Papillary Carcinomas. Most papillary carcinomas have gain-of-function mutations involving the genes encoding the RET or NTRK1 receptor tyrosine kinases, or in the serine/threonine kinase BRAF, which you will recall lies in the MAPK pathway (Fig. 24-18).

- The *RET* gene is located on chromosome 10q11, and the receptor tyrosine kinase it encodes is normally not expressed in thyroid follicular cells. In papillary cancers, either a paracentric inversion of chromosome 10 or a reciprocal translocation between chromosomes 10 and 17 places the tyrosine kinase domain of RET under the transcriptional control of genes that are constitutively expressed in the thyroid epithelium. The novel fusion genes that are so formed are known as *RET/PTC* (RET/papillary thyroid carcinoma) and are present in approximately 20% to 40% of papillary thyroid cancers. There are more than 15 fusion partners of *RET*, and two—designated as *PTC1* and *PTC2*—are most commonly observed in sporadic papillary cancers. The frequency of *RET/PTC* rearrangements is significantly higher in papillary cancers arising in the backdrop of radiation exposure. The *RET/PTC* rearrangements produce genes that encode fusion proteins with constitutive tyrosine kinase activity. Similarly, paracentric inversions or translocations of *NTRK1* on chromosome 1q21 are present in 5% to 10% of papillary thyroid cancers. These genetic events also produce constitutively active NTRK1 fusion proteins.
- *BRAF* encodes an intermediate signaling component in the MAP kinase pathway. One third to one half of papillary thyroid carcinomas harbor a gain-of-function mutation in the *BRAF* gene, which is most commonly a valine-to-glutamate change in codon 600 ($BRAF^{V600E}$). The presence of *BRAF* mutations in papillary carcinomas correlates with adverse prognostic factors like metastatic disease and extrathyroidal extension. As discussed in other chapters, a similar BRAF mutation is found in some other cancers as well, including melanomas, hairy cell leukemia and a subset of colon cancers, suggesting that diverse tumors may share a similar pathway to malignancy.

Because chromosomal rearrangements of the *RET* or *NTRK1* genes and mutations of *BRAF* have redundant effects on MAP kinase signaling, it is not surprising that they are usually (but not always) mutually exclusive events. The histologic variants of papillary carcinoma demonstrate some unique characteristics vis-à-vis the frequency or nature of *BRAF* mutation (see later). Of further interest, *RET/PTC* rearrangements and *BRAF* point mutations are not observed in follicular adenomas or carcinomas.

Follicular Carcinomas. **In contrast to papillary carcinomas, follicular carcinomas are associated with acquired mutations that activate RAS or the PI-3K/AKT arm of the receptor tyrosine kinase signaling pathway.** It is evident from Figure 24-18 that activated mutations in RAS would be expected to stimulate both the MAPK and PI3K signaling pathways. Why RAS mutations produce follicular neoplasms, rather than papillary neoplasms, is not understood, a point that highlights our lack of insight into the nuances of intracellular signaling. Approximately one third to one half of follicular thyroid carcinomas harbor gain-of-function point mutations of *RAS* or *PIK3CA* (the gene that encodes PI-3 kinase), *PIK3CA* amplifications, or loss-of-function mutations of *PTEN*, a tumor suppressor gene and negative regulator of this pathway (Fig. 24-18). These genetic alterations are almost always mutually exclusive in follicular carcinomas, in line with their functional equivalence. The progressive increase in the prevalence of *RAS* and *PIK3CA* mutations from benign follicular adenomas to follicular carcinomas to anaplastic carcinomas (see later) suggests a shared histogenesis and molecular evolution among these follicular tumors.

A unique (2;3)(q13;p25) translocation has been described in one third to one half of follicular carcinomas. This translocation creates a fusion gene composed of portions of *PAX8*, a paired homeobox gene that is important in thyroid development, and the peroxisome proliferator-activated receptor gene (*PPARG*), whose gene product is a nuclear hormone receptor implicated in terminal differentiation of cells. Fewer than 10% of follicular adenomas harbor *PAX8-PPARG* fusion genes, and these have not been documented thus far in other thyroid neoplasms.

Anaplastic (Undifferentiated) Carcinomas. These highly aggressive and lethal tumors can arise de novo, or more commonly, by "dedifferentiation" of a well-differentiated papillary or follicular carcinoma. Molecular alterations present in anaplastic carcinomas include those also seen in well-differentiated carcinomas (e.g., *RAS* or *PIK3CA* mutations). Other genetic "hits," such as inactivation of *TP53* or activating mutations of β-catenin, are essentially restricted to anaplastic carcinomas and may contribute to their aggressive behavior.

Medullary Thyroid Carcinomas. Familial medullary thyroid carcinomas occur in multiple endocrine neoplasia type 2 (MEN-2, see later) and are associated with germline *RET* mutations that lead to constitutive activation of the receptor. *RET* mutations are also seen in approximately one half of nonfamilial (sporadic) medullary thyroid cancers. Chromosomal rearrangements involving *RET*, such as the *RET/PTC* translocations reported in papillary cancers, are not seen in medullary carcinomas.

Environmental Factors. The major risk factor predisposing to thyroid cancer is exposure to *ionizing radiation*, particularly during the first 2 decades of life. In keeping with this, there was a marked increase in the incidence of papillary carcinomas among children exposed to ionizing radiation after the Chernobyl nuclear disaster in 1986. *Deficiency of dietary iodine* (and by extension, an association with goiter) is linked with a higher frequency of follicular carcinomas.

Papillary Carcinoma

Papillary carcinomas are the most common form of thyroid cancer, accounting for nearly 85% of primary thyroid malignancies in the United States. They occur throughout life but most often between the ages of 25 and 50, and account for the majority of thyroid carcinomas associated with previous exposure to ionizing radiation. The diagnosis of papillary carcinoma has increased markedly in the last 30 years, partly because of the recognition of follicular variants (see later) that were misclassified in the past.