process helps to standardize the histological diagnoses within the case series and decreases the possibility of misclassification.

Summary

Malignant and benign neoplasms are dissimilar in terms of degree of differentiation, rate of growth, mode of growth, ability to metastasize,

response to therapy, and eventual prognosis. Local invasion and metastases involve many complicated biological adaptations by the cancer cells, including angiogenesis, clonal selection, and the production of specialized enzymes. Cancers are classified on the basis of the initial anatomic location of the primary tumor and the histological features of the tumor cells. Classifying cancers according to the degree of differentiation of the tumor cells and the initial stage of the cancer at diagnosis provides important indicators of the prognosis following treatment. Anatomical and histological classification systems for categorizing tumors also have an important impact on the use of routinely collected cancer data in epidemiological research.

DISCUSSION QUESTIONS

1. Discuss the basic differences between benign and malignant neoplasms.
2. Discuss the pathologic features of malignant neoplasms in terms of various structural differences between normal cells and cancer cells.
3. Discuss the various components of the TNM tumor staging system and how these components are combined to create a summary cancer stage for each patient.
4. Discuss various ways in which tumor markers are used in cancer medicine.
5. Discuss the basic biological concepts involving angiogenesis.
6. Discuss the anatomic and histologic classification systems that are used to code benign and malignant neoplasms.
7. Discuss the process of spread of cancer through distant metastasis.

References

1. Wills RA. *The Spread of Tumors in the Human Body*. London: Butterworth & Co; 1952.
2. Franks, LM. What is cancer? In: Franks LM, Teich NM, eds. *Introduction to the Cellular and Molecular Biology of Cancer*. 3rd ed. New York: Oxford University Press; 1997:1–20.
3. Cotran RS, Kumar V, Robbins SL. *Robbins Pathologic Basis of Disease*. 5th ed. Philadelphia: WB Saunders Co; 1994.
4. Varmus H, Weinberg RA. *Genes and the Biology of Cancer*. New York: WH Freeman & Co; 1993:39–42.
5. Fidler IJ. Molecular biology of cancer: invasion and metastasis. In: DeVita VT, Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*. 5th ed. Philadelphia: JB Lippincott Co; 1997:135–152.

48 FUNDAMENTALS OF CANCER EPIDEMIOLOGY

6. Folkman J. Tumor angiogenesis. In: Bast RC, Kufe DW, Pollack RE, et al., eds. *Cancer Medicine*. 5th ed. London: BC Decker; 2000:132–152.
7. Lemoine NR, Stamp GWH. The molecular pathology of cancer. In: Franks LM, Teich NM, eds. *Introduction to the Cellular and Molecular Biology of Cancer*. 3rd ed. New York: Oxford University Press; 1997:343–352.
8. Sklar JL, Costa J. Principles of cancer management. In: DeVita VT, Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*. 5th ed. Philadelphia: JB Lippincott Co; 1997:259–284.
9. Chatterjee SK, Zetter BR. Cancer biomarkers: knowing the present and predicting the future. *Future Oncology*. 2005;1:37–50.
10. Nayfield SG, Karp JE, Ford LG, et al. Potential role of tamoxifen in prevention of breast cancer. *J Natl Cancer Inst*. 1991;83:1450–1459.
11. Sobin LH, Wittekind C, eds. *TNM Classification of Malignant Tumours*. 5th ed. New York: John Wiley & Sons; 1997.
12. Dukes CE. Discussion on major surgery on carcinoma of the rectum, with or without colostomy, excluding the anal canal and including the rectosigmoid. *Proc R Soc Med*. 1957;50:1031–1035.
13. Miller EB. Five-year review of carcinoma of the breast: analysis according to Columbia Classification. *Ann Surg*. 1966;163:4:629–633.
14. International Federation of Gynecology and Obstetrics. Announcements: FIGO Stages—1988 revision. *Gynecol Oncol*. 1989;35:125–127.
15. Ries LAG, Miller BA, Kosary CL, Harras A, Edwards BK, eds. *SEER Cancer Statistics Review, 1973–1991: Tables and Graphs, National Cancer Institute*. Bethesda, MD: National Institutes of Health; 1994. Pub. No. 94-2789.
16. Cooper GM. *Elements of Human Cancer*. Boston: Jones & Bartlett Publishers; 1992.
17. Kleihues P, Burger PC, Scheithauer BW, in collaboration with LH Sobin and pathologists in 14 countries. *Histological Typing of Tumours of the Central Nervous System*. 2nd ed. Berlin: Springer-Verlag; 1993.
18. World Health Organization (WHO). *The International Classification of Diseases*. 10th Revision. Vol 1. Geneva: World Health Organization; 1992.
19. World Health Organization (WHO). *International Statistical Classification of Diseases and Related Health Problems*. 10th Revision. Geneva: World Health Organization; 1992.
20. Percey C, Van Holten V, Muir C, eds. *International Classification of Diseases for Oncology (ICD-O)*. 2nd ed. Geneva: World Health Organization; 1990.
21. Nasca PC, Greenwald P, Chorost S, et al. An epidemiologic case-control study of ovarian cancer and reproductive factors. *Am J Epidemiol*. 1984;119:705–713.