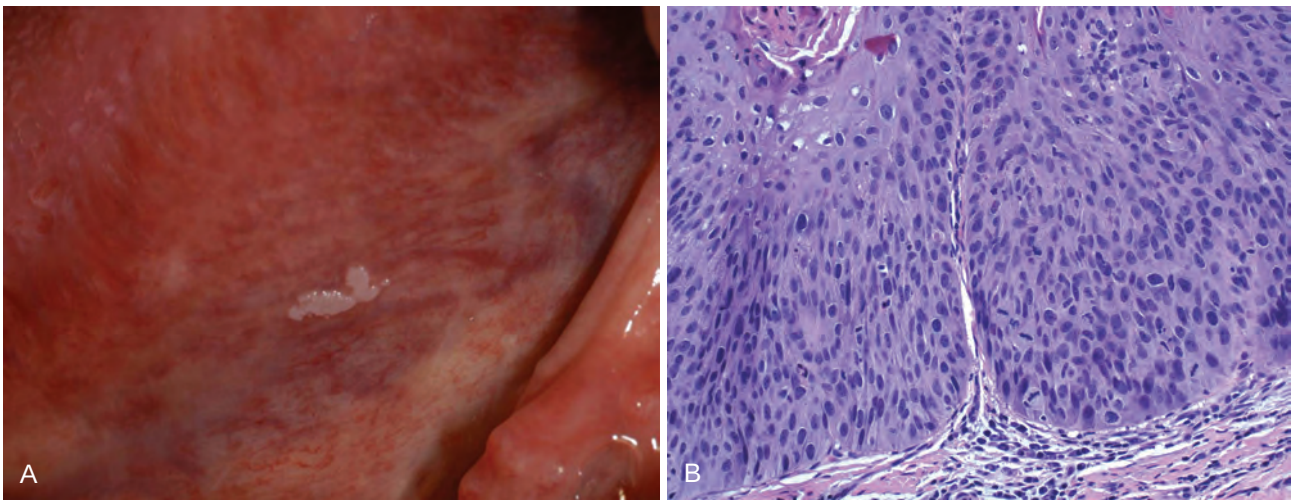

Figure 16-5 Leukoplakia. **A,** Clinical appearance of leukoplakias is highly variable. In this example, the lesion is relatively smooth and thin with well-demarcated borders. **B,** The histologic appearance of a leukoplakia showing severe dysplasia that is characterized by nuclear and cellular pleomorphism, numerous mitotic figures, and a loss of normal maturation.

The pathogenesis in this group of patients, who are nonsmokers and not infected with human papillomavirus (HPV), is unknown.

In the oropharynx, as many as 70% of SCCs, particularly those involving the tonsils, the base of the tongue, and the pharynx, harbor oncogenic variants of HPV, particularly HPV-16. HPV-associated SCC of the oropharynx has increased more than 2 -fold over the last 2 decades. It is predicted that by the year 2020, the incidence of HPV-associated head and neck SCC will surpass that of cervical cancer, in part because the anatomic sites of origin (tonsillar crypts, base of tongue, and oropharynx) are not readily accessible or amenable to cytologic screening (unlike the cervix) for premalignant lesions. Conversely, it should be noted that, unlike the oropharynx, HPV-associated SCC of the oral cavity is relatively uncommon.

Survival is dependent on a number of factors including the specific etiology of SCC. The 5-year survival rate of "classic" (smoking and alcohol related) early-stage SCC is approximately 80%, while survival drops to 20% for late-stage disease. Patients with HPV-positive SCC have greater long-term survival than those with HPV-negative tumors. The dismal outlook for the classic SCC is due to several factors, including the fact that the tumors are often diagnosed when the disease has already reached an advanced stage. Furthermore, the frequent development of multiple primary tumors markedly decreases survival. The rate of second primary tumors in these patients has been reported to be 3% to 7% per year, which is higher than for any other malignancy. This observation has led to the concept of "field cancerization," which postulates that multiple individual primary tumors develop independently in the upper aerodigestive tract as a result of years of chronic exposure of the mucosa to carcinogens. Because of such field cancerization, an individual who is fortunate to live 5 years after the detection of the initial primary tumor has an almost 35% chance of developing at least one new primary tumor within that period of time. An alternative hypotheses to explain multiple "primary" tumors is that they are actually intraepithelial metastases. The occurrence of new tumors can be particularly devastating for individuals whose initial lesions were small. The 5-year survival rate for the first primary tumor is considerably better than 50%, but in such individuals, second primary tumors are the most common cause of death. Therefore, the early detection of all premalignant lesions is critical for the long-term survival of these patients. Finally, the HPV vaccine, which is protective against cervical cancer, offers hope to stem the tide of HPV-associated head and neck SCC. Although clinical trails are ongoing, the vaccine has not yet been approved for this use.

Molecular Biology of Squamous Cell Carcinoma. As with other cancers, **the development of SCC is driven by the accumulation of mutations and epigenetic changes that alter the expression and function of oncogenes and tumor suppressor genes, leading to acquisition of cancer hallmarks (Chapter 7), such as resistance to cell death, increased proliferation, induction of angiogenesis, and the ability to invade and metastasize.** Deep sequencing of the classic SCC subset has revealed a large number of genetic alterations that bear a molecular signature consistent with tobacco carcinogen induced cancers (Fig. 16-6). These mutations frequently involve the p53 pathway as well as proteins responsible for the regulation of squamous differentiation, such as p63 and NOTCH 1. Conversely, HPV-associated SCCs contain far fewer and different genetic alterations and typically overexpress p16, a cyclin-dependent kinase inhibitor. In addition, owing to the expression of the HPV oncoproteins E6 and E7, there is inactivation of the p53 and RB pathways in much the same way as has been observed in cervical cancer (Chapter 22).

While the model outlined in Figure 16-6 is an acceptable working draft of the clinical, histologic, and molecular changes involved in development of carcinogen-induced SCC, it does not reflect the natural history of the disease for all lesions. Data regarding the incidence and timing of these changes in oral premalignancy are limited. Furthermore, it is not clear whether any of the genotypic changes, used individually or in a panel, can consistently predict which dysplastic lesions will progress to oral SCC. To complicate the matter further, SCC progression does not always occur in a linear fashion over a uniform period of time. Rather, there are subsets of lesions with histologic evidence of dysplasia that may or may not progress to