by split-thickness skin grafts. Surgery cannot remove all at-risk nevus cells, as some may penetrate into the muscles or central nervous system (CNS) below the nevus. Small- to medium-size congenital melanocytic nevi affect approximately 1% of persons; the risk of melanoma developing in these lesions is not known but appears to be relatively low. The management of small- to medium-size congenital melanocytic nevi remains controversial.

Personal and Family History Once diagnosed, patients with melanoma require a lifetime of surveillance because their risk of developing another melanoma is 10 times that of the general population. First-degree relatives have a higher risk of developing melanoma than do individuals without a family history, but only 5–10% of all melanomas are truly familial. In familial melanoma, patients tend to be younger at first diagnosis, lesions are thinner, survival is improved, and multiple primary melanomas are common.

Genetic Susceptibility Approximately 20–40% of cases of hereditary melanoma (0.2–2% of all melanomas) are due to germline mutations in the cell cycle regulatory gene cyclin-dependent kinase inhibitor 2A (*CDKN2A*). In fact, 70% of all cutaneous melanomas have mutations or deletions affecting the *CDKN2A* locus on chromosome 9p21. This locus encodes two distinct tumor-suppressor proteins from alternate reading frames: p16 and ARF ($p14^{ARF}$). The p16 protein inhibits CDK4/6-mediated phosphorylation and inactivation of the retinoblastoma (RB) protein, whereas ARF inhibits MDM2 ubiquitin-mediated degradation of p53. The end result of the loss of *CDKN2A* is inactivation of two critical tumor-suppressor pathways, RB and p53, which control entry of cells into the cell cycle. Several studies have shown an increased risk of pancreatic cancer among melanoma-prone families with *CDKN2A* mutations. A second high-risk locus for melanoma susceptibility, *CDK4*, is located on chromosome 12q13 and encodes the kinase inhibited by p16. *CDK4* mutations, which also inactivate the RB pathway, are much rarer than *CDKN2A* mutations. Germline mutations in the melanoma lineage-specific oncogene microphthalmia-associated transcription factor (*MITF*) predispose to both familial and sporadic melanomas.

The melanocortin-1 receptor (*MC1R*) gene is a moderate-risk inherited melanoma susceptibility factor. Solar radiation stimulates the production of melanocortin (α-melanocyte-stimulating hormone [α-MSH]), the ligand for *MC1R*, which is a G-protein-coupled receptor that signals via cyclic AMP and regulates the amount and type of pigment produced. *MC1R* is highly polymorphic, and among its 80 variants are those that result in partial loss of signaling and lead to the production of red/yellow pheomelanins, which are not sun-protective and produce red hair, rather than brown/black eumelanins that are photoprotective. This red hair color (RHC) phenotype is associated with fair skin, red hair, freckles, increased sun sensitivity, and increased risk of melanoma. In addition to its weak UV shielding capacity relative to eumelanin, increased pheomelanin production in patients with inactivating polymorphisms of *MC1R* also provides a UV-independent carcinogenic contribution to melanomagenesis via oxidative damage.

A number of other more common, low-penetrance polymorphisms that have small effects on melanoma susceptibility include other genes related to pigmentation, nevus count, immune responses, DNA repair, metabolism, and the vitamin D receptor.

PREVENTION AND EARLY DETECTION

Primary prevention of melanoma and nonmelanoma skin cancer (NMSC) is based on protection from the sun. Public health initiatives, such as the SunSmart program that started in Australia and now is operative in Europe and the United States, have demonstrated that behavioral change can decrease the incidence of NMSC and melanoma. Preventive measures should start early in life because damage from UV light begins early despite the fact that cancers develop years later. Biological factors are increasingly being understood, such as tanning addiction, which is postulated to involve stimulation of reward centers in the brain involving dopamine pathways, and cutaneous secretion of β-endorphins after UV exposure, and may represent another area for preventive intervention. Regular use of broad-spectrum sunscreens that block UVA and UVB with a sun protection factor (SPF) of at least 30 and protective clothing should be encouraged. Avoidance of tanning beds and midday (10:00 A.M. to 2:00 P.M.) sun exposure is recommended.

Secondary prevention comprises education, screening, and early detection. Patients should be educated in the clinical features of melanoma (ABCDEs; see following "Diagnosis" section) and advised to report any growth or other change in a pigmented lesion. Brochures are available from the American Cancer Society, the American Academy of Dermatology, the National Cancer Institute, and the Skin Cancer Foundation. Self-examination at 6- to 8-week intervals may enhance the likelihood of detecting change. Although the U.S. Preventive Services Task Force states that evidence is insufficient to recommend for or against skin cancer screening, a full-body skin exam seems to be a simple, practical way to approach reducing the mortality rate for skin cancer. Depending on the presence or absence of risk factors, strategies for early detection can be individualized. This is particularly true for patients with clinically atypical moles (dysplastic nevi) and those with a personal history of melanoma. For these individuals, surveillance should be performed by the dermatologist and include total-body photography and dermoscopy where appropriate. Individuals with three or more primary melanomas and families with at least one invasive melanoma and two or more cases of melanoma and/or pancreatic cancer among first- or second-degree relatives on the same side of the family may benefit from genetic testing. Precancerous and in situ lesions should be treated early. Early detection of small tumors allows the use of simpler treatment modalities with higher cure rates and lower morbidity.

DIAGNOSIS

The main goal is to identify a melanoma before tumor invasion and life-threatening metastases have occurred. Early detection may be facilitated by applying the ABCDEs: *a*symmetry (benign lesions are usually symmetric); *b*order irregularity (most nevi have clear-cut borders); *c*olor variegation (benign lesions usually have uniform light or dark pigment); *d*iameter >6 mm (the size of a pencil eraser); and *e*volving (any change in size, shape, color, or elevation or new symptoms such as bleeding, itching, and crusting). Benign nevi usually appear on sun-exposed skin above the waist, rarely involving the scalp, breasts, or buttocks; atypical moles usually appear on sun-exposed skin, most often on the back, but can involve the scalp, breasts, or buttocks. Benign nevi are present in 85% of adults, with 10–40 moles scattered over the body; atypical nevi can be present in the hundreds.

The entire skin surface, including the scalp and mucous membranes, as well as the nails should be examined in each patient. Bright room illumination is important, and a hand lens is helpful for evaluating variation in pigment pattern. Any suspicious lesions should be biopsied, evaluated by a specialist, or recorded by chart and/or photography for follow-up. A focused method for examining individual lesions, dermoscopy, employs low-level magnification of the epidermis and may allow a more precise visualization of patterns of pigmentation than is possible with the naked eye. Complete physical examination with attention to the regional lymph nodes is part of the initial evaluation in a patient with suspected melanoma. The patient should be advised to have other family members screened if either melanoma or clinically atypical moles (dysplastic nevi) are present. Patients who fit into high-risk groups should be instructed to perform monthly self-examinations.

Biopsy Any pigmented cutaneous lesion that has changed in size or shape or has other features suggestive of malignant melanoma is a candidate for biopsy. An excisional biopsy with 1- to 3-mm margins is suggested. This facilitates pathologic assessment of the lesion, permits accurate measurement of thickness if the lesion is melanoma, and constitutes definitive treatment if the lesion is benign. For lesions that are large or on anatomic sites where excisional biopsy may not be feasible (such as the face, hands, and feet), an incisional biopsy through the most nodular or darkest area of the lesion is acceptable; this should