later). What then can be said about the influence of heredity on sporadic malignant neoplasms, which constitute roughly 95% of cancers in the United States? While the evidence suggests that these cancers are largely attributable to environmental factors or acquired predisposing conditions, lack of family history does not preclude an inherited component. It is generally difficult to sort out the hereditary and nonhereditary contributions because these factors often interact. The interaction between genetic and nongenetic factors is particularly complex when tumor development depends on the action of multiple contributory genes. Even in tumors with a well-defined inherited component, the risk of developing the tumor can be greatly influenced by nongenetic factors. For instance, breast cancer risk in females who inherit mutated copies of the *BRCA1* or *BRCA2* tumor suppressor genes (discussed later) is almost threefold higher for women born after 1940 than for women born before that year, perhaps because of changes in reproductive history. Furthermore, genetic factors can significantly influence the likelihood of developing environmentally induced cancers. Inherited variations (polymorphisms) of enzymes that metabolize procarcinogens to their active carcinogenic forms can influence cancer susceptibility. Of interest in this regard are genes that encode the cytochrome P-450 enzymes. As discussed later, a polymorphism in one of the P-450 loci confers an inherited susceptibility to lung cancers in cigarette smokers. More associations of this type are likely to be found.

KEY CONCEPTS

Epidemiology of Cancer

- The incidence of cancer varies with geography, age, race, and genetic background. Cancers are most common in adults older than 60 years of age, but occurs in adults at all ages and in children and infants. The geographic variation is thought to mainly stem from different environmental exposures.
- Important environmental factors implicated in carcinogenesis include infectious agents, smoking, alcohol, diet, obesity, reproductive history, and exposure to environmental carcinogens.
- The risk of cancer is increased by reparative proliferations caused by chronic inflammation or tissue injury, certain forms of hyperplasia, and immunodeficiency.
- Interactions between environmental factors and genetic factors may be important determinants of cancer risk.

Molecular Basis of Cancer: Role of Genetic and Epigenetic Alterations

Evidence for the genetic origins of cancer have been building up for over several decades. However, a full accounting of the extent of these genetic aberrations is only now coming to light, made possible by technologic advances in DNA sequencing and other methods that permit genome-wide analysis of cancer cells. The complexity of these data is daunting and the messages hidden within them have yet to be fully decoded, but certain "genomic themes" have emerged that are likely relevant to every cancer.

- **Nonlethal genetic damage lies at the heart of carcinogenesis.** The initial damage (or mutation) may be caused by environmental exposures, may be inherited in the germline, or may be spontaneous and random, falling into the category of "bad luck." The term environmental, used in this context, refers to any acquired mutation caused by exogenous agents, such as viruses or environmental chemicals, or by endogenous products of cellular metabolism.
- **A tumor is formed by the clonal expansion of a single precursor cell that has incurred genetic damage (i.e., tumors are clonal).** Alterations in DNA are heritable, being passed to daughter cells, and thus all cells within an individual tumor share the same set of mutations that were present at the moment of transformation. Such tumor-specific mutations are most often identified by DNA sequencing (e.g., point mutations) or by chromosomal analyses (e.g., chromosomal translocations and copy number changes, discussed later).
- **Four classes of normal regulatory genes—the growth-promoting proto-oncogenes, the growth-inhibiting tumor suppressor genes, genes that regulate programmed cell death (apoptosis), and genes involved in DNA repair—are the principal targets of cancer-causing mutations.** Mutations that activate *proto-oncogenes* generally cause an excessive increase in one of more normal functions of the encoded gene product, or sometimes impart a completely new function on the affected gene product that is oncogenic. Because these mutations cause a "gain-of-function," they can transform cells despite the presence of a normal copy of the same gene. Thus, in genetic parlance, oncogenes are dominant over their normal counterparts. Mutations that affect *tumor suppressor genes* generally cause a "loss-of-function," and in most instances both alleles must be damaged before transformation can occur. Thus, mutated tumor suppressor genes usually behave in a recessive fashion. However, there are exceptions: sometimes loss of only a single tumor suppressor gene allele (a state termed *haploinsufficiency*) reduces the activity of the encoded protein enough to release the brakes on cell proliferation and survival. Such a finding indicates that two "doses" of the gene are essential for normal function. *Apoptosis-regulating genes* may acquire abnormalities that result in less death and, therefore, enhanced survival of the cells. These abnormalities include gain-of-function mutations in genes whose products suppress apoptosis and loss-of-function mutations in genes whose products promote cell death. Loss-of-function mutations affecting *DNA repair genes* contribute to carcinogenesis indirectly by impairing the ability of the cell to recognize and repair nonlethal genetic damage in other genes. As a result, affected cells acquire mutations at an accelerated rate, a state referred to as a *mutator phenotype* that is marked by *genomic instability.*
- **Carcinogenesis results from the accumulation of complementary mutations in a stepwise fashion over time** (Fig. 7-22).
  - **Malignant neoplasms have several phenotypic attributes referred to as *cancer hallmarks*,** such as excessive growth, local invasiveness, and the ability to form distant metastases, which stem from genomic

www.PTools.ir