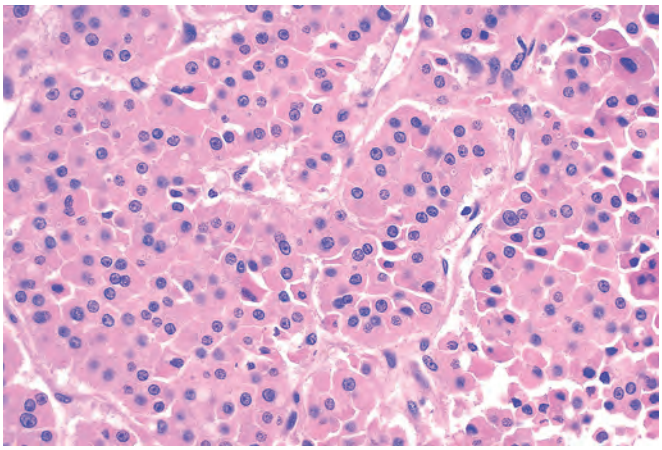

Figure 24-17 Hürthle cell (oxyphil) adenoma. A high-power view showing that the tumor is composed of cells with abundant eosinophilic cytoplasm and small regular nuclei. (Courtesy Dr. Mary Sunday, Duke University, Durham, N.C.)

the presence of an intact, well-formed capsule encircling the tumor. **Careful evaluation of the integrity of the capsule is therefore critical in distinguishing follicular adenomas from follicular carcinomas,** which demonstrate capsular and/or vascular invasion (see later). Extensive mitotic activity, necrosis, or high cellularity also warrants close inspection to exclude follicular carcinoma and the follicular variant of papillary carcinoma (see later).

Clinical Features. Many follicular adenomas present as unilateral painless masses that are discovered during a routine physical examination. Larger masses may produce local symptoms, such as difficulty in swallowing. Nonfunctioning adenomas take up less radioactive iodine than does normal thyroid parenchyma. On radionuclide scanning, therefore, nonfunctioning adenomas appear as *cold* nodules relative to the adjacent thyroid tissue. However, as many as 10% of cold nodules are malignant. Other techniques used to evaluate suspected adenomas are ultrasonography and fine-needle aspiration biopsy. **Because of the need for evaluating capsular integrity, the definitive diagnosis of adenomas can be made only after careful histologic examination of the resected specimen.** Suspected adenomas of the thyroid are therefore removed surgically to exclude malignancy. Follicular adenomas do not recur or metastasize and have an excellent prognosis.

Carcinomas

Carcinomas of the thyroid are relatively uncommon in the United States, accounting for about 1.5% of all cancers. A female predominance has been noted among patients who develop thyroid carcinoma in the early and middle adult years. In contrast, cases presenting in childhood and late adult life are distributed equally among males and females.

The major subtypes of thyroid carcinoma and their relative frequencies are as follows:

- Papillary carcinoma (>85% of cases)
- Follicular carcinoma (5% to 15% of cases)
- Anaplastic (undifferentiated) carcinoma (<5% of cases)
- Medullary carcinoma (5% of cases)

Most thyroid carcinomas (except medullary carcinomas) are derived from the thyroid follicular epithelium, and of these, the vast majority are well-differentiated lesions. Because of the unique clinical, molecular and biologic features associated with each variant of thyroid carcinoma, these subtypes are described separately. We begin with a discussion of the molecular pathogenesis of all thyroid cancers.

Pathogenesis

Genetic Factors. Distinct genetic events are involved in the pathogenesis of the four major histologic variants of thyroid cancer. As stated, medullary carcinomas do not arise from the follicular epithelium. **Genetic alterations in the three follicular cell–derived malignancies are in growth factor receptor signaling pathways (**Fig. 24-18**).** You will recall that in normal cells, these pathways are transiently activated by binding of soluble growth factor ligands to the extracellular domain of receptor tyrosine kinases, which results in autophosphorylation of the cytoplasmic domain of the receptor. This in turn sets in motion events that lead to activation of RAS and two downstream signaling arms involving MAP kinase (MAPK) and PI-3 kinase (PI3K). In thyroid carcinomas, as with many cancers (Chapter 7), gain-of-function mutations in components of these pathways lead to their constitutive activation, driving excessive cellular proliferation and increased cell survival.

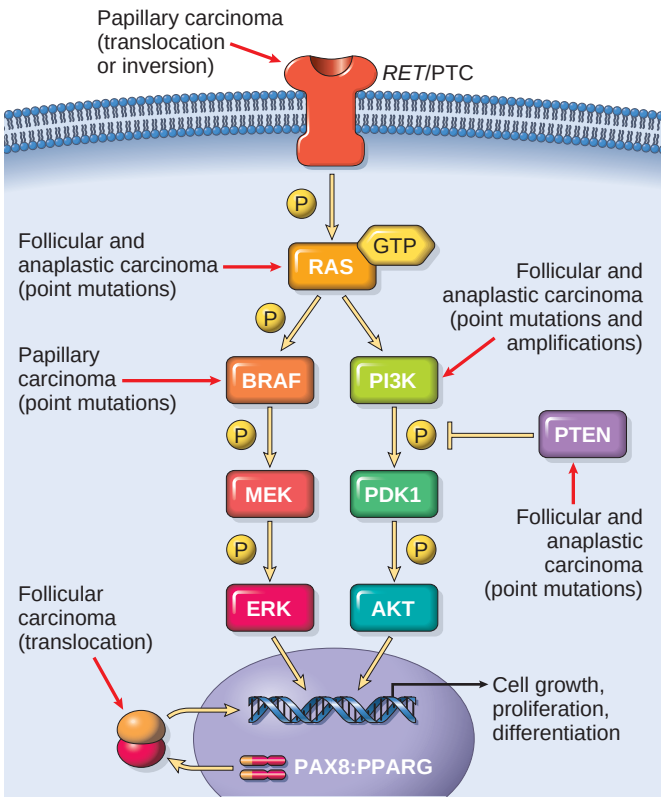

Figure 24-18 Genetic alterations in follicular cell-derived malignancies of the thyroid gland.