Review

Melanoma: Epidemiology, Risk Factors, Pathogenesis, Diagnosis and Classification

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Abstract. *This article reviews epidemiology, risk factors, pathogenesis and diagnosis of melanoma. Data on melanoma from the majority of countries show a rapid increase of the incidence of this cancer, with a slowing of the rate of incidence in the period 1990-2000. Males are approximately 1.5-times more likely to develop melanoma than females, while according to other studies, the different prevalence in both sexes must be analyzed in relation with age: the incidence rate of melanoma is grater in women than men until they reach the age of 40 years, however, by 75 years of age, the incidence is almost 3-times as high in men versus women. The most important and potentially modifiable environmental risk factor for developing malignant melanoma is the exposure to ultraviolet (UV) rays because of their genotoxic effect. Artificial UV exposure may play a role in the development of melanoma. The most important host risk factors are the number of melanocytic nevi, familiar hystory and genetic susceptibility. A patient with a personal history of melanoma must be considered at greater risk for subsequent melanoma. Indeed approximately 1-8% of patients with prior history of melanoma will develop multiple primary melanomas. We herein review the dermatological diagnosis and classification of melanoma.*

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Epidemiology

At the start of 21st century, melanoma remains a potentially fatal malignancy. At a time when the incidence of many tumor types is decreasing, melanoma incidence continues to increase (1). Although most patients have localized disease at the time of the diagnosis and are treated by surgical excision of the primary tumor, many patients develop metastases (2).

The incidence of malignant melanoma has been increasing worldwide, resulting in an important socio-economic problem. From being a rare cancer one century ago, the average lifetime risk for melanoma has now reached 1 in 50 in many Western populations (3). Starting from 1960s, the incidence of this cancer has increased in Caucasian populations and, thus, melanoma has become one of the most frequent cancers in fair-skinned populations (4). Melanoma is now regarded as the fifth most common cancer in men and the sixth most common cancer in women in the United States, where the incidence of malignant melanoma from 1973 to 2002 increased by 270%. Currently, 1 in 63 Americans will develop melanoma during their lifetime (5). It has been estimated by the U.S. Surveillance, epidemiology and End Result Program (SEER) that there are approximately 793,283 men and women alive in the United States who had a history of invasive melanoma (385,054 men and 408,229 women) (6). In 1973, the U.S. melanoma incidence rate was 6.8 per 100,000 and by 2003 to 2007, this rate has grown to 20.1 per 100,000.

According to data collected during the period 1998-2002, Mackie and colleagues showed that the highest recorded incidence of melanoma worldwide is in Queensland (Australia), where there is an incidence equal to $55.8/10^5$/annum for males and $41.1/10^5$/annum for females. The incidence of this cancer is also elevated in New Zealand

(34.8/10^5/annum and 31.4/10^5/annum for males and females, respectively). Reported incidence rates vary for Europe and are highest in Switzerland and the Scandinavian countries of Norway, Sweden and Denmark. Incidence rates in Europe are higher in the more affluent countries, compared to data from the Baltic states of Latvia, Lithuania, Estonia, Belarus and Serbia, although recent data show a rise in incidence in many East European countries (1)

The incidence of melanoma in Italy is equal to 5-7 cases per 100,000 inhabitants per year even though Mediterranean populations are considered to be at low risk for development of this tumor. Therefore, in Europe there is a gradient in incidence rates with the highest rates in Northern countries and the lowest ones in the Southern countries. This is probably due to increased protection against UV rays typical of highly pigmented skin (as the people who live in Southern European countries) but it is also due to the different pattern of sun (chronic rather than intermittent in Southern Europe) (7).

Summarizing, data on melanoma from the majority of countries show a rapid increase of the incidence of this cancer, with a slowing of the rate of incidence in the period 1990-2000 (1).

Parallel with this increase of the rate of incidence there is also an increase of melanoma related-mortality, albeit to a lower degree. In U.S. the mortality rate increased by 1.4% every year between 1977 and 1990. Since 1990, it has shown a small downward trend and decreased by 0,3% per year from 1990 to 2002 (5). According to Rigel *et al.*, from 2003 to 2007 the median age of death for malignant melanoma was 68 years (6). There is a greater mortality rate in men (+2.3% from 1975 to 1989 and +0.2% from 1989 to 2007) compared to women of the same age in U.S. (+0.8% between 1975-1989 and during the period between 1989-2007 as it appears to be decreasing by –0.6%) (6).

Unlike other solid tumors, melanoma mostly affects young and middle-aged people. The median age at the time of diagnosis of melanoma is 57 years and it was observed that the incidence of this cancer increases linearly after the age of 25 years until the age of 50 years and then slows, especially in females.

Regarding the incidence of melanoma in relation to sex, different studies show results that are not always coincident. According to Markovic *et al.*, males are approximately 1.5-times more likely to develop melanoma than females, while according to other studies, the different prevalence in both sexes must be analyzed in relation with age: the incidence rate of melanoma is grater in women than men until they reach the age of 40 years, however, by 75 years of age, the incidence is almost 3-times as high in men *versus* women (145.6 *vs*. 47.3 per 100,000) (6, 7).

The distribution of favoured sites of occurrence of the cancer is sex-dependent: the most common areas are the back for men and the arms and legs for women (5). The

incidence rate of this disease varies widely also in relation to race. The white population has an approximately 10-fold greater risk of developing cutaneous melanoma than black, Asian or Hispanic populations. However, both white and African American populations have a similar risk of developing plantar melanoma, while non-cutaneous melanomas (*e.g.* mucosal) are more common in non-white populations (8). According to the dates collected during the year 2007 by SEER, the incidence rate of melanoma in the white population was 27.5 per 100,000, while in black people was 1.1 per 100,000 (in U.S) (6).

Risk Factors

Nowadays melanoma is considered as a multi-factorial disease arising from an interaction between genetic susceptibility and environmental exposure.

The most important and potentially modifiable environmental risk factor for developing malignant melanoma is the exposure to UV rays, because of their genotoxic effect. Elwood *et al.* studied the correlation between melanoma and sun exposure concluding that intermittent sun exposure appears to be a major determinant of risk for melanoma (9). Sunburn history may be a marker of intense intermittent sun exposure, moreover a history of sunburns in childhood are associated with the highest risk (10). By contrast, the chronic continuous pattern of exposure is associated more with actinic keratosis and non-melanomatous skin cancers (11). Artificial UV exposure may play a role in the development of melanoma; indeed the amount of UVA occurring in a typical tanning bed session is significantly higher in comparison to the exposure during ordinary outdoor activities or even during sunbathing (12). Also the psoralen–UV-A radiation photochemotherapy used for treating psoriasis has also been associated with an increased risk of melanoma (13).

The most important host risk factors are the number of melanocytic nevi, familiar hystory and genetic susceptibility. Melanocytic nevi are benign accumulations of melanocytes or nevus cells and may be congenital or acquired. Approximately 25% of melanoma cases occur in conjunction with a pre-existing nevus (14). Moreover, the total nevus count is positively correlated with melanoma risk and it varies on the basis of number, size and type of nevi (15-17). The outcome of a recent meta-analysis underlined that patients with more than 100 nevi have a 7-fold increased risk for melanoma (18). Regarding the size, larger (>5 mm) and giant (>20 cm) nevi are associated with a significantly higher risk of melanoma (19). An atypical nevus is usually large, at least 5 mm, with a flat component and has atypical features such as variable pigmentation, irregular asymmetric outline and indistinct borders. Twenty-nine to 49% of non-familial melanoma cases occur in the setting of a pre-existing dysplastic nevus (20). Not

Table I. *Dermoscopic criteria for diagnosis of melanoma (reference 41).*

	Naevus	Melanoma
Pigment network	Reticular pattern with brown network small symmetrical holes and thin network lines	Black, brown, or gray network Irregular holes and thick lines Irregularly distributed and ending abruptly at the periphery
Dots/globules	Regular in size and shape and evenly distributed	Irregular dots and globules for the shape, size
Streaks	Regular and symmetrical and typical of Spitz or Reed nevi	Irregular and unevenly distributed
Irregular pigmentation	Not present	Black, brown, and gray pigmented areas with irregular shape and/or distribution
Regression structure	Not present	White scare-like areas, blue areas, or a combination of both
Blue-whitish veil	Not present	Confluent, irregular, and structureless area of whitish-blue dllfusc pigmentation associated with pigmented network, dots, globules, and streaks.
Vascular pattern	Not present	Irregular hairpin vessels, dotted vessels, linear irregular vessels, or vessels within regression structures

only atypical nevi are associated with an increased risk of melanoma; the presence of even a single nevus with atypical features enhances the risk. The presence of five atypical nevi give a six-fold increase for melanoma development (18, 21). Melanomas, which develop in the setting of previous nevi, are usually located on the trunk in younger patients and belong to the superficial spreading variety (22).

A family history of melanoma constitutes a strong risk factor for the disease. Considering that familial clustering of a disease is an indicator of possible heritable causes, there has been an explosion in research directed at elucidating the genetic basis for melanoma in the past two decades.

Tsao *et al*. studied families with inherited melanoma demonstrating the presence of a clear pattern of autosomal-dominant inheritance with multiple family members affected in more than the first generation. Mutations in cyclin-dependent kinase inhibitor 2A (*CDKN2A* or p16) were the most common genetic abnormalities found in these families, whereas mutation in cyclin-dependent kinase 4 (*CDK4*), was a more rare event (23). Patients with an underlying genetic predisposition to develop melanoma usually show occurrence at a younger age (<40 years), multiple primary melanomas or a history of precursor lesions such as dysplastic nevi and are more likely to have tumors that are superficially invasive and have a better prognosis (24-25). Additionally, patients with family cancer syndromes, *e.g.* familial retinoblastoma, Li-Fraumeni cancer syndrome and Lynch syndrome type II, show higher risk of developing melanoma (5).

Certain phenotypic characteristics such as red hair, fair skin, numerous freckles, light eyes, sun sensitivity and an inability to tan, raise the risk of developing melanoma by approximately 50% (26).

Patients belonging to the lower photo-types often develop featureless or amelanotic melanomas that are difficult to detect. For this reason its appears reasonable that they should be followed by a dermatologist independent of the presence of other risk factors (5).

Diagnosis

Early detection of malignant melanoma remains the key factor in lowering mortality. The prognosis in melanoma is directly proportionate to the depth of the neoplasm, which in turn increases with time. Indeed, in melanoma diagnosis, timely recognition, detection and rapid treatment of melanoma remain critical. Malignant melanoma, compared to other cancers, has the advantage of the cutaneous location, which permits its early detection through non-invasive approaches. Nevertheless, pathological examination remains the gold standard for diagnosis.

Skin self-examination. Skin self-examination has great potential as a simple, convenient method of screening for melanoma and precancerous lesions (27, 28). Before the 1980s, melanomas were often recognized by identifying clinically macroscopic features; they were often detected in an advanced stage when they appeared large, ulcerated and fungating (29).

The early recognition of melanoma is becoming an important public health priority (30). The challenge lies in identifying interventions to increase accuracy of skin self-examination for detecting lesions that have the highest probability for being melanoma.

Since there was a need to educate physicians and the public to recognize melanoma in its early clinical presentation, the "ABCD" criteria were developed in 1985. The ABCD acronym stands for Asymmetry, Border irregularity, Color variegation, Diameter >6 mm. Later the letter "E" was added

Table II. *Melanoma clinical subtypes*.

	%	Sun exposure	Localization	Clinical aspects	Colors
Superficial spreading melanoma	70	Intermittent	Back-Man Legs-Woman	Flat Papule Nodule	Tan, Brown, Gray, Black Violaceous, Pink
Nodular melanoma	5	Intermittent	Trunk Limb	Nodule Ulcerated polyp Elevated plaque	Brown Black Achromic
Lentigo maligna melanoma	4-15	Long term	Head Neck	Flat Papula	Brown Black
Acral lentiginoso melanoma	5	N/A	Glabrous skin (palmoplantar, subungueal)	Flat Nodule Plaque	Irregular, poorly circumscribed pigmentation
Desmoplastic melanoma	2	Long term	Head Neck	Papule Nodule	Erythemato us Flash colored Achromic
Melanoma arising from blu nevus	Rare	N/A	Head	Recent history of enlargement or change in pre-existing nevus	Blu-Black
Melanoma arising in a giant Congenital nevus	Rare	N/A	Trunk	Nodule growing in A nevus	Dark, brown Black
Melanoma of childhood	0,4	N/A	Think	SSM or NM	SSM: Tan, Brown, Gray, Black, Violaceous, Pink
Nevoid melanoma	1-2	N/A	Leg, trunk	Small papule	Tan to dark, brown

for Evolving, which is especially important for the diagnosis of nodular melanomas (31, 32). This criteria were intended to be a simple tool to alert both public and non-dermatologists healthcare professionals in differentiating common moles from cutaneous lesions most suspicious for early melanoma. They were not meant to provide a comprehensive template for the recognition of all melanomas, as a "good clinical eye" is still fundamental in the evaluation of the lesion (?). Adopting the ABCD(E) criteria, the sensitivity of self skin examination ranges from 57% to 90% (33, 34, 35).

Other clinical approaches have been developed to enhance early diagnosis, such as the Glasgow 7-point checklist, which includes 3 major criteria (change in size, shape, color) and 4 minor criteria (sensory change, diameter of 7 mm or greater; and the presence of inflammation, crusting or bleeding) (36). This checklist, because of its sophistication, has been less widely adopted than the ABCD criteria. Another paradigm is the "ugly duckling" sign. It is based on the perception that a pigmented lesion "looks different from all of its neighbours". This criteria for revealing suspected lesions has been shown to be sensitive for melanoma detection, even for non-dermatologists (37, 38).

Dermoscopy. In the diagnosis of melanoma various assistive optical devices are becoming essential. These devices include high-resolution optical handheld devices that have been designated as dermoscopes or dermatoscopes or epiluminescent microscopes (5).

Dermoscopy is a non-invasive diagnostic technique for *in vivo* observation of the skin; this device uses optic magnification to permit visualization of morphological structures that are not visible to the naked eye. Dermoscopy has increased the accuracy of melanoma detection since this approach renders early signs of the disease visible in the pigmented lesions much before clinical changes. There are, however, some dermoscopic criteria for the diagnosis of melanoma, the "melanoma-specific criteria" (39):

1. Atypical pigment network. One of the characteristics of melanocytic lesions is the reticular pattern, which is characterized by a pigmented light-to-dark brown network with small symmetrical holes and thin network lines covering most part of the lesion. Little changes in this pigmented network can be appreciated in early melanomas and when the atypical network is present, then, the likelihood of melanoma is increased. These changes lead to an atypical pigmented reticular pattern characterized by a black, brown or gray network with irregular holes and thick lines irregularly distributed throughout the lesion, usually ending abruptly at the periphery. However this atypical reticular pattern may also be present in benign melanocytic naevi especially in atypical melanocytic lesions rendering, thus, the differential diagnosis is difficult (39).

2. Irregular dots/globules. In pigmented lesions there is a possible presence of aggregated dots and globules. In benign melanocytic lesions dots and globules are regular in size and shape and are evenly distributed, while in malignant lesions irregular dots and globules (for the shape, size and the distribution within the lesion) are observed (39).

3. Irregular streaks. Streaks, also called radial streaming, radial streaks or pseudopods, are linear structures that may be observed throughout a lesion but are more apparent in the periphery. The presence of irregular streaks is strongly associated with melanoma, particularly when they are unevenly distributed. However, regular and symmetrical streaks are typical of some benign lesions such as Spitz or Reed nevi (39).

4. Irregular pigmentation. It is possible to observe black, brown and gray pigmented areas with irregular shape and/or distribution in melanoma cases (39).

5. Regression structure. Regression structures are also a characteristic of malignant lesions. During the process of regression, fibrosis and melanosis are usually found together and, thus, the regression structures appear as white scare-like areas, blue areas or a combination of both (39).

6. Blue-whitish veil. The blue-whitish veil is a confluent, irregular, structureless area of whitish-blue diffuse pigmentation associated with pigmented network, dots and globules, as well as streaks. It is relatively frequent in a malignant lesion and can be used for the diagnosis of melanoma (39).

7. Vascular pattern. Melanoma can be associated with irregular hairpin vessels, dotted vessels, linear irregular vessels or vessels within regression structures (39).

Total-body photographic images and short-term surveillance. Some melanomas can be diagnosed neither with the naked eye nor dermoscopically. But it is possible to create images that can be electronically captured, archived, retrieved and analyzed. In this way it is possible to detect minimal changes in the first stages of melanoma development. With this approach it is possible to follow the dynamic evolution of the melanocytic naevi over time (5, 39).

Reflectance Confocal Microscopy (RCM). Reflectance confocal microscopy has been shown to be a valuable imaging tool in the diagnosis of malignant melanocytic lesions. RCM allows non invasive examination of native skin in real-time at a nearly histologic resolution. The reflectance confocal microscope emits a near-infrared, coherent laser beam by which the human skin is illuminated. As the laser beam passes through the upper skin layers, it is partially backscattered due to the natural refractive index of microanatomical structures. This backscattered light has to pass through a narrow pinhole, which guarantees that only light reflected from structures "in focus" is detected; light

from elsewhere is blocked. After passing the pinhole, the beam is diverted by a semi-reflective mirror system and, finally, directed to a detector. The obtained data are processed and visualized by special software on a computer screen. In contrast to histological slides, which show colored vertical sections, the black-and-white RCM images correspond to horizontal (enface) sections at a selected depth within the skin. RCM reveals skin changes at a cellular level (39). Some of the major advantages of this non invasive imaging tool are: improvement of diagnostic accuracy, improved assessment of dermoscopic-histologic correlation, *in vivo* biopsy side selection, surgical margin assessment and response control of conservative therapies in skin disease (40). RCM is a promising diagnostic technique for melanocytic lesions although currently it is not used routinely.

Classification of Cutaneous Melanoma

In relation to clinical and histological features, melanoma can be divided into 3 main subtypes: superficial spreading melanoma, nodular melanoma and lentigo maligna melanoma.

Superficial Spreading Melanoma (SSM). SSM is the most common type of melanoma accounting for approximately 70% of the cases. It is related to the intermittent exposure to the sun and it is localized most often on the back of the legs of women and on the backs of men. Superficial spreading melanomas may arise de novo or in association with a nevus (5). From the clinical point of view, this cancer shows a variety of colors including tan, brown, gray, black, violaceus, pink and rarely blue or white. The lesion outline is usually sharply marginated with one or more irregular peninsula-like protrusions. The surface may have a palpable papule or a nodule that extends several millimeters above the skin surface.

Nodular Melanoma (NMM). It accounts for 5% of melanomas and most often occurs on the trunk and limbs of patients in the fifth or sixth decade of life; it is more common in males than females. Nodular melanomas are often ulcerated. It does not have a radial growth phase but it has only a vertical growth phase correlated with more rapid growth and higher rate of metastasis (5). Clinically, NMM has a relative uniform brown, black, or blue-black color; it can present as a smoothly-surfaced nodule, as an ulcerated polyp or as an elevated plaque with irregular outlines. In almost 50% of cases, NMM can be achromic. It is related with the intermittent exposure to the sun. Histologically, NMM is characterized by a predominance of dermal invasive tumor. An intradermal component may be present but directly overlies the invasive melanoma. The tumor is composed of small nests and aggregates of cancer cells that together form the overall tumor nodule (2).

Lentigo Maligna Melanoma (LMM). LMM accounts for 4% to 15% of cutaneous melanomas and, unlike NMM and SSM, correlates with long-term sun exposure and increasing age. This cancer may evolve for decades before invading into the papillary dermis (5). Clinically, it shows a variety of colors black, brown or brown on a tan background. It has irregular outlines and although the tumor is often relatively large and flat, a focus of invasion may be detected as a papule. It is located mainly at the neck and head (2). Histologically, it is characterized by a proliferation of cells that are localized to the basal layers of the epidermis.

Acral Lentiginous Melanoma (ALM). This skin cancer is uncommon, accounting for 5% of melanomas in white people but it is the most common type of melanoma among Asian, Hispanic and African patients. Typically, it affects elderly patients, with a female predominance. ALM is mainly localized on glabrous skin and adjacent skin of digits, palms and soles; it usually involves the nail bed of the great toe or thumb (5).

Desmoplastic Melanoma (DM). Desmoplastic melanoma often occurs in individuals between the age of 60 and 70 years, it rises on the head and neck but it can occur on a variety of cutaneous and mucosal areas. It is slightly more common in men. Clinically, desmoplastic melanoma may be amelanotic and it can present as an erythematous or pale or flash-colored nodule or plaque arising in sun-damaged skin. This cancer is positive for S100 and it may be difficult to differentiate desmoplastic melanoma from scars tissue because S100-positive cells can also be seen in dermal scars. This cancer often shows nerve infiltration and it is characterized by high recurrence rates due to their highly infiltrative growth and frequent perineural invasion. It has a high incidence of local recurrence but it rarely metastasizes to the lymph nodes; however, it has a propensity to metastasize to the lungs (5).

Other Rare Forms of melanoma have been also described, notably balloon cell melanoma, myxoid melanoma, osteogenic melanoma, rhabdoid melanoma, that will be discussed in another review.

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