in clinical practice. Prostatic carcinoma can be suspected when elevated levels of PSA are found in the blood. However, PSA screening highlights problems encountered with virtually every tumor marker. Although PSA levels are often elevated in cancer, PSA levels also may be elevated in benign prostatic hyperplasia (Chapter 18). Furthermore, there is no PSA level that ensures that a person does not have prostate cancer. Thus, the PSA test suffers from both low sensitivity and low specificity, limitations discussed in detail in Chapter 18.

Other tumor markers occasionally used in clinical practice include *carcinoembryonic antigen* (CEA), which is elaborated by carcinomas of the colon, pancreas, stomach, and breast, and *alpha-fetoprotein* (AFP), which is produced by hepatocellular carcinomas, yolk sac remnants in the gonads, and occasionally teratocarcinomas and embryonal cell carcinomas. Unfortunately, like PSA, the serum levels of both of these markers can be elevated by a variety of nonneoplastic conditions as well. Thus, as with PSA, CEA and AFP assays lack both specificity and sensitivity required for the early detection of cancers, but they are useful for detection of recurrences after excision. With successful resection of the tumor, these markers disappear from the serum; their persistence or reappearance almost always signifies tumor lurking within.

Other widely used markers include *human chorionic gonadotropin* (HCG) for testicular tumors, *CA-125* for ovarian tumors, and *immunoglobulin* in multiple myeloma and other secretory plasma cell tumors. The development of tests to detect cancer markers in blood and body fluids is an active area of research, and are focused in particular on the analysis of DNA that is shed from dying tumor cells. Some of the cell-free DNAs being evaluated as tumor markers include mutated *APC, TP53,* and *RAS* sequences in the stool of individuals with colorectal carcinomas; mutated *TP53* and hypermethylated genes in the sputum of persons with lung cancer and in the saliva of persons with head and neck cancers; and mutated *TP53* in the urine of patients with bladder cancer.

With all of the advances in genomic analyses and targeted therapies, one can safely predict that we are on the cusp of the golden age of tumor diagnosis and treatment. Those of you who are in medical school now can safely assume that the expectations for rapid advances in cancer diagnosis and therapy will be realized while you are still in practice. Get ready!

KEY CONCEPTS

Laboratory Diagnosis of Cancer

- Several sampling approaches exist for the diagnosis of tumors, including excision, biopsy, fine-needle aspiration, and cytologic smears.
- Immunohistochemistry and flow cytometry studies help in the diagnosis and classification of tumors, because distinct protein expression patterns define different entities.
- Molecular analyses are used to determine diagnosis, prognosis, the detection of minimal residual disease, and the diagnosis of hereditary predisposition to cancer.
- Molecular profiling of tumors by RNA expression profiling, DNA sequencing, and DNA copy number arrays are useful in molecular stratification of otherwise identical tumors or those of distinct histogenesis that share a mutation for the purpose of targeted treatment and prognostication.
- Proteins released by tumors into the serum, such as PSA, can be used to screen populations for cancer and to monitor for recurrence after treatment.
- Assays of circulating tumor cells and of DNA shed into blood, stool, sputum, and urine are under development.

SUGGESTED READINGS

Cancer Epidemiology

de Martel C, Ferlay J, Franceschi S, et al: Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. *Lancet Oncol* 13:607–15, 2012. *[A recent analysis that estimates that approximately 16% of cancers (2 million cases per year) are attributable to infectious agents]*

Faulds MH, Dahlman-Wright K: Metabolic diseases and cancer risk. *Curr Opin Oncol* 24:58–61, 2012. *[A review focused on evidence linking metabolic disorders such obesity and diabetes to increased cancer risk]*

Liang J, Shang Y: Estrogen and Cancer. *Annu Rev Physiol* 75:225–40, 2013. *[A summary of epidemiologic evidence connecting hyperestrogenism to cancer and of current understanding of the oncogenic mechanisms of estrogen signaling]*

Roberts DL, Dive C, Renehan AG: Biological mechanisms linking obesity and cancer risk: new perspectives. *Annu Rev Med* 61:301–16, 2010. *[Discussion of possible biological processes that increase cancer risk in the obese]*

Cancer "Evolution"

Gerlinger M, Rowan AJ, Horswell S, et al: Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. *N Engl J Med* 366:883–92, 2012. *[A paper highlighting the challenges that genomic instability and genomic evolution of cancers present to molecular diagnosticians and clinicians employing targeted therapies to treat cancer]*

Greaves M, Maley CC: Clonal evolution in cancer. *Nature* 481:306–13, 2012. *[A discussion of the iterative processes of clonal expansion, genetic diversification and clonal selection that promote cancer evolution and ultimately lead to therapeutic failure]*

Ma QC, Ennis CA, Aparicio S: Opening Pandora's Box–the new biology of driver mutations and clonal evolution in cancer as revealed by next generation sequencing. *Curr Opin Genet Dev* 22:3–9, 2012. *[A review summarizing driver mutations and their roles in directing clonal patterns of tumor evolution]*

Hallmarks of Cancer

Hanahan D, Weinberg RA: Hallmarks of cancer: the next generation. *Cell* 144:646–74, 2011. *[An update of a classic paper describing the key features common to all cancers]*

Oncogenes

Cilloni D, Saglio G: Molecular pathways: BCR-ABL. *Clin Cancer Res* 18:930–7, 2012. *[A discussion of the functional consequences and clinical significance of aberrant tyrosine kinase activity in chronic myeloid leukemia mediated by the constitutive enzyme activity of BCR-ABL]*

Dang CV: MYC on the path to cancer. *Cell* 149:22–35, 2012. *[A review of the widespread oncogenic role of the transcription factor MYC in cancer]*

Pao W, Chmielecki J: Rational, biologically based treatment of EGFR-mutant non-small-cell lung cancer. *Nat Rev Cancer* 10:760–74, 2010. *[A review summarizing recent work aimed at treating and ultimately curing lung cancers associated with activating mutations in the receptor tyrosine kinase EGFR]*

Pylayeva-Gupta Y, Grabocka E, Bar-Sagi D: RAS oncogenes: weaving a tumorigenic web. *Nat Rev Cancer* 11:761–74, 2011. *[A description of how RAS oncogenes activate multiple downstream signaling pathways to drive cellular transformation and oncogenesis]*

Tumor Suppressor Genes

Goh AM, Coffill CR, Lane DP: The role of mutant p53 in human cancer. *J Pathol* 223:116–26, 2011. *[Discussion of emerging oncogenic roles of mutant p53 proteins]*