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Melanoma Epidemiology, Risk Factors, and Clinical Phenotypes

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1. Introduction

Malignant melanoma is an aggressive malignancy responsible for nearly 60% of death from skin cancers. Recent advancements in the biology and molecular genetics of melanoma are accompanied by an improved appreciation of the roles of both intrinsic and extrinsic risk factors in their contribution to disease. This chapter reviews the epidemiology, risk factors, and clinical phenotypes of melanoma.

2. Melanoma epidemiology

Over the past two decades we have observed increases in the incidence of malignant melanoma in the Caucasian population, while overall mortality rates have remained somewhat stable. The incidence and mortality of melanoma is considered in terms of geography and ethnicity using data from the United States and worldwide.

2.1 U.S. melanoma epidemiology

Melanoma trends in the United States were examined using data from the Surveillance, Epidemiology, and End Results (SEER) Program, a National Cancer Institute program that collects cancer and survival data from approximately 26% of the U.S. population. The SEER data revealed an increase in age-adjusted incidence rates of melanoma, which more than doubled among females and nearly tripled among males between 1973 and 1997 (Jemal *et al.*, 2001). After an additional 7 years of SEER data, it was found that among young adults (aged 15–39 years) there was an increase in melanoma incidence among young women, and the authors suggested a possible role of ultraviolet radiation exposure, as discussed in further detail below (Purdue *et al.*, 2008). Melanoma incidence has increased at 3.1% per year, with increases in tumors of all subtypes and thicknesses, and non-significant increases in melanoma mortality (Linos *et al.*, 2009). The median age of melanoma diagnosis is 60 years, with an age-adjusted incidence of 20.1 per 10,000 individuals, from 2003–2007 (SEER website, accessed 2011).

There are differences in melanoma incidence and mortality dependent upon ethnicity. The SEER data shows the highest incidence among Caucasians (19.1 females and 29.7 males per 100,000), followed by Hispanics (4.7 females and 4.4 males per 100,000), American Indians/Alaska Natives, Asian/Pacific Islanders, and Blacks (1.0 females and 1.1 males per 100,000)(SEER website, accessed 2011). Incidence data are depicted in Figure 1. Among U.S.

Hispanics and non-Hispanics from 2004–2006, it was noted that Hispanic melanoma patients had poorer prognostic characteristics (stage, tumor depth, and ulceration) at the time of diagnosis (Merrill *et al.*, 2011). Comparing the same ethnic groups over different regions of the country, male Hispanic Floridian patients had a 20% higher and non-Hispanic black Floridian patients had a 60% higher incidence of melanoma compared to non-Florida patients of the same gender and ethnicity (Rouhani *et al.*, 2010). The SEER data projected that, in 2010, there would be 68,130 new melanoma diagnoses and melanoma-related deaths among 8,700 men and women (SEER website, accessed 2011). The median age at death is 68 years, with the highest death rates among the U.S. Caucasian population (2.0 females and 4.5 males per 100,000), followed by American Indian/Alaska Natives, Hispanics, Blacks, and Asian/Pacific Islanders, from 2003–2007 (SEER website, accessed 2011). Overall mortality is depicted in Figure 1. African American patients with melanoma have poor overall survival outcomes, which were not explained by external factors such as treatment discrepancies or socioeconomic status (Zell *et al.*, 2008). One plausible contributor is the anatomic distribution of melanomas in patients of differing cutaneous pigmentation. Whereas melanomas are most likely to occur on typical cutaneous surfaces in Caucasians, they are proportionally more common (though of similar overall incidence) on acral (hairless) or mucosal surfaces among darkly pigmented individuals—surfaces commonly associated with thicker lesions at diagnosis.

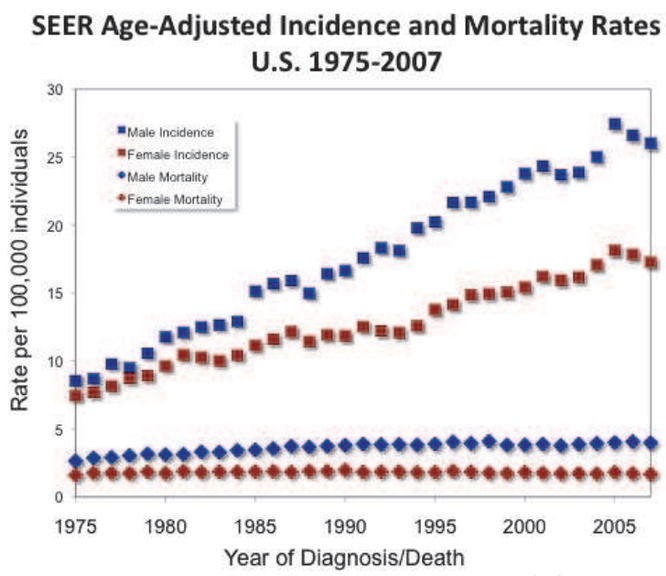

Fig. 1. Melanoma Incidence and Mortality Rates in the United States from 1975-2007. Data was extracted from the SEER database (SEER website, accessed 2011).

2.2 Global melanoma epidemiology

Data from a variety of countries and latitudes show similar trends in the incidence of melanoma. The role of geographic latitude on sun exposure was examined through pooled analysis of case-control studies including 5,700 melanoma cases (Chang *et al.*, 2009a; Chang *et al.*, 2009b). A meta-analysis of risk factors for cutaneous melanoma found that latitude is an important risk factor for melanoma (P=.031), and higher latitudes (distant from the equator) conferred an increased risk for sunburns (another melanoma risk factor), possibly

due to intermittent intense sun exposure (Gandini *et al.*, 2005a). The role of sun and ultraviolet exposure will be explored in further detail below.

Epidemiological data on melanoma incidence is available from a number of countries. In Australia between 1990 and 2006, there was a stabilization of the thin melanoma rate, and the highest rates of melanomas occurred in the northern tropical regions; however, there was also an increase in the number of thick melanomas, particularly in the southern regions (Baade *et al.*, 2011). The authors speculated that the decrease in thick melanomas may be positively affected by early detection and skin awareness campaigns (Baade *et al.*, 2011). A 10-year study of melanoma in a central England population revealed an increase in thin melanoma, particularly among younger patients, and a slower increase in thick (>4mm) and intermediate (1.01–4mm) melanomas (Hardwicke *et al.*, 2011). In Northern Ireland, a seasonal variation of melanoma diagnosis timing suggested that incidence of cutaneous melanoma is highest in the summer; the trend was most prominent for women (Chaillol *et al.*, 2011). Analysis of malignant melanoma incidence in Turkey from 1988–2007 showed a median age of melanoma diagnosis of 52 years and statistically significant increases of melanoma incidence with increasing age (Tas, 2011).

Global data for melanoma is available from the World Health Organization (WHO), which states that the incidence of melanoma has been increasing over the past decades, with 132,000 melanomas occurring globally each year (WHO website, accessed 2011). The annual incidence increase varies among populations (estimated 3–7%), while overall mortality rates have been increasing at a lesser rate (Diepgen and Mahler, 2002; Lens and Dawes, 2004). From the mid-1950s through the mid-1980s, melanoma mortality rose among young and middle-aged adults in most of Europe, North America, Australia, and New Zealand (La Vecchia *et al.*, 1999). Between 1985 and 1995, there was a continued increase in mortality (though at lesser rates) in middle-aged men and declining mortality rates in middle-aged women in northern Europe, North America, Australia, and New England (La Vecchia *et al.*, 1999). Overall global increases in cutaneous malignant mortality were reported in 2000, based upon data from countries with a minimum time series of 30 years and 100 deaths annually in one sex from melanoma. This analysis revealed small decreases in mortality rates in Australia, Nordic countries, and the United States; lesser decreases in the United Kingdom and Canada; and ongoing increases in melanoma mortality rates in France, Italy, and Czechoslovakia (Severi *et al.*, 2000). Mortality also continued to increase among patients in Spain (Nieto *et al.*, 2003). Regional and worldwide campaigns to increase melanoma awareness have been launched, as survival is associated with thickness of lesion at the time of diagnosis.

2.3 Trends in melanoma epidemiology data

There exists some debate over the explanation for the observed trends in epidemiological measures, which suggest overall increases in disease incidence, with some stabilization of mortality rate over time. Likely there is some contribution associated with longer life expectancy and improved detection of cancer (Balducci and Beghe, 2001); however, the debate among experts continues as to whether there is a true increase in disease versus better detection with improved surveillance (Lamberg, 2002). It has been questioned whether the increased disease surveillance programs have succeeded to identify melanomas with more indolent behavior (Swerlick and Chen, 1996), as it is shown that the incidence of biopsy rates between 1986 and 2001 was associated with an increase in diagnosis of in situ and local melanomas, but not the incidence of advanced melanomas, in nine geographical areas of the United States (Welch *et al.*, 2005). More frequent thinner melanoma detection

was also noted in Germany and France (Lasithiotakis *et al.*, 2006; Lipsker *et al.*, 2007). A large-scale prospective randomized survival-based study has not been carried out to prove benefit of skin cancer screening—although the requirement for such a study, or the ethics of being randomized to a non-screening arm, remains controversial.

While the expansion of skin screening programs may have increased the detection of relatively indolent melanomas, other studies have found that there are also increases in melanomas of all thicknesses (Linos *et al.*, 2009), so the detection of more histologically aggressive melanomas may be increasing as well. To address concern that the histological diagnosis of melanoma has drifted over time, with lesions classified more severely over time, a large 9-country review of pigmented lesions was conducted. This study examined diagnoses of pigmented lesions between approximately 1930 and 1980 and found only a 2.8% shift of melanoma cases from benign to malignant classification (van der Esch *et al.*, 1991), thus the increased disease incidence cannot be solely attributed to drift in histological interpretation. The debate over whether the increase in melanoma incidence reflects a true "melanoma epidemic" is also complicated by a number of biases and controversies, including surveillance intensity, length-time bias, diagnostic uncertainty, the cancer-relevant medico-legal climate, and problems related to data collection and recording (Swerlick and Chen, 1997; Florez and Cruces, 2004). Questions have been raised regarding a potential underreporting of melanoma over time, with estimates as high as 17% in the SEER database (Purdue *et al.*, 2008). Regardless of the interpretation of epidemiology measures, these studies have offered insights on trends in melanoma incidence and mortality, in addition to the intrinsic and extrinsic risk factors that are increasingly important in the management and prevention of future disease.

3. Melanoma risk factors

Melanoma risk factors include both intrinsic (genetic and phenotype) and extrinsic (environmental or exposure) factors. While intrinsic factors are inherent to the patient and cannot be modified, it is important to identify the at-risk population of patients. Conversely, extrinsic factors, from environment to behaviors, should be examined and minimized as possible, especially for the population with intrinsic increased melanoma risk. Major risk factors for melanoma include ultraviolet radiation exposure, family history, nevi (dysplastic, large number, or giant congenital nevi), increased age, fair skin phototype, occupation, and BMI (Rigel, 2010).

3.1 Intrinsic risk factors

Intrinsic melanoma risk factors are non-modifiable attributes that influence one's risk of melanoma, including age and gender, Fitzpatrick skin phototype (which is a gauge of one's skin color and burning or tanning response to sun exposure), and nevi pattern (quantity, size, clinical atypia, or dysplasia), which are readily apparent on examination. Also considered are the impacts of a patient's family history of melanoma, personal history of skin cancer, and underlying medical conditions including obesity, immunosuppression, cancer, and Parkinson's disease.

3.1.1 Age and gender

Melanoma is among the most rapidly rising cancers in the United States, with highest melanoma risk among elderly males (Jemal *et al.*, 2001). There is a general increase in

lifetime melanoma risk with advancing age for both men and women (Psaty *et al.*, 2010). Among patients with melanoma, the incidence of development of a second primary melanoma is 5.3% at 20 years and is also highest in older male patients (Goggins and Tsao, 2003). Older patients were found to have lentigo maligna melanoma more often than younger patients, with 75% occurring on the head and neck (Elwood *et al.*, 1987). Risk based upon sex is greater overall in males; however, incidence is higher in women until the age of 40 and then greater in males, with a ratio of 2:1 males: females by age 80 (Rigel, 2010). The SEER dataset shows the highest mortality among elderly males in all races from 1992-2007, with a mortality rate of 30.9 per 100,000 among males over age 85, in contrast to the highest female mortality rate of 12.4 per 100,000 for patients over age 85. Elderly males have disproportionately greater melanoma mortality, with mortality rates that are greater than double the female mortality rate when comparing all age groups over 55 years (SEER website, accessed 2011).

3.1.2 Skin phototype

An increased risk of melanoma has long been associated with characteristics of low Fitzpatrick skin phototype, such as pale skin, blond or red hair, freckles, and tendency to burn and tan poorly (Bataille and de Vries, 2008). The greatest risk is among patients with red hair or fair complexions, followed by those who burn easily, tan poorly, and freckle (Rigel, 2010). Fitzpatrick phototype I skin versus phototype IV imparts a relative risk of 2.09 of developing melanoma, with an increased relative risk for individual physical attributes such as fair skin color (2.06 versus dark), blue eye color (1.47 versus dark), red hair color (3.64 versus dark), and high density of freckles (relative risk of 2.10), as calculated by systematic meta-analysis of observational studies of melanoma risk factors (Gandini *et al.*, 2005b). A large prospective study from Norway and Sweden (>100,000 women) showed statistically significant risk of melanoma associated with hair color (red versus dark brown/black), in addition to other factors such as large body surface area (at least 1.79 m2) and number of large asymmetric nevi on legs (Veierod *et al.*, 2003), as reviewed below. The genetics associated with a clinical phenotype of red-haired patients with melanoma is discussed in further detail in Section 4.

3.1.3 Nevi

Dysplastic nevi are markers for increased melanoma risk, for both the individual and his or her family (Rigel, 2010). The presence of more than 50 common nevi, dysplastic nevi, or large nevi is associated with increased melanoma risk. Pooled studies involving 5,700 melanoma patients supported an increased risk with a nevus phenotype including greater whole body nevus counts, presence of clinically atypical nevi, or presence of large nevi, regardless of latitude (Chang *et al.*, 2009b). Their data showed a strongly increased risk with the presence of large nevi on the body and arms, and it suggested that an abnormal nevus phenotype is associated with melanomas on intermittently sun-exposed body sites (Chang *et al.*, 2009b). Clinically dysplastic nevi were associated with increased melanoma risk depending upon their number: One dysplastic nevus imparts 2-fold risk, while 10 or more dysplastic nevi impart a 12-fold increased risk of melanoma (Tucker *et al.*, 1997). Presence of a scar was identified as an independent risk factor for melanoma, as a scar may suggest the prior removal of a clinically atypical nevus at the site (Tucker *et al.*, 1997).

Nondysplastic nevi are also associated with increased melanoma risk when there are a large number of nevi and/or giant pigmented congenital nevi. The presence of large numbers of

nondysplastic nevi confers a lesser risk than dysplastic nevi. Having many small nevi imparts approximately 2-fold increased risk, and the presence of both small and large nondysplastic nevi imparts a 4-fold risk (Tucker *et al.*, 1997). Congenital nevi were not associated with increased melanoma risk (Tucker *et al.*, 1997); however, giant pigmented congenital nevi (covering >5% body surface area) confer substantial melanoma risk (Swerdlow *et al.*, 1995).

3.1.4 Changing skin lesions

Changing skin lesions are associated with melanoma risk, as 75% of melanoma patients presented with a symptom or complaint associated with their melanoma lesion, most commonly "increase in size" (Negin *et al.*, 2003). Patient complaints that strongly associated with an increased Breslow depth of melanoma upon multivariate analysis include bleeding, pain, lump, itching, and change in size (Negin *et al.*, 2003).

3.1.5 Personal history of skin cancer

An important risk factor for melanoma is having a prior skin cancer, of either melanoma or non-melanoma type. Among patients diagnosed with a primary melanoma, 11.4% will develop a second primary melanoma within five years, and the risk is further increased if the patient also has a positive family history of melanoma or dysplastic nevi (Ferrone *et al.*, 2005). Risk of a second primary cutaneous melanoma among melanoma patients is found to be 6.01 per 1,000 person years after analysis of 20 years of follow-up in Queensland from 1982–2003 (McCaul *et al.*, 2008). Analysis of a Swiss registry found the 20-year incidence of second primary melanoma to be 5% (Levi *et al.*, 2005).

A retrospective study of patients with multiple primary melanomas identified several risk factors for multiple melanomas such as early age at diagnosis, dysplastic nevi (diagnosed clinically or histologically), family history of dysplastic nevi or melanoma, and history of dysplastic nevus with a family history of melanoma (Stam-Posthuma *et al.*, 2001). In a large prospective cohort study of Queensland patients, risk factors for development of a second cutaneous melanoma were found to be similar: high nevus count, high familial melanoma risk, fair skin, inability to tan, an *in situ* first primary melanoma, and male sex (Siskind *et al.*, 2011).

A prior diagnosis of non-melanoma skin cancer is generally indicative of a history of UV exposure, which is an extrinsic risk factor that will be discussed in detail below. Patients with a history of squamous cell carcinoma, basal cell carcinoma, or pre-malignant actinic keratoses are reported to have a relative risk of developing melanoma of 4.28–17 (Marghoob *et al.*, 1995; Gandini *et al.*, 2005b). Interestingly, other cutaneous neoplasms that don't associate as strongly with ultraviolet exposure have also been associated with an increased melanoma risk. Patients with mycosis fungoides carry a relative risk of 15.3 for development of melanoma, which may be related to immunosuppression or pathophysiology caused by the disease and/or associated therapies (Pielop *et al.*, 2003). In Merkel Cell Carcinoma, an increased risk for melanomas has not been established, though the high fatality and advanced age of Merkel Cell Carcinoma patients may reduce the opportunity to develop additional cancers (Howard *et al.*, 2006).

3.1.6 Family history of melanoma

A family history of melanoma has long been associated with increased melanoma risk; having a primary relative with melanoma imparts a relative risk of 1.74 of developing

melanoma (Gandini *et al.*, 2005b). The highest risk occurs when a parent has multiple melanomas, with a relative risk of 61.78 (Hemminki *et al.*, 2003). The Familial Atypical Multiple Moles and Melanoma (FAMMM) syndrome describes a syndrome in which two or more primary relatives have multiple dysplastic nevi and a history of melanoma (Fusaro and Lynch, 2000). Often these patients carry mutations in the *CDKN2A* gene or the related pathway, as described below. Among melanoma prone-families followed prospectively, the cumulative risk of developing melanoma at a young age (before age 50) was 48.9% (Tucker *et al.*, 1993), and close surveillance is recommended. As described below, a family history of melanoma may arise from shared environmental risks, rather than purely genetically based risks.

3.1.7 Other personal medical history

A variety of medical conditions beyond a personal history of cutaneous carcinomas have reported associations with melanoma. Inherent diseases are described in this section, while associations with medical treatments are considered external risk factors and discussed in further detail below.

There may be an increased risk of melanoma with elevated body mass index, as a meta-analysis of 141 articles revealed a statistically significant positive association between increased BMI and malignant melanoma in men, though not as strong of an association that exists for esophageal, thyroid, colon, or renal cancers (Renehan *et al.*, 2008).

Both the immune system and DNA repair mechanisms are known to have important roles in protection from melanoma. Accordingly, in AIDS, there appears to be elevated risk of melanoma, which is highest among men who have sex with men, according to analysis of population-based U.S. AIDS and cancer registries in 2009 (Lanoy *et al.*, 2009). A history of organ transplantation carries increased melanoma risk, with melanoma occurring in 6% of adult transplant recipients and 14% of patients who received organ transplantation in childhood (Penn, 1996). However, non-melanoma skin cancers, particularly squamous cell carcinomas, present with higher frequency than melanomas after organ transplantation (Moloney *et al.*, 2006). Organ transplantation also carries a risk of transmission from the donor organ if the donor was previously affected with melanoma, and a diagnosis of melanoma requires careful consideration about whether to donate, or to revise the recipient patient's transplant immunosuppression regimen (Zwald *et al.*, 2010). Another population at increased risk of melanoma includes patients with xeroderma pigmentosum, who have defective DNA repair capability and are diagnosed with melanoma at a 5% rate. In these patients, 65% of their melanomas occurred on locations exposed to ultraviolet radiation such as the face, head, or neck (Kraemer *et al.*, 1987). Ultraviolet radiation is associated with gene mutations and increased melanoma risk as discussed in further detail below.

A number of non-cutaneous carcinomas have been shown to have associations with melanoma. Among women with a history of previous breast cancer, there is a standardized incidence ratio of 1.4 signifying an increased risk for cutaneous malignant melanoma among a Swiss Cancer Registry including 9,729 breast cancer patients followed over 24 years (Levi *et al.*, 2003). The Breast Cancer Linkage Consortium studied cancer risks in *BRCA* mutation carriers and found that *BRCA2* mutation carriers have an increased risk of developing malignant melanoma (2.58 relative risk) (The Breast Cancer Linkage Consortium, 1999), while *BRCA1* mutation carriers have an increased risk for colon cancer and prostate cancer, but no significant excesses in rates of cancers of other body sites (Ford *et al.*, 1994). Patients with a history of chronic lymphocytic leukemia or non-Hodgkin's lymphoma have an

increased risk of melanoma, as malignant melanoma is among the most common presenting second cancer in both patient populations (Travis *et al.*, 1991; Travis *et al.*, 1992).
Associations with pancreatic carcinoma and renal cell carcinoma are explored based upon the discovery of gene mutations that are similar to those mutated in familial melanomas. In a study of familial pancreatic carcinoma families, 12% of these families carried a *CDKN2A* mutation (Lynch *et al.*, 2002). There is also an association of patients with melanoma and renal cell carcinoma, as both types of cancer carry an increased risk for the other. A study of 42 patients with both melanoma and renal cell carcinoma found a high frequency of positive melanoma family history, though the identification of only two *CDKN2A* mutant carriers in this series suggests that there may be a *CDKN2A*-independent genetic association involved (Maubec *et al., 2011*).
A putative association between Parkinson Disease and melanoma has been controversial and was perhaps based on the fact that both diseases involve cells that metabolize tyrosine via dopaquinone intermediates (albeit using distinct enzymes, tyrosine hydroxylase vs. tyrosinase). Literature review does not offer evidence that levodopa therapy is associated with development of malignant melanoma (Pfutzner and Przybilla, 1997). In 1978, levodopa therapy, a mainstay of Parkinson Disease management, was examined in a prospective query of 1,099 melanoma patients; at the time of presentation, only one patient had been taking levodopa (Sober and Wick, 1978). A family history of melanoma conferred an increased multivariate relative risk of developing Parkinson Disease among 157,036 individuals followed prospectively, with no associations between a family history of other major types of cancer or several environmental risk factors (Gao *et al.*, 2009). In addition, a recent study showed an increased melanoma risk in patients with Parkinson disease (prevalence was 2.24-fold higher than age and sex-matched SEER population data), and it was recommended that these patients be followed closely for skin changes over time (Bertoni *et al.*, 2010).

3.2 Extrinsic risk factors

In this section, external factors that are associated with melanoma risk are considered. Aspects of a patient's social history, such as their occupation, socioeconomic status, and marital status, have been shown to impact melanoma risk, though the mechanism for these interactions is not well understood. The risk of ultraviolet exposure is more readily explained, and data have accumulated regarding the effects of both natural and artificial ultraviolet radiation. Medications and chemical exposures can influence melanoma risk, and new studies have examined whether medications can play a role in modification of one's melanoma risk.

3.2.1 Social history

Analysis of 29,792 cases of melanoma in California for trends involving socioeconomic status showed that individuals who lived in areas of highest socioeconomic status were at increased risk for melanoma (Linos *et al.*, 2009). Low socioeconomic status is also regarded as a poor predictor of melanoma outcomes and has been associated with disparities in utilization of sentinel lymph node biopsy (Zell *et al.*, 2008; Bilimoria *et al.*, 2009). Financial concerns were found to influence outcomes of disease in melanoma patients; a retrospective study found that perceived financial difficulty (compared to patients with an equivalent deprivation score) was related to recurrence risk, after adjusting for histological characteristics of the melanoma (Beswick *et al.*, 2008). Examination of SEER data of

melanoma patients for the effect of marital status on melanoma stage, after controlling for a number of factors including histology, anatomic site, and socioeconomic status, suggested that unmarried patients had a higher risk of late-stage cutaneous melanoma diagnosis (McLaughlin *et al.,* 2010).

Occupation is associated with greater melanoma incidence in indoor workers and those with higher education, in addition to occupation-specific associations that have been observed utilizing cancer registries (Rigel, 2010). Analysis of cancer registries in England, Wales, and Sweden found the highest occupation-associated risk to be with airline pilots, finance and insurance brokers, professional accountants, dentists, inspectors, and supervisors in transport, with many of these professions sharing a high level of education (Vagero *et al.*, 1990). Among males in a California cancer database that listed fire fighter as their occupation, there was an increased risk of melanoma, in addition to increased risks of testicular cancer, brain, esophageal, and prostate cancers, compared to other types of cancer (Bates, 2007). Occupation-specific non-solar exposures impart increased melanoma risks for workers in the petroleum, printing, electronics, automobile, and agricultural industries (Fortes and de Vries, 2008), and specific occupational chemical exposures are reviewed below.

Those who are employed outdoors may have altered melanoma risk based upon ultraviolet exposure, an independent risk factor for melanoma. In 2005, Gandini *et al.* performed a meta-analysis and found an inverse association of high occupational sun exposure with melanoma (Gandini *et al.*, 2005a), while others have shown that occupational exposure carries an increased risk of melanoma of the head and neck, especially at low latitudes (Chang *et al.*, 2009a). The shift hours associated with one's occupation has also been shown to impact melanoma risk, though the mechanism is not clear. Among 68,336 women in the Nurses' Health Study from 1988–2006, there was a 44% decreased risk of skin cancer among nurses working 10 or more years on rotating night shifts compared to nurses who never worked night shifts, after adjustment for melanoma risk factors (Schernhammer *et al.*, 2011).

3.2.2 Ultraviolet exposure

The International Agency for Research on Cancer (IARC) identified solar and ultraviolet radiation as a significant environmental risk factor for cutaneous malignant melanoma (IARC, 1992), and in 2009 an IARC working group classified UV-emitting devices as group 1 carcinogens (El Ghissassi *et al.*, 2009). Ultraviolet radiation reaching the earth's surface is comprised of ultraviolet A and ultraviolet B radiation. Ultraviolet A light generally causes guanosine to thymine transversions, possibly due to oxidation of DNA bases (Pfeifer *et al.*, 2005). Ultraviolet B light characteristically generates mutations at dipyrimidine sequences with cytosine (which occurs in approximately 35% of *p53* gene mutations). Overall, the ultraviolet radiation-induced DNA mutations render DNA repair machinery an important protection against melanoma, which is particularly problematic for patients with defective DNA repair. Some have raised concern that climate change and ozone depletion will lead to increased solar ultraviolet radiation exposure, which may further correlate with increases in skin cancer (Diffey, 2004). Recently, the 10-year follow-up of a prospective study of daily or discretionary sunscreen application showed that daily sunscreen use reduced the rate in total melanomas and significantly reduced the rate of invasive melanomas as well (Green *et al.*, 2011).

Recreational or intermittent sun exposure was associated with increased melanoma risk of the trunk and limbs, but not head and neck, regardless of latitude of residence (Chang *et al.*,

2009a). Intermittent sun exposure is also associated with increased numbers of nevi (a potent melanoma risk factor) and nevi located at intermittently exposed body sites (Newton-Bishop *et al.,* 2010). Solar (actinic) keratoses and reported sun exposure strongly influence melanomas localized to the head and neck, while sporadic intermittent exposures, blistering sunburns, and self-reported sunburns are associated with an overall increased melanoma risk on all major body sites (Olsen *et al.*, 2010; Rigel, 2010).

While intermittent sun exposure and a history of sunburns are associated with up to 65% of malignant melanomas, the cumulative ultraviolet radiation exposure and pattern are also significant considerations. In a systematic review of case-control studies, melanoma risk was positively associated with intermittent sun exposure and sunburn at all ages (adult, adolescence, and childhood), in contrast to a reduced rate of melanoma in individuals with high occupational ultraviolet exposure (Elwood and Jopson, 1997). Ultraviolet exposure pattern can also impart risk for specific melanoma subtypes. The lentigo maligna melanomas were less strongly related to intermittent sun exposure or skin reaction to sun, in contrast to superficial spreading melanomas and nodular melanomas. Of these types, superficial spreading melanomas were most strongly associated with vacation sun exposures (Elwood *et al.*, 1987).

3.2.3 Molecular features of mutations

Although UV radiation is strongly associated with risk for development of melanoma, it is striking that signature UV mutations (pyrimidine dimers) are much less frequent within mutated oncogenes of melanomas than in non-melanoma skin cancers. An important terminology is used to discriminate genomic mutations which actively promote oncogenic behavior from those which are biologically silent. "Driver" mutations are functionally important in conferring cancerous phenotypic changes, whereas "passenger" mutations are indicative of carcinogenic exposure, but do not actively contribute to malignant behavior of the cell. A human melanoma was the first malignancy for which complete genomic sequencing was reported, and compared to a matched lymphocyte cell line derived from the same patient (Pleasance *et al.*, 2010). In this study thousands of mutations were observed, including numerous pyrimidine dimers indicative of prior UV exposure. However comparatively few mutations were observed within gene coding regions (vs. intergenic zones of the genome) suggesting relatively efficient transcription-coupled DNA repair. Indeed the patterns of UV signature mutation were more informative about the molecular geneology of the tumor than the nature of its precise oncogenic "drivers."

3.2.4 Recreational tanning

A recent study in Denmark examining travel and sun-related behavior from 2007–2009 found that 69% of subjects tanned intentionally, and this was the most important factor in sunburn on vacation (Koster *et al.,* 2011). Prospective data from The Women's Lifestyle and Health Cohort Study including over 100,000 women from Norway and Sweden indicated that sunburns and solarium use (described below), particularly during adolescence and early adulthood (ages 10–39), are associated with increased melanoma risk (Veierod *et al.*, 2003).

Typical 5-minute sunlamp tanning exposures increase melanoma risk by 19% for frequent users (over 10 sessions) and by 3% for occasional users (less than 10 sessions), with primary melanomas most commonly located on sites that are not generally exposed to sunlight

(Fears *et al.,* 2011). Hery *et al*. described a significant increase in melanoma incidence in Iceland between 1954 and 2006, with increased incidence rates in women younger than 50 years (Hery *et al.,* 2010). They had postulated that UV-emitting tanning devices would increase melanoma incidence on the trunk (Boniol *et al*., 2004) and presented data suggestive of a possible influence of indoor tanning bed use on this increase (Hery *et al.,* 2010). From 1975–2006, SEER data revealed an increase in melanomas arising on the trunk among young women in the United States (Bradford *et al., 2010*). Examination of the Australian Melanoma Family Study data regarding indoor tanning bed use and melanoma risk identified associations of tanning bed use with increased early-onset melanoma, with increased risks for those who use tanning beds more frequently and at an earlier age (Cust *et al., 2010*).

Several studies have indicated clear associations between indoor tanning and elevated melanoma risk. Lazovitch *et al.* observed increased melanoma risk in multiple groups of indoor tanning bed users (Lazovich *et al.*, 2010). The data were in agreement with a prior meta-analysis of the same question published by the The International Agency for Research on Cancer Working Group on artificial ultraviolet (UV) light and skin cancer (*Int J. Cancer,* 2007). This study demonstrated elevated melanoma incidence in users of indoor tanning beds, and formed the basis for the subsequent designation of tanning beds as Class I carcinogens by the World Health Organization. An additional important aspect of indoor tanning is its association with addictive behavioral patterns. Studies by Feldman and colleagues revealed evidence of withdrawal-like symptoms in frequent tanning bed users who volunteered to receive a dose of the opiate antagonist naltrexone (Kaur *et al*., 2006). Frequent tanners were also able to discriminate UV-emitting tanning beds from "sham" tanning beds in a blinded study (Feldman *et al*., 2004). A recent questionnaire-based analysis of a cohort of frequent tanners indicated that 39% met DSM IV criteria for addiction to indoor tanning (Mosher and Danoff-Burg, 2010). The precise underlying mechanism(s) of this addiction remain to be determined, but it is plausible that such behaviors may underlie the unremitting increases in melanoma incidence described above.

3.2.5 Medications

Medications such as psoralens can artificially increase ultraviolet induced damage, significantly increasing melanoma risk. Patients receiving photochemotherapy with oral methoxsalen and ultraviolet A light have increased melanoma risk with a large number of treatments (at least 250), and the risk increases at 15 years after the first treatment (Stern *et al*., 1997) and appears to continue to increase with further passing of time (Stern, 2001).

Some data exist for a decreased risk of melanoma with long-term (>5 years) use of cholesterol-lowering drugs in analysis of the Cancer Prevention Study II Nutritional Cohort from 1997–2007 (Jacobs *et al*., 2011), and higher doses of statin medications were associated with decreased melanoma risk upon analysis of a Veteran's Administration pharmacy database (Farwell *et al*., 2008). However, the effect of long-term statin use on melanoma risk was not evident upon analysis of the Kaiser Permanente database (Friedman *et al*., 2008).

Female sex hormones and oral contraceptive use have been called into question regarding a potential increased risk of melanoma, given the slightly higher risk of breast cancer patients for melanoma (Levi *et al*., 2003), and the fact that estrogens can increase melanocyte counts and cause cutaneous hyperpigmentation. An examination of Nurses' Health Study and Nurses' Health Study II cohorts revealed a 2-fold increase in melanoma risk among oral contraceptive users, and a further increased risk among premenopausal women who took oral contraceptives for 10 or more years (Feskanich *et al*., 1999). Since that time, a number of

case reports and small cohort studies have offered conflicting information regarding hormonal therapy and melanoma risk. A Netherlands retrospective study found a cumulative dose-dependent increased risk of melanoma with hormone replacement therapy use (Koomen *et al.*, 2009b), though the same authors found no association of estrogen use with increased anatomic thickness of cutaneous melanoma (Koomen *et al.*, 2009a). Studies in mice demonstrated that the antiestrogen tamoxifen inhibited both development and metastasis in mouse melanoma (Matsuoka *et al.*, 2009), though study of tamoxifen in patients with melanoma showed no improvement in overall response rate, complete response rate, or survival rate when administered with systemic chemotherapy (Lens *et al.*, 2003). Pregnancy had no influence on disease-free survival in patients with a history of stage I cutaneous malignant melanoma (Albersen *et al.*, 2010).

Pooled analysis of case control studies including 5,590 women found a lack of association between melanoma risk and pregnancy, and no relation between melanoma and exogenous hormone use (Lens and Bataille, 2008). Regarding the facts and controversies surrounding a hormonal influence on melanoma risk, at this time, exogenous hormone use is not contraindicated, though counselling should be performed on an individualized basis (Gupta and Driscoll, 2010). While the role of estrogens have not been definitively demonstrated in melanoma, some still suspect melanoma may be a hormone-related neoplasm (de Giorgi *et al.*, 2011).

3.2.6 Chemical exposures

A possible association of melanoma exists with ionizing radiation, as well as chemicals and pollutants such as arsenic (Rigel, 2010). Occupational exposures to chemicals such as vinyl chloride, polychlorinated biphenyls, and petrochemicals have been linked to a possible increased risk of melanoma, though the contribution of these exposures to overall melanoma risk has not been consistently demonstrated in clinical studies (Markovic *et al.*, 2007). Fortes and deVries have reviewed the literature for occupation-specific exposures with cutaneous melanoma and summarized the evidence implicating polycyclic aromatic hydrocarbons, benzene, and polychlorinated biphenyls; trichloroethylene solvents, dioxin, and polyvinyl chloride; pesticides; and ionizing and non-ionizing radiation (Fortes and de Vries, 2008). Agricultural pesticides including mancozeb, parathion, and carbaryl were shown to associate significantly with cutaneous melanoma after adjustment for confounding factors (Dennis *et al., 2010*). There is concern that residential pesticide use may also impart increased cutaneous melanoma risk, as data from Italy supports a 2.18 odds ratio for high use of indoor pesticides (four times annually) versus low use (once annually) (Fortes *et al.*, 2007).

3.2.7 External factors and melanoma risk modification

Recent prospective data offers a role for daily sunscreen use in the reduction of melanoma frequency and invasion (Green *et al.*, 2011). Whereas prior studies had failed to consistently demonstrate such a benefit, this study incorporated 10-year followup, suggesting a longer latency between UV exposures for melanoma as compared to cutaneous squamous cell carcinoma. Additionally, attempts have been made to demonstrate benefit for supplementation of one's diet with vitamin D or non-steroidal anti-inflammatory drugs, for which conclusive positive effect has not been demonstrated at this time.

There remains controversy regarding the optimal level of serum vitamin D with respect to bone health, cancer, and wellness. A prospective cohort study suggested that vitamin D (serum 25-hydroxy-vitamin D3) levels are associated with lower Breslow thickness of

melanoma at the time of diagnosis, as well as being protective of survival in terms of melanoma relapse and death independent of melanoma thickness (Newton-Bishop *et al.*, 2009). However, at this time, there are no data to indicate that supplementation with vitamin D after diagnosis is protective for melanoma (Hutchinson *et al.*, 2010).

Studies have explored a potential protective effect of non-steroidal anti-inflammatory drugs and acetylsalicylic acids, based on a chemopreventative effect for other cancer types in addition to promising *in vitro* laboratory studies that suggested a potential role in the inhibition of melanoma migration and invasion. A large, Dutch case-control study found that continuous use of low-dose acetylsalicylic acids imparted a significantly reduced incidence of melanoma in women, but not in men (Joosse *et al.*, 2009). A large cohort study of self-reported NSAID use over the previous 10 years found no association between NSAID use and melanoma risk, tumor thickness, invasion, or metastasis, after statistical adjustments for melanoma risk factors and indications for NSAID use (Asgari *et al.*, 2008).

4. Melanoma clinical phenotypes

For many years, scientists have noted that there are distinct sets of genetic alterations in melanoma, and some of these are associated with distinct clinical phenotypes. Several of the functionally important signalling pathways in melanoma are depicted in Figure 2. Mutations in either *BRAF* or *NRAS* are found in a significant majority of the most common cutaneous melanoma types, highlighting the importance of the RAS-RAF-MAPK-ERK signaling cascade in disease pathogenesis. A number of genes have emerged as therapeutic targets, but it is not yet known whether they have a particular phenotypic correlation. Conversely, clinical phenotypes such as lentigo maligna melanoma, melanomas arising in chronically sun-exposed skin, aggressive melanomas in the elderly, melanomas of unknown primary site, dysplastic, and amelanotic melanomas do not have a known specific genetic mutation at this time. There is an increasing appreciation of certain clinical phenotypes with genetic associations, and this knowledge may be leveraged for current and future therapeutic approaches.

4.1 Intermittent ultraviolet exposures & sunburn-associated melanoma

BRAF mutations are identified in over 60% of cutaneous melanomas (Smalley, 2010), with over 80% of these mutations characterized by an amino acid substitution (V600E mutation) (Davies *et al.*, 2002). These melanomas often occur on skin with little histopathologic evidence of chronic sun damage (such as solar elastosis), occur in younger individuals, and are most associated with intense recreational/intermittent sun exposure (Junkins-Hopkins, 2010). Comparison of the characterization of melanomas with and without marked microscopic solar elastosis (associated with chronic sun-induced damage) suggest that *BRAF* mutations were found in patients without chronic actinic damage, and *NRAS* mutations were found only in samples without *BRAF* mutation but were not specific for a melanoma subtype (Curtin *et al.*, 2005). Analysis of Australian patients found that BRAF(V600E) mutation was significantly associated with a younger age at diagnosis of distant metastasis (56 versus 63 years) (Long *et al.*, 2011).

4.2 Melanoma in patients with red hair

Individuals with red hair, pale skin, tendency to freckle, and the inability to tan are known to have specific melanocortin-1 receptor (*MC1R*) variant alleles, found in over 80% of

individuals with this pigmentation phenotype (Valverde *et al.*, 1995). In 2000, an Australian study showed that patients with three active *MC1R* alleles (R151C, R160W, and D294H) have a doubled risk of cutaneous malignant melanoma for each active allele they carry. This increased risk persists among medium and dark-skinned individuals who carry one of the three designated *MC1R* variant alleles (Palmer *et al.*, 2000). A meta-analysis on the nine most studied *MC1R* variants suggested that they may play a role in the pathogenesis of melanoma both via pigmentary and non-pigmentary mechanisms (such as generation of reactive oxygen species), as some of the variants were only associated with melanoma and not the pigmentary phenotype (Raimondi *et al.*, 2008).

Based upon their Fitzpatrick skin phototype, red-haired *MC1R* variant allele patients are particularly susceptible to environmental ultraviolet exposure and sunburns, and they should take precautions according to their increased melanoma risk. These patients may lack the phenotype of chronically sun-damaged skin (including microscopic solar elastosis), while acquiring a lifetime of intermittent intense ultraviolet exposure as described above. Accordingly, *MC1R*-melanoma risk has been associated with *BRAF* mutations. In a study of two Caucasian populations with non-chronic solar damage melanomas, *BRAF* mutations were identified in over 80% of patients with two variant *MC1R* alleles and in only approximately 30% of individuals with wild type *MC1R* (Landi *et al.*, 2006). Patients carrying one or two *MC1R* variants in an Italian population were shown to have a 5–15 fold increase risk of *BRAF*-mutant melanomas regardless of actinic damage, and no *BRAF*-negative melanomas were identified among this population (Fargnoli *et al.*, 2008).

4.3 Melanomas in specific locations: Uveal, acral, and mucosal melanomas

Melanomas arising in specific locations are associated with specific genetic mutations. Uveal melanoma is characterized by distinct genetic mutations compared to cutaneous melanoma, as 83% of uveal melanomas exhibit somatic activation mutations of *GNAQ* or *GNA11* pathways, and they generally lack mutations in *BRAF, NRAS,* and *KIT* (Van Raamsdonk *et al.*. 2010). Oculodermal melanocytosis or Nevus of Ota is a risk factor for uveal melanoma (Singh *et al.*, 1998), and uveal melanomas often metastasize to the liver (Singh *et al.*, 2005). A large number of blue nevi contain similar genetic mutations (Van Raamsdonk *et al.,* 2010). Acral and mucosal melanomas have been shown to possess more genomic instability and chromosomal aberrations (in terms of DNA losses or gains, changes in amplicons, or changes in total copy-number transitions)(Curtin *et al.*, 2005). The *c-KIT* mutations are seen in up to one-third of acral and mucosal melanomas, in addition to those that arise in chronically actinically damaged skin (Curtin *et al.*, 2006).

4.4 Hereditary melanomas

Among newly diagnosed melanoma patients, an estimated 5–10% have an affected primary family member. Familial melanomas account for ~10% of malignant melanomas and about half of these are associated with known genetic lesions. The hereditary melanoma syndrome may involve mutation in the cyclin-dependent kinase inhibitor 2A (*CDKN2A*) gene locus, imparting a loss or inactivation of p16 or its alternative reading frame gene (ARF) (Goldstein *et al.*, 2006). Cell cycle regulator p16 protein mutations are found in 41% of familial cutaneous melanoma cases (Goldstein *et al.*, 2006). The cyclin dependent kinase 4 (*CDK4*) enzyme, which is inhibited by *p16* binding, is also found to be mutated in small sets of cutaneous melanoma families (Zuo *et al.*, 1996). A microsphere-based array assay was recently developed to detect over 30 variants of p16 pathway mutations for genotyping of

familial melanoma samples (Lang *et al.*, 2011). Additional familial melanoma genes are being identified using high throughput genomics methodologies.

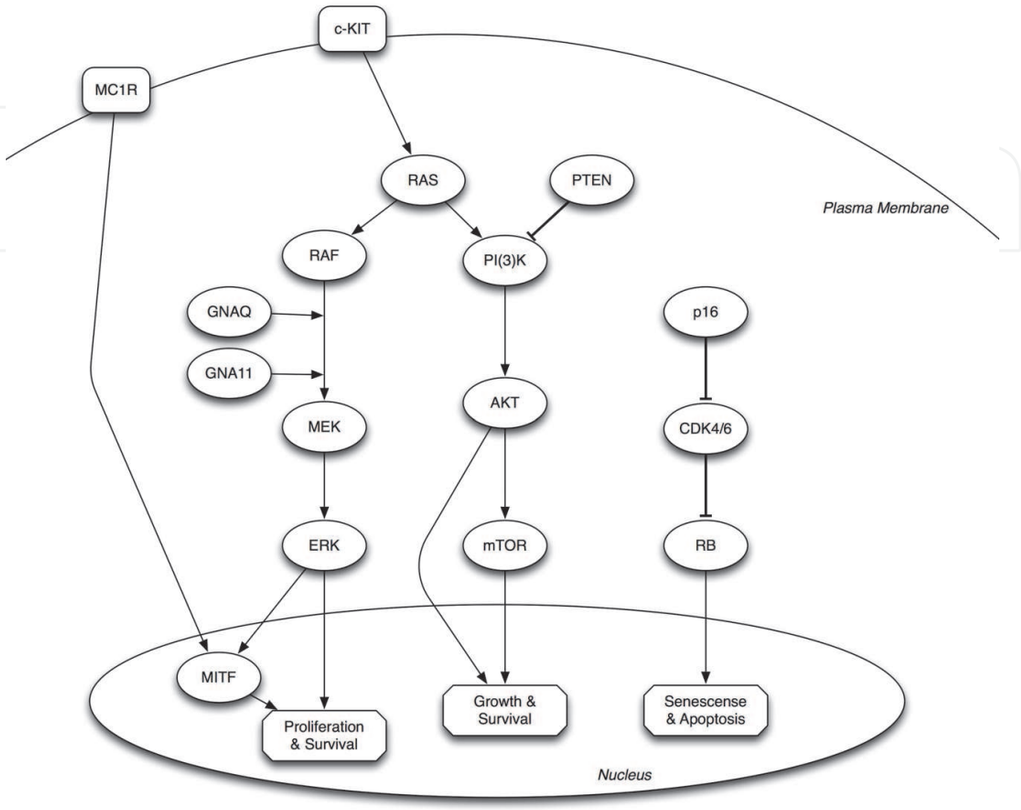

Fig. 2. Cellular Signaling Pathways Relevant to Melanoma Clinical Phenotypes. *BRAF* gene mutations disrupt Ras signaling in patients with intermittent/sunburn ultraviolet exposure, and are also more prominent among red-haired patients carrying *MCR1* variant alleles. Uveal melanomas may carry activating mutations of *GNAQ* or *GNA11*, while mucosal and acral melanomas often have *c*-KIT mutations. Hereditary melanomas with *CDKN2A* mutation have altered p16 pathway signaling. Metastatic melanoma involves transformation of several of these and additional signaling pathways.

4.5 Metastatic melanoma

Advances in melanoma genetics have enabled the identification of key oncogenic pathways that promote the transformation of primary to metastatic melanoma. A number of cell cycle regulatory proteins have mutations that contribute to melanoma pathogenesis, such as *AKT* family member activation mutation in up to 43–60% of melanomas (Stahl *et al.*, 2004) and loss of *PTEN* expression in 38% of primary and 58% of metastatic melanomas (Birck *et al.*, 2000). Constitutive activation of several other pathways may contribute to melanoma pathogenesis, including Src, JAK/STAT, Wnt, hedgehog, nuclear factor kappa B, and Notch signaling pathways (Smalley, 2010). A nested case-control study of DNA repair pathway genes in malignant melanoma patients and matched controls found a significant association of a *PARP1* gene variant with melanoma risk (Zhang *et al.*, 2011).

A number of oncogenic pathways have been targeted for therapies for malignant melanoma, including RAS/mitogen-activated protein (MAP) kinase family, RAF family members, MEK, c-KIT, and the P13K/AKT/mTOR pathways, in addition to downstream mediators of pathogenic pathways including apoptosis, anti-angiogenic, and immunological targets (Ko and Fisher, 2011). The MITF transcription factor is a lineage specific master regulator of melanocyte development and is amplified in ~20% of metastatic melanomas (Garraway *et al*., 2005). It is becoming increasingly apparent that targeting one established mutation (for example, the V600E mutation of *BRAF* or mutant *KIT* in acral/mucosal melanomas) can yield impressive therapeutic responses in some patients (Flaherty *et al*., 2010; Hodi *et al*., 2008). Generally, the mutation-specific therapy provides a temporary improvement before disease progression, suggesting the potential for *de novo* mutations, activation of alternative signaling pathways such as NRAS or MAPK signaling, and evolution of melanoma (Johannessen *et al*., 2010; Nazarian *et al*., 2010). Clinical trials for combinatorial therapy targeting multiple pathways may provide improved therapeutic outcomes in patients who appear to develop tolerance or resistance to specific genetically-targeted therapeutic approaches (Solit and Sawyers, 2010), and one may consider evaluating the genome of progressing melanoma over time to enable improved personalized medicine, as is currently being pursued for other aggressive carcinomas (Singer, 2011).

5. Conclusions

With improved understanding of the risk factors and the relationship between clinical phenotype and genetics of melanoma, there are new opportunities for novel prevention strategies and therapeutic approaches for this devastating disease. Genome sequencing technologies have enabled the analysis and cataloging of somatic mutations from human cancers, and efforts are underway to expand this type of analysis to many additional melanomas in order to discriminate between driver and passenger mutations. Similar high throughput methodologies are being applied to populations at risk for melanoma formation, in order to identify predisposition genes and link them to specific environmental exposures or risks. Simultaneously, unprecedented progress has been made in translating the discovery of melanoma oncogenes into novel therapeutic strategies by exploiting targeted small molecule inhibitors of activated oncogenic kinases. Although the eventual emergence of resistance appears to be common, new research efforts are underway to reveal the mechanism(s) of such resistance and hopefully discover strategies to prevent disease progression. Collectively the past 10 years have produced unprecedented progress in understanding and attacking virtually every aspect of melanoma biology and clinical behavior. The continued characterization of melanoma mutations and risk factors will provide increasing opportunity to understand disease pathophysiology, and hopefully enable us to both meaningfully diminish melanoma risk as well as tailor treatments on the basis of informed molecular targeting.

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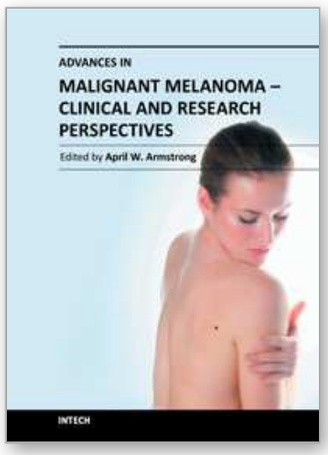

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This book titled Advances in Malignant Melanoma - Clinical and Research Perspectives represents an international effort to highlight advances in our understanding of malignant melanoma from both clinical and research perspectives. The authors for this book consist of an international group of recognized leaders in melanoma research and patient care, and they share their unique perspectives regarding melanoma epidemiology, risk factors, diagnostic and prognostic tools, phenotypes, treatment, and future research directions. The book is divide into four sections: (1) Epidemiology and Risk Factors of Melanoma, (2) Clinical Phenotypes of Melanoma, (3) Investigational Treatments for Melanoma and Pigmentary Disorders, and (4) Advances in Melanoma Translational Research. This book does not attempt to exhaustively cover all aspects of the aforementioned topics. Rather, it is a compilation of our authorsâ€™ pearls and unique perspectives on the relevant advances in melanoma during the recent years.

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