Original Article

Progress in the studies of etiology, epidemiology and pathogenesis of ocular melanomas

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Abstract
Our population-based epidemiological studies demonstrated that the epidemiological aspects of ocular melanomas are different from those in cutaneous melanoma. The incidences of conjunctival melanoma increased in the past decades and was higher in the South (greater sun exposure), which is consistent with the occurrence of cutaneous melanoma. On the contrary, incidences of uveal melanoma are in the opposite direction of cutaneous melanomas.This indicates that solar radiation does not cause an increase of incidences of melanoma in ocular tissues (uveal melanoma) that are not exposed to solar radiation. Solar radiation increases the incidence of melanoma only in tissues exposed to said radiation, such as in conjunctival and eyelid melanomas.Uveal melanoma incidences in light-pigmented individuals are much greater than in dark-pigmented individuals.This result cannot be attributed to a melanin photo-screening effect, and is possibly related to melanin's biophysical and biochemical effects. The difference in incidences between light-and dark-pigmented individuals in conjunctival melanomas, as well as in vulvar and vaginal melanomas, are much lower than that in the uveal and cutaneous melanomas. This difference may be related to the different histological structures in these melanomas; conjunctival and vaginal melanomas occur in the mucous membrane, whereas cutaneous melanomas occur in the skin. Recent molecular biological studies indicate that each type of melanoma has its own molecular changes which are different from the others. Therefore, independent studies are required for each type of melanoma to discover their own etiology and pathogenesis, and to develop relevant novel prevention and treatment procedures.

Keywords: Ocular melanoma; Uveal melanoma; Conjunctival melanoma; Incidence; Race/ethnicity; Solar radiation; Melanin

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Ocular melanomas mainly include uveal and conjunctival melanomas.Uveal melanoma is the most common non-cutaneous melanoma and is the most common intraocular malignant tumor in adults in Western nations. Most uveal melanomas occur in the choroid and ciliary body.Iris melanomas are very rare and account for less than 5% of uveal melanoma cases.Therefore, uveal melanoma as mentioned in this paper primarily refers to choroidal and ciliary body melanomas.

Risk factors in the occurrence of cutaneous melanoma

In the last century, great progress has been made through etiological and epidemiological studies of cutaneous melanoma. Solar radiation and racial/ethnic differences have been established as the two most important risk factors relevant to the occurrence of cutaneous melanoma[1].

Solar radiation

There is strong evidence linking the occurrence of cutaneous melanoma to exposure to solar radiation. In the past decades, there was a significant increase in the annual incidence of cutaneous melanoma in the United States (US), coinciding with an increase of outdoor activities in US residents.Furthermore, incidences of cutaneous melanoma in US residents in the south (greater sun exposure) are higher than those in the north (less sun exposure). In vivo and in vitro studies have found that ultraviolet (UV) radiation causes DNA damage and plays a role in the pathogenesis of malignant cell transformation[1].

Race/ethnicity

The incidence of cutaneous melanoma in the light-

pigmented individuals (whites) is much higher than that of dark-pigmented individuals (blacks and Asians). It has been assumed that melanin has a photo-screening effect that can protect tissues and cells from solar radiation. Melanin content in epidermal melanocytes in dark-pigmented individuals is higher than in light-pigmented individuals. This can explain the difference in cutaneous melanoma incidences between different racial/ethnic groups[1,2].

Risk factors in the occurrence of ocular melanomas

In the last century, the exploration of risk factors for the occurrence of ocular melanomas has mainly followed the results of cutaneous melanoma studies. However, the relationship between the solar radiation and the occurrence of ocular melanoma remained obscure and contradictory through numerous reports[3,4]. Most studies on the relationship between the incidence of ocular melanoma and solar radiation are based on case-control studies, and most of the data relevant to the incidences of ocular melanoma in various racial/ethnic groups were based on consecutive pathologic specimens, or on a series of patients from the referral center. Population-based data on these aspects were scarce. Therefore, very little were known on the risk factors in the occurrence of ocular melanomas[3,4].

Our work on the risk factors and pathogenesis of ocular melanomas

Two important changes have occurred in epidemiological studies of ocular melanomas in the past decades. First, data from national and international cancer registries provided a reliable population-based incidence of ocular melanomas among millions-strong populations, which can be used to explore the relationship between the incidence of ocular melanomas, solar radiation, and pigmentation. Second, it is recognized that the ocular melanomas consist of two entirely different types of melanoma: external (conjunctival) and internal (uveal) melanoma. The former is exposed to the sun radiation and the later not, therefore, the sun radiation plays different roles in the occurrence of these two different types of ocular melanomas[5,6].

Two different types of ocular melanoma

Ocular melanocytes consist of two different cell types: conjunctival and uveal melanocytes. Melanocytes in the bulbar conjunctiva are exposed to solar radiation, and are the most common location of conjunctival melanoma.

Uveal melanocytes are located in the uveal tract. Most uveal melanomas (over 90%) are ciliary body/choroidal melanomas. Melanocytes in the ciliary body and choroid are covered by the cornea (absorbs all UVC, most UVB, and a small amount of UVA radiation), the iris (blocks most UV radiation and visible light that enter the eye; less than 10% of light passing through the pupil can transmit to the inner eye), the lens (absorbs virtually all UVB radiation and 80% of UVA radiation that passes through the pupil in adults), and the densely-pigmented ciliary and retinal pigment epithelium[7]. Therefore, melanocytes in the ciliary body and choroid are virtually not exposed to solar radiation, including visible light and UV radiation[7].

Population-based epidemiological studies on the incidence of ocular melanomas

We studied the relationship between the incidence of ocular melanomas and various risk factors in the US by using data provided by the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program, covering 14% of the US population, one of the largest series of ocular melanomas in the world. The incidence of conjunctival and uveal melanomas was calculated and analyzed separately[4,8-11].

Time trends of ocular melanomas

We found that from 1973 to 1999, there was a very significant increase in the annual incidence of conjunctival melanoma in the United States, coinciding with an increase in outdoor activities and increased incidences of cutaneous melanomas[8]. On the contrary, during the same period, there was a small but significant decrease in the annual incidence of uveal melanomas[11]. A study in the Sweden obtained a similar time-trend result for uveal melanomas from 1960 to 1998[12].

Latitude and incidence of ocular melanomas

Our studies demonstrated that the lower the latitude (more sunlight), the higher the risk of external ocular melanomas (eyelid and conjunctival melanomas) was among non-Hispanic whites (we only studied the incidence in a special race/ethnic group to avoid the influence of differences in melanoma incidences for various racial/ethnic groups); to the contrary, incidences of uveal melanoma were increased in higher latitudes (north, with less solar radiation), indicating that solar radiation may decrease, and at least does not increase, the risk of uveal melanomas[4].

Direct and indirect effects of solar radiation on the occurrence of ocular melanoma

Our studies indicate that solar radiation may have two different effects on the pathogenesis of melanoma. Direct irradiation of cells by solar radiation may cause gene mutations and increase the incidence of melanoma, such as cutaneous and conjunctival melanomas. In cells not exposed to solar radiation, the direct effects do not exist (e.g. in uveal melanomas), so we can surmise that solar radiation does not cause an increase in incidences of melanoma.On the other hand, there is a small but significant inverse correlation between solar radiation and the incidence of uveal melanoma. Therefore, we hypothesized that there may be an indirect protective effect of solar radiation on the occurrence of melanoma[4,6]. This is consistent with the fact that the incidences of various internal malignant tumors (not exposed to solar radiation) also show a negative correlation with solar radiation. The mechanism of the indirect protective effect has not been determined. One of the possible mechanisms is an increased production of vitamin-D in the skin by the photobiological effects of solar radiation. This induces a cascade of biochemical changes that results in the increase of 1, 25-dihydroxyvitamin D3 (VD3) levels in various tissues. It has been reported that VD3, by the activation of vitamin-D nuclear receptors, inhibits the growth, stimulates differentiation, and induces apoptosis of various malignant tumors in vitro and inhibits the growth, invasion, and metastasis of malignant tumors in experimental animal models[4]. The validity of the vitamin-D hypothesis requires further investigation.

Incidence of ocular melanomas in various races and ethnic groups

Our studies found that, from 1992 to 2000, the annual incidence of uveal melanomas (per 1 million population) was 0.31 in blacks, 0.38 in Asians, 1.67 in Hispanics, and 6.02 in non-Hispanic whites, with a white: black incidence ratio at 18:1[9]. This result excludes the possibility that racial/ethnic difference in incidences of uveal melanomas is due to the melanin photo-screening effect, because uveal melanocytes are not exposed to solar radiation. The protective effect of melanin is possibly relevant to its biophysical/biochemical effects[9]. Oxidative stress can induce damage of DNA, proteins, and lipids in the cell, and plays a role in tumorigenesis. Melanin is an antioxidant and a weak free-radical scavenger.Melanin in uveal melanocytes may protect the cells and tissues from oxidative stress-induced damage and reduce the incidence of uveal melanoma in dark-pigmented individuals[6,13]. Furthermore, the nature of melanin also plays a role in the protective effects. There are mainly two different types of melanin: eumelanin and pheomelanin.Both eumelanin and pheomelanin are antioxidants, but pheomelanin more easily transforms into a pro-oxidant under high oxidative stress, which is harmful for cells. Therefore, eumelanin is more protective than pheomelanin[6,14,16]. A collaborative study by Ito and us demonstrated that uveal melanocytes from dark-pigmented individuals have a higher eumelanin level than light-pigmented indi viduals[15]. Uveal melanoma cells have a lower content of eumelanin compared to normal uveal melanocytes[16]. Therefore, both the nature and quantity of melanin plays a role in the occurrence of uveal melanoma.

Our epidemiological studies found that the annual incidence of conjunctival melanoma (per 1 million population) from 1992 to 2003 was 0.18 in blacks, 0.15 in Asians, 0.33 in Hispanics, and 0.49 in non-Hispanic whites, with a white: black incidence ratio at 2.6:1. This ratio is much lower than that of cuta neous melanoma (15:1). 10 Both cutaneous and conjunctival melanomas are exposed to solar radiation; therefore, this difference in the white/black ra-

tio is not determined by the photo-screening protective effects of melanin, but is perhaps related to different histological structures. Conjunctival melanoma is located in the mucous membrane that is different from the skin in many aspects. We studied the incidences of melanoma in various racial/ethnic groups in two other types of melanoma, one locates in the mucous membrane (vaginal melanoma), and the other locates in the transition area between the skin and mucous membrane (vulvar melanoma). There was a difference in incidences of vulvar melanoma between various racial/ethnic groups, with a white/black incidence ratio at 2.1∶1. No significant difference in incidences of vaginal melanoma could be detected between various racial/ethnic groups, and shows a white/black ratio at 1.04∶1[17]. These results indicate that different histological structures play a role in the racial/ethnic differences of incidences in various melanomas. Melanomas in the mucus membrane have a lower white/black incidence ratio; the cause of this difference requires further study[10,17].

Recent progress of molecular biological studies in melanomas

Mutations, amplifications, and deletions of various oncogenes and tumor suppresser genes have been found in different types of melanomas. A BRAF mutation mainly occurs in cutaneous and conjuncti val melanomas, but not in uveal melanomas[18]. GNAQ or GNA11 constitutively active mutations are discovered in 83% of uveal melanomas, but not in cutaneous, conjunctival, or other mucosal melanomas (with the exception of blue nevi)[19,20]. Activating mutations or amplifications of KIT have been found to occur in mucosal melanomas and one specific type of cutaneous melanoma (acral lentiginous melanoma), but not in uveal melanoma[21,22]. All of these findings indicate that each type of melanoma has a unique oncogenic pathway for tumor development.

Furthermore, recent collaborative studies between us and the Wenzhou Medical College found that micro-RNA, which acts as a tumor suppressor, also plays a role in the pathogenesis of uveal melanomas. Overexpression of the MicroRNA-34a inhibits the proliferation and migration of uveal melanoma cells through a down-regulation of the c-met gene[23]. Overexpression of MicroRNA-182, a p53-dependent microRNA, suppressed the expression of multiple targets in uveal melanoma cells and resulted in the inhibition of the proliferation and invasion of uveal melanoma cells[24].

Summary

In the past decade, our epidemiological studies on the incidence of ocular melanoma using one of the largest population-based datasets, and our in vitro studies on the cell biology of melanocytes and melanoma cells and the nature and function of ocular melanin indicate:

1.The effects of solar radiation depend on the difference in accessibility of cells to solar radiation. In cells exposed to solar radiation, the incidences of melanoma increase significantly with an increase of solar radiation (conjunctival melanoma). In cells not exposed to solar radiation, solar radiation does not cause any increase in incidences of melanoma (uveal melanoma), and may slightly reduce the occurrence of melanomas.

2.The incidence of uveal melanoma in light-pigmented individuals is significantly greater than in dark-pigmented individuals. Because uveal melanoma is not exposed to solar radiation, therefore, this effect can not be attributed to the melanin photo-screening effects, and can be better explained by melanin's biophysical and biochemical effects (antioxidative effects).

3.The low white-black incidence ratio in melanomas located in the conjunctiva and vagina, as compared to that of cutaneous melanomas, may indicate that this difference is due to different histological structures in the mucous membrane and skin.

4.Based on our studies, each type of melanoma (vulvar, vaginal, cutaneous, uveal, conjunctival, and other mucosal)is different from the others. Therefore, each one should be considered a different and independent disease entity. Independent studies are required for each type of melanoma to discover their own pathogenesis, and to develop relevant novel treatments.

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