Malignant melanoma is an aggressive, therapy-resistant malignancy of melanocytes. The incidence of melanoma has been steadily increasing worldwide, resulting in an increasing public health problem. Exposure to solar UV radiation, fair skin, dysplastic nevi syndrome, and a family history of melanoma are major risk factors for melanoma development. The interactions between genetic and environmental risk factors that promote melanoma genesis are currently the subject of ongoing research. Avoidance of UV radiation and surveillance of high-risk patients have the potential to reduce the population burden of melanoma. Biopsies of the primary tumor and sampling of draining lymph nodes are required for optimal diagnosis and staging. Several clinically relevant pathologic subtypes have been identified and need to be recognized. Therapy for early disease is predominantly surgical, with a minor benefit noted with the use of adjuvant therapy. Management of systemic melanoma is a challenge because of a paucity of active treatment modalities. In the first part of this 2-part review, we discuss epidemiology, risk factors, screening, prevention, and diagnosis of malignant melanoma. Part 2 (which will appear in the April 2007 issue) will review melanoma staging, prognosis, and treatment.


The current spectrum of malignant melanoma includes 2 clinical extremes. At one end of the spectrum, thin primary cutaneous melanoma is characterized by a relatively uniform treatment and a high cure rate. At the opposite end, metastatic melanoma is characterized by no proven effective therapy and poor outcomes. In recent decades, a heightened awareness of melanoma has led to an increased rate of diagnosis of early-stage disease. Notwithstanding the fact that treatment of advanced melanoma still remains in the realm of experimental and early-phase clinical trials, tremendous research efforts in melanoma biology, melanoma genetics, and tumor immunology are providing hope for a cure.

Although more than 95% of tumors are found in the skin, melanoma is not exclusively a skin cancer. Sites of primary extracutaneous melanoma include ocular, mucosal, gastrointestinal, genitourinary, leptomeninges, and lymph nodes (melanoma of unknown primary cancer). With the exception of neuroectodermally derived melanocytes that give rise to the retinal pigment epithelium, melanocytes originate from neural crest cells. During the early weeks of gestation, melanocyte precursors differentiate and migrate from the neural crest to numerous tissues (including the skin).

The function of melanocytes is best studied and defined in the skin. Within the basal layer of the epidermis, each melanocyte develops an intimate relationship with many keratinocytes, sending out slender dendritc processes that transfer packets of melanin pigment (melanosomes) to keratinocytes. The melanin granules orient in an umbrella-like fashion over the keratinocyte nucleus parallel to the skin surface. Melanin absorbs ultraviolet radiation (UVR) and possesses potent antioxidant properties capable of neutralizing UVR-generated free radicals. Paradoxically, melanocytes are injured and transformed by the same agent that melanocytes are programmed to defend against, UVR. Moreover, the cancers that melanocytes help prevent (squamous cell and basal cell carcinoma) are less lethal than the cancer that melanocytes become (melanoma).

Melanoma is rare among deeply pigmented ethnic groups relative to individuals of Northern European descent. The type of melanin pigment (eumelanin vs pheomelanin), as well as the number, size, and density of melanosomes, determines skin pigmentation. Anthropological and genetic studies trace human pigment dilution to the migra-
tion of early human groups to northern latitudes. Mutations of genes that govern skin pigmentation and/or are associated with increased melanoma risk were likely propagated by selective pressures (sexual selection) and/or a founder effect.

The causal relationship of UV exposure to melanoma is complex, and acute, intense, intermittent sun exposure in youth equates to higher risk of melanoma. The risk of melanoma also increases with proximity to the equator. The intensity of UVR increases considerably at midday, around which time (10 AM to 3 PM) sun avoidance is strongly encouraged. Fueled in part by public education campaigns, stories of melanoma diagnoses among celebrities, and marketing efforts by the manufacturers of sunscreen and photoprotective clothing, melanoma awareness and sun avoidance behaviors have substantially increased. However, sunbed use, low sun protection factor sunscreens, and sun-seeking behaviors remain popular among young people.

Every clinician encounters patients at risk for melanoma. Additionally, depending on the tumor location and stage, melanoma is a disease that requires the unique expertise and collaboration of medical, surgical, and pathology specialists. This review is intended to provide clinicians with a comprehensive, multispecialty overview of melanoma.

**EPIDEMIOLOGY**

Melanoma is the fifth most common cancer in men and the sixth most common cancer in women in the United States. An estimated 62,190 new cases of melanoma were diagnosed in the United States during 2006. According to data from Surveillance, Epidemiology, and End Results (National Cancer Institute), in 2000 approximately 629,822 people (304,097 men and 325,725 women) alive had a history of melanoma. The annual age-adjusted incidence of and mortality from melanoma in the United States is 18.3 per 100,000 persons per year and 2.7 per 100,000 persons per year, respectively. Internationally, the incidence rates vary 100-fold among different populations, with Australia having the highest rates worldwide; in Queensland, Australia, the cumulative incidence in the population older than 50 years is 1 in 19 for men and 1 in 25 for women. The incidence of malignant melanoma is increasing rapidly worldwide, including in countries with historically low incidence rates. This increase is occurring at a faster rate than for any other neoplasm, with the exception of lung cancer in women. In the United States, the incidence of malignant melanoma from 1973 to 2002 increased by 270%. Currently, 1 in 63 Americans will develop melanoma during their lifetime; historically, the risk was 1 in 1500 in 1935 and 1 in 250 in 1980. Parallel with this increasing incidence is an increase in melanoma-related mortality, albeit to a lower degree. In the United States, the mortality rate from malignant melanoma increased by 1.4% every year between 1977 and 1990. Since 1990, the mortality rate has shown a small downward trend and decreased by 0.3% per year from 1990 to 2002. Currently, 1 person dies each hour from metastatic melanoma. The annual direct cost of treating newly diagnosed melanoma in the United States was estimated to be $563 million in 1997.

Melanoma is notorious for affecting young and middle-aged people, unlike most other solid tumors, which mainly affect older adults. The median age at diagnosis of melanoma is 57 years, and the median age at death is 67 years. The incidence of melanoma increases linearly after the age of 15 years until the age of 50 years and then slows, especially in females. Approximately half the incidence is in people between the ages of 35 and 65 years, with approximately 80% occurring in those in the age range of 20 to 74 years. The age distribution is likely to show a leftward shift with a trend toward an increase in the incidence of melanoma among children, as well as due to an increase in skin biopsy rates. Males are approximately 1.5 times more likely to develop melanoma than females. The distribution of favored sites of occurrence of melanoma is sex dependent: the most common areas are the back for men and the arms and legs for women.

White populations have an approximately 10-fold greater risk of developing cutaneous melanoma than black, Asian, or Hispanic populations. This presumably relates to the higher sensitivity of white skin to sun exposure. However, both white and African American populations have a similar risk of developing plantar melanoma. Noncutaneous melanomas (eg, mucosal) are more common in non-white populations.

**RISK FACTORS**

Several factors have been hypothesized to be responsible for the worldwide increase in the incidence of melanoma. Of these, the major factors that are responsible for most of this increase are increased exposure to UVR, predominantly due to the depletion of the ozone layer, allowing penetration of UV rays into the atmosphere but possibly also due to behavioral change (such as increased use of sun or tanning beds), and increased surveillance. These factors are summarized in Table 1 and reviewed subsequently.

**ENVIRONMENTAL FACTORS**

Sunlight. A large body of evidence supports the role of solar UVR exposure as the most important environmental
TABLE 1. Summary of Risk Factors for Malignant Melanoma by Evidence

<table>
<thead>
<tr>
<th>Strong evidence</th>
<th>Weak evidence</th>
<th>Inconclusive or no increased risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Environmental and lifestyle factors</td>
<td>Tanning beds, sunlamps</td>
<td>Exogenous hormones</td>
</tr>
<tr>
<td>Exposure to sunlight</td>
<td>Obesity</td>
<td>Alcohol, smoking</td>
</tr>
<tr>
<td>Geographical location</td>
<td>Industrial occupation</td>
<td>Coffee</td>
</tr>
<tr>
<td>Host factors</td>
<td>Personal history of skin cancer</td>
<td>Vitamins A and E</td>
</tr>
<tr>
<td>Number of nevi</td>
<td>Higher socioeconomic status</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Dysplastic nevi</td>
<td>Brown hair</td>
<td></td>
</tr>
<tr>
<td>Family history of melanoma</td>
<td>Male sex</td>
<td></td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>Endogenous hormones</td>
<td></td>
</tr>
<tr>
<td>Sun sensitivity or inability to tan</td>
<td>(age at menarche, parity)</td>
<td></td>
</tr>
<tr>
<td>Blue or green eyes; blond or red hair</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

risk factor for developing malignant melanoma. Multiple studies have shown that intermittent sun exposure, assessed indirectly by history of sunburns, appears to be a major determinant of risk for melanoma (in contrast to non-melanomatosus skin cancers, which are linked more to cumulative sun exposure). This etiological link is further supported by the finding of higher melanoma incidence in populations that live in lower latitudes, higher incidences in white populations, lower incidences among dark-skinned populations, and data from genetic and migration studies. The risk of melanoma developing in people who have had sunburns is double that in people who have never had a sunburn. Moreover, the age at which sunburns occur appears to be important; sunburns in childhood are associated with the highest risk. Further evidence for the role of UVR comes from studies of immigrant populations in Australia, which have shown that the risk of melanoma is proportional to the length of stay and inversely to age at arrival. Likewise, further support for the role of UVR as a risk factor for melanoma comes from clinical evidence. Patients with xeroderma pigmentosum (a genetic disorder characterized by deficient DNA repair mechanisms and a corresponding hypersensitivity to UVR damage) have a substantially higher risk of developing melanoma, particularly in sun-exposed skin. The use of psoralen–UV-A radiation photochemotherapy for psoriasis has also been associated with an increased risk of melanoma.

Other Sources of UVR. A relationship between increased risk of melanoma from nonsolar sources of UVR (eg, fluorescent light, sunlamps, sunbeds and tanning beds) has been postulated, but data have been inconclusive. A recent meta-analysis of 12 case-control studies and 1 cohort study suggested that sunbed and sunlamp exposure might lead to a slightly higher risk of melanoma (odds ratio, 1.25; 95% confidence interval, 1.05-1.49). The risk was higher with longer duration of exposure and earlier age at exposure.

Protection From UVR Exposure. The relationship established between UVR exposure and melanoma risk has prompted researchers to hypothesize that sunscreen use may reduce the risk of melanoma developing. However, studies to prove this hypothesis have been inconclusive. Proper use of sunscreens with broad-spectrum sun protection factor 30 has been shown to reduce the number of acquired nevi that develop in children by 30% to 40%. Because acquired nevi are markers for sun exposure (and thereby for increased risk of developing melanoma), sunscreen use may have a role in melanoma prevention. However, other studies found that by protecting against sunburns, sunscreen use results in an increase in the actual duration of intentional (ie, recreational) sunlight exposure and may increase the total exposure to UVR. Therefore, reliance on sunscreen as a sole method of sun protection is not recommended, and other methods (eg, long-sleeved clothing) should be used in conjunction with sunscreen.

Occupation. Because exposure to sunlight is a major risk factor for melanoma, a concern has been that people occupationally exposed to sun, such as farmers, would have a higher risk of developing melanoma. However, although farmers are indeed at a higher risk of developing skin cancers such as squamous cell carcinoma, they appear to have no increased risk for melanoma. Swedish airline pilots, compared with the general male Swedish population, have been identified to have an increased incidence of melanoma. The same study reported that Swedish military pilots did not have an increased risk of melanoma but only of nonmelanoma skin cancer. These findings support the hypothesis that intermittent (rather than cumulative) sun exposure increases the risk of melanoma. Occupational exposure to ionizing radiation, vinyl chloride, polychlorinated biphenyls, and petrochemicals has been linked to a possible increase in the risk of melanoma; however, the risk attributable to these factors appears to be small. Moreover, this link has not been shown consistently in different studies.
Reproductive Factors and Oral Contraceptive Use. Estrogen and progesterone have been postulated to increase the risk of melanoma by stimulating melanocyte proliferation.40,41 Furthermore, patients with breast cancer have a slightly higher risk (odds ratio, 1.4) of developing melanoma,42 which has led to speculation that the development to melanoma is influenced by the hormonal milieu. A few early studies indicated that oral contraceptive pill or hormone replacement therapy use increased the risk of melanoma.43 However, more recent studies and a pooled analysis failed to validate these findings.44,45 A link between an increased risk of melanoma and several reproductive factors (eg, age at menarche, menopausal status, age at menopause, number of live births) has been noted, again suggesting the influence of estrogen on melanogenesis. A recent pooled analysis of 10 case-control studies suggested that women with both earlier age at first birth (<20 years) and higher parity (≥5 live births) had a lower risk than women with later age at first birth and lower parity (odds ratio, 0.33).44,46 Presumably, endogenous rather than exogenous hormones act as risk factors. Of note, pregnancy does not seem to significantly affect the risk of malignant melanoma.47

Anthropometric, Dietary, and Lifestyle Factors. Obesity has been postulated to increase the risk of melanoma, plausibly because of a larger body surface area exposed to sun or differential hormonal profiles.45,46 Epidemiological studies evaluating the role of dietary vitamins have been inconclusive.48-50 Similarly, the relationship with other dietary factors, including intake of fat, vitamin E, alcohol, coffee, and smoking, has been inconsistent.48-52

HOST FACTORS
Melanocytic Nevi. Melanocytic nevi are benign accumulations of melanocytes or nevus cells and may be congenital or acquired. The risk of melanoma varies on the basis of type, size, number, and location of nevi. In approximately 25% of cases, melanoma occurs in conjunction with a preexisting nevus.59

The risk of melanoma has been directly correlated to the total number of benign nevi (both dysplastic and nondysplastic) on the body. The risk is approximately 1.5-times higher in people with 11 to 25 nevi (compared with ≤10 nevi) and appears to be doubled with every increase of 25 nevi.51,52,53,54,55 Similarly, larger nevi (particularly >5 mm) are associated with a higher risk of melanoma.66-68 Giant nevi (>20 cm) are associated with a significantly higher risk of melanoma.69,70

Dysplastic nevi (ie, melanocytic nevi with cytological atypia) are associated with an increased risk of melanoma.61,62,71 Nonfamilial melanoma may occur in the setting of a preexisting dysplastic nevus in up to 29% to 49% of cases.63 In a person with a family or a personal history of melanoma, the presence of dysplastic nevi is a marker for a significantly increased risk of melanoma.72 Moreover, the presence of dysplastic nevi is a risk factor for the development of multiple primary melanomas. Dysplastic nevi often cluster in families, particularly in families with melanoma.73-81 A familial syndrome variously referred to as dysplastic nevus syndrome, atypical mole syndrome, or familial atypical multiple mole and melanoma syndrome82 has been recognized. Patients with this syndrome have almost a 100-times higher risk of developing melanoma, and approximately 50% of these patients develop melanoma by the age of 50 years.73

Melanomas that develop in the setting of previous nevi are more likely to be on the trunk, occur in younger patients, and belong to the superficial spreading variety.79,82

Family History. A family history of melanoma is a strong risk factor for melanoma. Patients with a history of melanoma in a first-degree relative have approximately a 2-times higher risk of developing melanoma than those without a family history; the risk increases in the presence of other risk factors.73,83 Familial melanoma is thought to account for 10% of all melanoma cases.83 Presence of a familial melanoma syndrome should be considered in patients with a family history of pancreatic cancer or astrocytoma. Some families with inherited melanoma demonstrate a clear pattern of autosomal dominant inheritance with multiple family members affected in more than 1 generation. Mutations in CDKN2A (or p16) are the most common genetic abnormalities found in these families. A second mutation, CDK4, has been found much more rarely.84,85 Features in a patient with melanoma that indicate an underlying genetic predisposition include occurrence at a younger age (<40 years),84-92 multiple primary melanomas, or a history of precursor lesions such as dysplastic nevi. Patients with a genetic predisposition to melanoma are more likely to have tumors that are superficially invasive and have a better prognosis.93,94 Additionally, melanoma is known to cluster in families with family cancer syndromes such as familial retinoblastoma, Li-Fraumeni cancer syndrome, and Lynch syndrome type II.

A genetic predisposition to melanoma may also occur in a patient without a suggestive family history. Such patients may have a new mutation, including an alteration in the CDKN2A gene or CDK4 gene. Once acquired, this predisposition can be passed on to offspring in an autosomal dominant fashion.

Immunosuppression. Immunosuppression has been associated with a higher risk of melanoma. This has been noted in patients with acquired immunodeficiency syndrome, those with hematological malignancies, and those receiving immunosuppressive agents after solid organ transplantation.95-100

Phenotypic Characteristics and Variations in Melanocortin-1 Receptor. Certain phenotypic characteristics, such as eye color (blue or green), hair color (red > blond > brown compared with black), presence of freckles, sun sensitivity, and an inability to tan, have been associated with approximately a doubling of the risk of developing melanoma.22,45,71,101-102 One possible mechanism for the increased risk relates to variation in melanocortin-1 receptor. Variation in melanocortin-1 receptor alleles has been found to result in the development of both sporadic cutaneous melanomas and an increased risk of melanoma among those predisposed to familial melanoma. Studies have found that red hair, presence of freckles, and sun sensitivity are associated with specific genetic variations in melanocortin-1 receptor and possibly account to some extent for the increased risk seen with the phenotype.

Other Factors. Higher socioeconomic status has been associated with a higher risk of melanoma. A personal history of melanoma (and other skin cancers) can increase the risk of subsequent melanoma developing. However, both of these associations appear to be confounded by an increased exposure to sunlight and better surveillance.15,93,94,103-112

RISK PREDICTION MODELS
Risk prediction models have been developed to estimate an individual's lifetime risk of melanoma.83,84,113 Risk factors that have been consistently demonstrated to increase the risk of melanoma include family history of melanoma, higher number of nevi, history of severe sunburn (>3 before the age of 20 years), marked freckling on the upper back, and light hair color. When compared with the risk in the general population, the presence of 1 or 2 of these risk factors is associated with a 2- to 4-times higher risk, and occurrence of 3 or more factors results in approximately a 20-fold risk.83,84,113

SCREENING AND PREVENTION
Prevention and public health measures are essential to decrease the risk of melanoma. Melanoma prevention is well divided into primary, secondary, and tertiary prevention.

Primary prevention (prevention of occurrence) of melanoma entails reduction of known risk factors in high-risk populations. Reducing UV exposure, especially intense, intermittent sun exposure, is the most important modifiable behavior for melanoma prevention. Reducing UV exposure would include avoiding excessive sun exposure (midday sun), covering skin with clothing, wearing broad-brimmed hats, using detergent that increases the photoprotective ability of one’s clothing, and applying sunscreen.114 These measures should also be emphasized in individuals with a personal or family history of melanoma. Sunburn avoidance in childhood is paramount.115 Educating the population and especially parents about sun protection, risk factors for skin cancer, and the skin self-examination (ABCD of melanoma) is essential.116,117 Photoprotective measures (sun-safe behavior) should also be emphasized for all individuals, especially those with a personal or family history of melanoma. The most successful example of such population-based cancer education programs is the effort of the Anti-Cancer Council of Victoria in Australia. The council has been organizing sun protection programs (Slip! Slap! Slop! and SunSmart) for more than 20 years. These programs have resulted in marked reductions in sun exposure and have helped change society’s approach to the sun.118 Also noteworthy are primary chemoprevention efforts using statins and fibrates in patients at risk for melanoma. As yet, there does not appear to be conclusive evidence of the benefit of such interventions.119-121

Secondary prevention of melanoma is accomplished by diagnosis and treatment of early-stage (highly curable) melanoma. People at high risk for development of melanoma should be identified and evaluated. Screening of high-risk patients is cost-effective and likely to be associated with an improved survival.122 Individuals with xeroderma pigmentosum, giant congenital nevi, immunosuppression, familial atypical multiple mole and melanoma syndrome, unusual-appearing nevi, numerous (>50) nevi, changing nevi, and a family history of melanoma and men older than 50 years should receive complete baseline and periodic follow-up skin examinations by a physician.123-125 Additionally, such people should be encouraged to conduct skin self-examinations. Patients with a history of melanoma should be educated on the need for continued surveillance for subsequent additional primary melanomas and for recurrence and metastasis.126 Melanoma screening includes complete skin examination as part of a general medical examination by primary care physicians, during evaluations for other skin problems by a dermatologist, and community-based screening programs. Each of the foregoing screening methods has afforded increased rates of melanoma detection.127,128 Both the value and the need for sustained melanoma education were demonstrated by a nationwide melanoma awareness campaign in Australia, resulting in reduction of the median melanoma thickness overall and a higher percentage of thin (<0.75 mm) melanomas diagnosed during the campaign year. After the campaign, both measurements rebounded to precampaign year values. Tertiary prevention of melanoma involves limiting morbidity and extending survival in patients with advanced disease.

DIAGNOSIS OF MELANOMA
The diagnostic clinical features of melanoma range from subtle to obvious characteristics. A well-established guide
to examine and interpret pigmented lesions for both health care professionals and patients has been the ABCDE acronym. This list of features, which is easy to memorize and use, stands for Asymmetry, Border irregularity, Color variation, Diameter (>6 mm), and the recently added E, for Evolving (or changing), has been widely popularized during the past 2 decades. Evolving encompasses any significant change in size, shape, surface (raised, bleeding, crusting), shades of color, or symptoms (itching, tenderness) and was only recently added to the list since most patients with melanoma have been found to observe these component changes occurring within suspicious pigmented lesions.\textsuperscript{130}

Various assistive optical devices for a more detailed examination of the skin and, in particular, pigmented lesions are becoming part of routine clinical practice. These devices include high-resolution optical handheld devices that have been designated dermoscopes (or dermatoscopes or epiluminescent microscopes). In addition, portable scanning units using visible, infrared, and UV sources create images or spectroscopic outputs that can be electronically captured, archived, retrieved, and analyzed. A number of these devices are continually being developed, refined, and tested in clinical studies aimed at improving the diagnostic accuracy and sensitivity of melanoma detection. Several excellent reviews are recommended for further reading.\textsuperscript{131-134}

During evaluation of suspicious pigmented lesions, clinicians must heed the observation of the patient or the patient’s family member of a changing or new pigmented skin lesion. Pigment variation (Figure 1), an irregular or ill-defined border, asymmetry in color or shape, ulceration, development of a nodule within a preexisting lesion (Figure 2), and pigment loss (Figure 3) are clinical clues for melanoma. However, a definitive diagnosis or an exclusion of melanoma requires biopsy and experienced pathological review of the specimen. An established diagnosis of malignant melanoma can be made only after histopathologic analysis. Even then, the diagnosis can be challenging. Malignant melanoma must be distinguished from conventional melanocytic nevi, proliferation nodules in congenital nevi, atypical or dysplastic nevi, and unusual nevus variants such as Spitz nevi, pigmented spindle cell nevi, deep penetrating nevi, plexiform spindle cell nevi, clonal nevi, genital nevi, acral nevi, flexural nevi, cellular blue nevi, and recurrent melanocytic nevi, among many others. Unusual morphologic variants of malignant melanoma must be recognized to prevent misdiagnosis as an epithelial or mesenchymal neoplasm. The histologic evaluation of the tumor also provides prognostic information needed by the clinician and surgeon to formulate the treatment plan.

Criteria for the histologic diagnosis of cutaneous malignant melanoma are based on architectural and cytologic features and need to be interpreted in the context of the
clinical situation. A junctional melanocytic proliferation that shows areas of pagetoid spread from an acral site of a pediatric patient would likely be interpreted differently than a similar proliferation on sun-damaged skin of the face of an elderly patient. Additionally, partial or incisional biopsies of larger lesions are well-known pitfalls in the diagnosis of malignant melanoma. There is no absolute criterion for the diagnosis of malignant melanoma. A constellation of architectural and cytologic features is evaluated along with clinical information.

Architectural features of malignancy include large size, asymmetry, poor circumscription, pagetoid spread, confluence of growth, effacement of the rete ridges, scalloping of the dermal-epidermal junction, marked cellularity, sheet-like growth pattern, effacement of underlying dermal architecture, lack of architectural and cytologic maturation with depth, and perineural invasion, among many others. Cytologic features of malignancy include enlarged nuclei, prominent nucleoli, thick and irregular nuclear membranes, abnormal cytoplasmic melanization, dermal mitotic activity, and atypical mitotic figures.

Complicating the diagnosis of melanoma is the understanding that many of these histologic features can be seen in benign melanocytic nevi. Generally, the larger the size of a lesion the more suspicious for melanoma; however, congenital melanocytic nevi can be large and melanomas can be small. Small melanomas, measuring only 2 to 3 mm in diameter, are well documented. Pagetoid spread is thought to be one of the most important features for the diagnosis of malignant melanoma; however, pagetoid spread is seen in most nevi of palms and soles, recurrent nevi, and genital nevi and is seen in a proportion of Spitz nevi, pigmented spindle cell nevi, and nevi of infancy and childhood. Confluence of growth along the dermal-epidermal junction is often seen in malignant melanoma, but a confluence of junctional theques (aggregations of nevus cells) can also be seen in genital nevi. Mitotic figures, particularly deep and atypical mitotic figures, are often seen in malignant melanoma, but mitotic figures can also be seen in benign melanocytic nevi. Nevocel melanomas “mimic ordinary compound or intradermal melanocytic nevi when the melanoma cells are small, or Spitz’s nevi when the cells are large.” Thus, the diagnosis of malignant melanoma requires careful evaluation of numerous histologic features in each patient.

Conventional melanomas are classified as superficial spreading, nodular, lentigo maligna, and acral lentiginous. However, this classification may be difficult to apply in small incisional biopsy specimens. Malignant melanomas can show such heterogeneity that they may not always be classifiable. A number of studies suggest that different types of melanoma (eg, nodular, acral lentiginous) may have a different prognosis, but the importance of the histologic type of melanoma may decrease with multivariate analysis. This classification is not included in the American Joint Committee on Cancer staging system but is generally included on pathology reports.

Superficial spreading is the most common type of malignant melanoma, accounting for approximately 70% of cases. Superficial spreading melanomas most often occur on the back of the legs of women and on the backs of men. These tumors are commonly found on sun-exposed skin, particularly areas of intermittent sun exposure. Such tumors usually show prominent pagetoid spread and are composed of epithelioid melanoma cells. By convention, superficial spreading melanomas extend 3 rete ridges beyond the dermal component. Superficial spreading melanomas may arise de novo or in association with a nevus.

Nodular melanoma accounts for 5% of melanomas and most often occurs on the trunk and limbs of patients in the fifth or sixth decade of life, with males more commonly affected than females. Nodular melanomas are often ulcerated and when amelanotic may be mistaken for a vascular neoplasm. Nodular melanomas do not have a radial growth phase; they have only a vertical growth phase. Nodular melanomas are not frequently associated with regression or an associated nevus. Polypoid melanomas are considered a variant of nodular melanoma.

Acral lentiginous melanoma is uncommon, accounting for 5% of melanomas among white people. Although acral lentiginous melanoma is uncommon in all ethnic groups, it is the most common type of melanoma among Asian patients, Hispanic patients, and patients of African descent. The overall incidence of melanoma in these ethnic groups is low compared with that in white patients. Acral lentiginous melanoma occurs on glabrous skin and adjacent skin of the digits, palms, and soles. On the soles, acral lentiginous melanomas often involve heels. Digit melanomas usually involve the nail bed of the great toe or thumb and more commonly affect elderly people, with a female predominance. Superficial spreading and nodular melanomas may also involve acral sites, including the nail bed. In a study of 100 subungual melanomas, approximately half were acral lentiginous type.

Lentigo maligna accounts for 4% to 15% of cutaneous melanoma and correlates with long-term sun exposure and increasing age. Additionally, lentigo maligna is known as Hutchinson melanotic freckle and precancerous melanosis of Dubreuilh. Lentigo maligna melanomas are composed of single melanocytic cells and dysesive nests along an atrophic dermal-epidermal junction. The tumor cells often show extension down into hair follicles. These tumors usually arise in the skin, showing...
marked solar elastosis and other features of long-term sun damage. Among the types of in situ melanoma, lentigo maligna can be difficult to distinguish from melanocytic hyperplasia in sun-damaged skin. This lesion may evolve for decades before invading into the papillary dermis. To distinguish between lentigo maligna and malignant melanoma in situ, the term lentigo maligna has been proposed. In the precursor lesion lentigo maligna, there is an increase in atypical melanocytic cells singly disposed along the dermal-epidermal junction, whereas in malignant melanoma in situ, the lentigo maligna type shows nesting along the junction, confluence, and pagetoid spread. Progression to invasive melanoma from malignant melanoma in situ of the lentigo maligna type is thought to be similar to other forms of melanoma in situ, whereas progression from lentigo maligna, as a precursor lesion, is hypothesized to occur over a much longer time.

**UNUSUAL VARIANTS OF MALIGNANT MELANOMA**

Unusual variants of melanoma (Table 2 and Figure 4) are rare and can be confused with epithelial or mesenchymal neoplasms. These unusual variants of malignant melanoma generally behave similarly to conventional types of melanoma when prognostic factors such as depth of invasion are taken into account. The most important aspect of these variants is knowledge of their existence to avoid misdiagnosis as another tumor or as a scar in the case of desmoplastic melanoma.

**DESMOPLASTIC MELANOMA**

Desmoplastic malignant melanoma often arises on the head and neck but can occur on a variety of cutaneous and mucosal areas, including the conjunctiva, gingiva, genitalia, and perianal areas. Desmoplastic melanoma occurs in older individuals from the sixth to eighth decades of life and is slightly more common in men. Generally, desmoplastic melanoma may be amelanotic and present as an erythematous or pale or flesh-colored nodule or plaque arising in sun-damaged skin or with pigmentation overlying a dermal nodule. Some desmoplastic melanomas arise in association with a lentigo maligna melanoma, but they may also arise in association with superficial spreading melanoma, mucosal melanoma, or acral lentiginous melanoma.

Desmoplastic melanomas are positive for S100, but many commonly used markers of melanocytic differentiation, including HMB45, Mart 1, and Melan A, are usually negative. Differentiating desmoplastic malignant melanoma from scar tissue in reexcised specimens can be particularly difficult because S100-positive cells can also be seen in dermal scars. Desmoplastic melanomas often show nerve infiltration. When this occurs, they have been referred to as desmoplastic neurotropic melanomas. When matched for depth of invasion, desmoplastic melanomas have a lower risk of metastases than conventional melanomas of similar depth. Desmoplastic melanomas may show immunopositivity for actin and can be confused with smooth muscle tumors. Thus, immunoperoxidase studies need to be interpreted with caution in cases of desmoplastic melanoma.

Desmoplastic melanomas have high recurrence rates due to their highly infiltrative growth and frequent perineural invasion and are usually deeply invasive at diagnosis. A large retrospective study from the Mayo Clinic demonstrated that desmoplastic melanomas have a high incidence of local recurrence, rarely metastasize to the lymph nodes, and have a propensity to metastasize to the lungs. The same clinical behavior has been confirmed by other groups, with the incidence of lymph node metastases ranging from 0% to 8%. A distinction must be made between pure desmoplastic melanomas and melanomas with a desmoplastic component. The pure desmoplastic melanomas have unique clinical behaviors, whereas melanomas with desmoplastic components behave as other cutaneous melanomas; this may explain the conflicting reports of older clinical studies that found a higher rate of lymph node metastases. The difference between pure desmoplastic melanomas and cutaneous melanomas has been further distinguished by gene profiling in which desmoplastic melanomas have down-regulation of melanocyte differentiation and up-regulation of neurotropic factors. On the basis of the predilection for local recurrence, the North Central Treatment Group has embarked on a phase 2 study evaluating the

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**TABLE 2. Unusual Variants of Melanoma**

<table>
<thead>
<tr>
<th>Melanoma variant</th>
<th>References</th>
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<tbody>
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<td>Desmoplastic melanoma</td>
<td>161, 162, 183-213</td>
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<td>Mucosal melanoma</td>
<td>214-219</td>
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<tr>
<td>Malignant melanoma arising in blue nevus (malignant blue nevus)</td>
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<tr>
<td>Nevus melanoma</td>
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utility of adjuvant radiation for the treatment of desmoplastic melanoma.

When matched for depth of invasion, desmoplastic melanomas have a lower risk of metastases than conventional melanomas of similar depth. Comparing desmoplastic melanomas with conventional types with a depth of invasion more than 4 mm, the 5-year survival for desmoplastic melanoma is 72% compared with 37% to 48% for conventional melanoma. Overall survival for both groups was similar to that for patients with other cutaneous melanomas. Factors associated with higher rates of local recurrence were surgical margin clearance less than 1 cm and neurotropism. However, desmoplastic melanomas showed a lower rate of regional lymph node metastasis at presentation than conventional melanomas.

**Balloon Cell Melanoma**

Balloon cell melanoma is a rare histologic variant of malignant melanoma that resembles balloon cell nevus but effaces the dermal architecture with sheets of tumor cells and shows cytologic atypia, nuclear pleomorphism, and mitoses. Balloon cell melanomas must be differentiated from cutaneous clear cell tumor and metastases. The clear cytoplasm has been thought to represent degenerating melanosomes, lipid, or glycogen. Immunohistochemical and electron microscopic findings suggest that the tumor cells are likely metabolically active melanocytic cells. The prognosis of these rare histologic variants usually correlates with tumor thickness and is similar to that in other types of melanoma. These melanomas are often deeply invasive at diagnosis, which reflects in the overall poor survival.
MYXOID MELANOMA

Myxoid melanoma can easily be confused with other myxoid and mucinous neoplasms. Prominent myxoid change can be seen in primary melanomas, metastases of malignant melanoma with signet ring cell cytomorphologic features have been described in lymph nodes, and recurrences, and metastases. Benign melanocytic neoplasms can also show myxoid and mucinous change.

In primary cutaneous tumors, the presence of a junctional component helps to confirm a diagnosis of myxoid melanoma. Melanomas with only foci of myxoid change are also less difficult to diagnose than those that are predominantly myxoid. Myxoid melanomas often show a vaguely lobular architecture with pushing margins and paraseptal and perivascular accentuation of cells. The tumor cells may be small, stellate, spindled, or large and epithelioid and are arranged singly, in cords, or rarely as pseudo-glandular structures. Myxoid change can be seen in metastases even when not present in the primary tumor.

Thus, a high index of suspicion is needed to diagnose melanoma in a metastasis that shows myxoid change. Cutaneous tumors in the differential diagnosis include myxoma, nerve sheath myxoma, malignant chondroid syringoma, myxoid dermatofibrosarcoma protuberans, myxoid atypical fibrous histiocytoma, mucinous eccrine carcinoma, and metastases.

Immunohistochemical studies can be helpful for diagnosis because myxoid melanomas are positive for S100, NKIC3, vimentin, and HMB45. Keratin immunopositivity and negative staining for S100 are helpful in ruling out a myxoid melanoma.

SIGNET RING CELL MELANOMA

Signet ring cell melanoma is a rare but well-recognized variant of malignant melanoma. Signet ring cell features are more common in metastases than in primary melanomas. The presence of signet ring cells in a melanocytic neoplasm is not diagnostic of malignancy because signet ring cells have been described in melanocytic nevi. The importance of a signet ring cell phenotype is unknown, but it is important to consider this variant in the differential diagnosis of a primary cutaneous tumor or a metastasis with signet ring cell features. Signet ring cells are most common in mucin-secreting adenocarcinomas but may be seen in lymphomas, liposarcomas, basal and squamous cell carcinomas, ovarian stromal tumors, epithelioid smooth muscle tumors, hridadenomas, and cylindromas, among others.

Metastases of malignant melanoma with signet ring cell cytomorphologic features have been described in lymph nodes, in the lungs, and as peritoneal effusions. The immunohistochemical profile can clarify the diagnosis, but a high index of suspicion, particularly in a metastasis, is necessary.

OSTEOGENIC MELANOMA

Osteogenic melanomas usually occur on the digits (particularly subungual) and in the nose and sinuses and are often deeply invasive at the time of diagnosis. Melanomas may also show cartilaginous differentiation in these sites. Men and women appear to be equally affected, and the tumor is most common in middle-aged and elderly patients. Osteogenic melanomas mimic osteosarcomas, chondrosarcomas, and metaphastic carcinomas. Osteogenic melanomas must be differentiated from osteosarcomas because their treatment is different. Strong immunoreactivity for S100 protein, HMB45, and Melan A is helpful in differentiating osteogenic melanomas from osteosarcomas and tumors with osteoid metaplasia.

RHABDOID MELANOMA

Malignant melanoma with rhabdoid cytomorphologic features has been described in both primary and metastatic lesions. Primary rhabdoid melanomas usually show junctional activity or a background of more conventional cells, which are helpful in recognizing the differentiation of the tumor. Although rhabdoid melanomas are positive for S100, they often lose HMB45 expression. Additionally, focal aberrant expression of both keratin and smooth muscle actin has been noted in these tumors. The rhabdoid phenotype may represent further evolution to a more primitive dedifferentiated form. The prognosis for patients with melanoma metastases with rhabdoid features is similar to that of conventional melanoma metastases.

Not enough data are available to evaluate whether rhabdoid morphologic findings have prognostic significance in the primary tumor.

BASOMELANOCYTIC TUMORS

Biphasic tumors with epithelial and melanocytic components are rare. Four squamomelanocytic tumors have been described, but none of the patients were reported to die of metastatic melanoma or squamous cell carcinoma. In a recent report, a patient with a basomelanocytic tumor died of metastatic malignant melanoma, suggesting that at least a subset of biphasic tumors may have a more aggressive biologic potential than previously known. Biphasic tumors show an intimate admixture of melanocytic cells and basaloid cells or squamous cells, in contrast to collision tumors in which there are usually distinctly separate components of melanocytic and epithelial cells. However, a recent report of a malignant melanoma metastatic to a basal cell carcinoma showed an intimate association of the melanoma cells within the basal cell carcinoma. Another case of a malignant melanoma colonizing a basal cell carcinoma has been reported, but the malignant melanoma was limited to the epidermis. The cells in basomelanocytic tumors...
may arise from a common precursor and show biphasic immunophenotypic differentiation. Overall, these are rare tumors in which a subset appears to have a more aggressive biologic potential than previously known.

CONCLUSION

This review represents a condensed summary of the current state of knowledge regarding the epidemiology, risk factors, screening, prevention, and diagnosis of malignant melanoma with emphasis on clinical practice. A discussion of the extensive basic science works that have provided the mechanistic interpretations of the clinical observations in malignant melanoma was thought to be beyond the scope of this review. Maintaining a clinical emphasis, part 2 of this review (in the April issue of Mayo Clinic Proceedings) will summarize the current state-of-the-art in the staging, prognosis, and treatment of melanoma.

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REFERENCES

MALIGNANT MELANOMA IN THE 21ST CENTURY


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The Symposium on Solid Tumors will continue in the April issue.