Received Date : 19-Jun-2013
Revised Date : 25-Jul-2013
Accepted Date : 03-Aug-2013
Article type : Invited Review



## Invited Review

# Implication of ultraviolet light in the etiology of uveal melanoma: a review

Justin D. Mallet[1,2], Sébastien P. Gendron[1,2], Marie-Catherine Drigeard Desgarnier[1,2] and Patrick J. Rochette[1,2,3,*]

1. Centre de Recherche FRQS du CHU de Québec, Axe Médecine Régénératrice, Hôpital du Saint-Sacrement, Québec, Canada

2. Centre LOEX de l'Université Laval, Québec, Canada

3. Université Laval, Faculté de Médecine, Département d'Ophtalmologie et ORL - chirurgie cervico-faciale, Université Laval, Québec, Canada.

* Corresponding author:
Dr. Patrick J. Rochette
Phone: (418) 682-7568
Fax: (418) 682-8000
E-mail: Patrick.rochette@orlo.ulaval.ca

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/php.12161

**ABSTRACT**

Uveal melanoma is the most frequent intraocular cancer and the second most common form of melanoma. It metastasizes in half of the patients and the prognostic is poor. Although ultraviolet (UV) radiation is a proven risk factor for skin melanoma, the role of UV light in the etiology of uveal melanoma is still contradictory. We have compared epidemiological and genetic evidence of the potential role of UV radiation in uveal melanoma with data on cutaneous melanoma. Even though frequently mutated genes in skin melanomas (e.g. *BRAF*) differ from those found in uveal melanoma (i.e. *GNAQ*, *GNA11*), their mutation pattern bears strong similarities. Furthermore, we provide new results showing that RAC1, a gene recently found harboring UV-hallmark mutation in skin melanoma, is also mutated in uveal melanoma. This article aims to review the work done in the last decades in order to understand the etiology of uveal melanoma and discuss new avenues, which shed some light on the potential role of UV exposure in uveal melanoma.

With 5.1 cases per million in the US population, uveal melanoma is the second most common form of melanoma (after the skin) and is the most common ocular cancer (1, 2). Approximately 3% of all melanomas are from uveal origin (2-4) and are predominately located in the choroid (90%, 7% and 3% in the choroid, the ciliary body and the iris, respectively) (2, 5). In 50% of the patients, uveal melanoma metastasizes, mainly to the liver where it is fatal within 1 year (6-8). The etiology of uveal melanoma is not well understood, but accumulation of solar UV exposure is one of the suspected risk factors. This review aims to present evidences related to the possible role of UV exposure in this neoplasia.

**Genotoxic effects of ultraviolet light**

Exposure to the sunlight's ultraviolet (UV) radiations is the preeminent risk factor in skin cancer development (9-11). The sun emits the whole UV spectrum (i.e., UVC, UVB and UVA). However, wavelengths under 290 nm (UVC and short UVB) are completely absorbed by the stratospheric ozone layer. Therefore, UVA and long UVB are the only UV wavelengths reaching the earth surface. UV light induces different types of DNA damage including cyclobutane pyrimidine dimers (CPD), (6-4) pyrimidine-pyrimidone photoproducts (6-4PP) and oxidatively generated DNA damage. Although 6-4PP were found mutagenic in *E. coli* (12), CPD are considered as the main promutagenic DNA adducts induced by UV wavelengths (13). They are the most abundant UV-induced DNA damage (up to 85% of all photodamage), and they are repaired in a relatively slow manner by nucleotide excision repair (NER) in humans. It is also well established that cytosine deamination is drastically accelerated within a CPD (14, 15) and that some translesional DNA polymerases (e.g. pol zeta and kappa) misincorporate an adenine when polymerizing over a cytosine in a CPD (16-18). Consequently, cytosine-containing CPD are highly mutagenic, leading to C:G→T:C transition mutations and CpC:GpG→TpT:ApA tandem transitions (19). Those mutations are the signature of UV exposure (20, 21).

**UV light and skin melanoma**

The role of UV light from natural sunlight and from UV-emitting tanning devices in the occurrence of non-melanoma skin cancer is well established (11, 21, 22). More recently, the International Agency for Research on Cancer (IARC) concluded that there is also a

causative relationship between UV light from both the sun and tanning devices and skin melanoma (9, 10).

Epidemiological evidences have determined that a cumulative strong exposure to sunlight and sunburn episodes at a relatively young age (pre-adult) catalyze the formation of skin melanoma (23, 24). Moreover, the UV portion of sunlight has been epidemiologically associated with the development of skin melanoma (25-27). More precisely, UVA wavelengths rather than UVB are preferentially linked to skin melanoma (28-37).

Many genes are found mutated in skin melanoma. Among them, *BRAF* is the most frequently mutated gene with 70% of human skin melanoma harboring mutations in this gene. Up to 90% of *BRAF* mutations are localized in or around the codon 600 of the exon 15 (38). Mutations reported in this codon are not the classical UV signature mutations (i.e. C:G→T:C at dipyrimidinic sites), but rather predominantly A:T→T:A transversion mutations (38). Moreover, 29% of these mutations are found as tandem mutations (39-41). Although they are not the classical UV signature mutations, a model has been proposed to explain their induction by UV light (39, 42). It has been hypothesized that an error prone translesional DNA polymerase crossing a dipyrimidinic site at or close to the codon 600 of *BRAF* gene would result in nucleotide base misincorporation at codon 600. On the other hand, *TP53* and *CDKN2*, other genes found mutated in skin melanoma, harbor predominately C:G→T:C mutations in the sporadic form, consolidating a potential role of UV light in the etiology of this cancer (43-45).

Recently, Krauthammer et al. (46) have sequenced the exome of 147 primary or metastatic skin melanomas. In addition to the already known mutated genes (e.g. *BRAF*, *TP53* and *CDKN2*), this study led to the identification of mutations in *RAC1* and *PPP6C* genes. In the *RAC1* gene, the predominant mutation is a C:G→T:C transition mutation in a pyrimidine run (5'TTTCCT), strongly suggesting a role of UV-light in the induction of this mutant. This study reported a predominance of C:G→T:C mutations at dipyrimidinic sites in mutated genes of skin melanomas, confirming the role of UV light in the etiology of this cancer (46). Previous studies have also determined that skin melanoma harbors predominantly UV-signature mutations (47, 48). Altogether, the epidemiological and genetic evidences presented confirm the role of UV light in the etiology of skin melanoma.

**UV light and uveal melanoma**

*Epidemiology*

The occurrence of uveal melanoma is 200 times higher in Caucasians compared to the black population (2, 49). Moreover, light-colored irides, blond hair and fair skin color are risk factors (50-57). As for cutaneous melanoma, this uveal melanoma ethnic predisposition may appear as an evidence of the oncogenic effect of sunlight on the etiology of this cancer. However, epidemiological studies have failed so far to validate the role of sunlight in the occurrence of uveal melanoma. More precisely, case studies have determined either a weak positive (54, 58) or no statistically significant (59, 60) correlation between UVB-light exposure during life and the risk of uveal melanoma. Moreover, a very weak to not significant correlation between time spent outdoors and sunbathing and the risk of uveal melanoma is reported (54, 55). In fact, epidemiological studies on the influence of

occupational sunlight exposure seem to indicate that sunlight has a protective effect against uveal melanoma. Indeed, case-control studies reported that indoor workers have a significant increased risk to develop uveal melanoma whereas outdoor workers such as farming workers do not have a significant increased risk (59, 61-66). On the other hand, several studies provide evidence of a causative relationship between the use of UV-emitting tanning devices and uveal melanoma (9, 54, 55, 67). In summary, the epidemiological studies published so far about a possible implication of UV-light exposure in the occurrence of uveal melanoma are contradictory and the subject is still under debate.

Using epidemiological analyses to establish solar UV exposure as a risk factor for uveal melanoma is hazardous for some reasons. First, epidemiological studies do not distinguish between UVA and UVB exposure. Also, solar exposure of an individual during its lifetime cannot be precisely measured using the available tools. The measurement of UV across populations is challenging especially because multiple components contribute to an individual's exposure at any given time, including wearing prescription glasses, sunglasses or contact lenses; extent of shade coverage; length of forelock hairs; protrusion of the brow; eyelid anatomy; posture; activity, leisure and occupation; day of the year, latitude, elevation; environmental condition (air quality, cloud cover) (68). It is virtually impossible to precisely gather all this information with an activity diary and/or a survey. However, the first thing to consider is the penetration of UV light in the eye. Beyond the UV dose to which an individual is exposed during its lifetime, one important consideration is whether UV light reaches the posterior segment of the human eye where the choroïdal melanocytes are located.

*UV light penetration in the ocular media*

UV light transmittance of the human eye is documented. The human cornea is the first ocular layer in contact with the sun's UV rays and it absorbs wavelengths below 295 nm. Some of the long UVB, UVA and wavelengths above pass through the cornea and reach the iris and the lens (69-71). The iris is opaque to the UV rays and the adult lens absorbs all wavelengths below 370 nm, letting through less than 2% of UVA between 370 and 400 nm (69, 70). In the lens of younger humans (<8 years old) the formation of 3-hydroxy kynurenine and its glucoside that absorb 300 to 400 nm UV wavelengths is not completed (72-74). Consequently, a portion of these wavelengths is transmitted through the lens of those children (69, 70) and their retina is exposed to UVA and UVB light. This means that exposure to the sun at an early age may lead to the formation of genotoxic DNA damage in structures from both the anterior and the posterior segment of the eye. Therefore, juvenile solar overexposure may be a risk factor to develop uveal melanoma, as it is for skin melanoma (23, 24). However, this would be challenging to assess and to our knowledge, it has not been epidemiologically documented.

*Genetics*

Unlike skin melanoma, uveal melanoma does not harbor mutations in *BRAF* and *NRAS* genes. Mutations are rather concentrated in *GNAQ* and *GNA11* genes, both coding for the q class of heterotrimeric G-protein α subunit (Gαq and Gα11, respectively) sharing 91% of amino acid homology.

Van Raamsdonk et al. reported that the codon 209 of both *GNAQ a*nd *GNA11* genes is mutated in 45% and 32% of all uveal melanomas and in 22% and 57% of all uveal melanoma metastases, respectively (75, 76). Mutations found in the codon 209 (CAG) of *GNA11* are mainly A:T→T:A transversions (95%) and less often A:T→C:G, ApG:CpT→TpA:TpA and ApG:CpT→TpT:ApA. In *GNAQ*, the mutations found in the codon 209 (CAA) occur on the second A. They are mainly A:T→T:A, A:T→C:G and, less often, A:T→G:C. They are "gain of function" mutations converting *GNAQ* into a dominant acting oncogene (76). It can be speculated that *GNA11* mutations have the same impact on protein function but it has not been demonstrated. Although there are potential UV-targets (i.e. CC, CT or TC) in or near codon 209 of both *GNAQ* and *GNA11*, none of the mutations found are UV-signature mutations. This could be explained by the fact that a C:G→T:A transition in the codon 209 of both *GNAQ* and *GNA11* would prevent phenotypic expression of the mutated genes, as this mutation would result in either a stop codon or a silent mutation. As can be seen for the *BRAF* gene in skin melanoma, all mutations found in codon 209 of *GNAQ* and *GNA11* implicates a CpA:TpG dinucleotide and tandem mutations are seen at this dinucleotide. As hypothesized by Besaratinia and Pfeifer, there may be an unidentified dimeric photoproduct in this sequence related to melanin or tyrosine photochemistry in skin and uveal melanocytes (77).

In addition to the codon 209, the codon 183 of *GNAQ* (CGA) and *GNA11* (CGC) has been found mutated in around 2.5% of uveal melanomas and 5.9% of metastases from uveal origins (75). All mutations found at this codon are C:G→T:A transitions at dipyrimidine sites, the signature of UV-light induced genotoxicity. In addition, a tandem mutant has been

reported carrying the CpC:GpG→TpT:ApA UV-signature mutation in codons 182/183 of *GNA11* (75, 76).

Mutational spectrum of *GNAQ* and *GNA11* in uveal melanoma brings some indications of a role of UV-light in the occurrence of this cancer. First, mutations found in codon 209 of *GNAQ* and *GNA11*, although they are not UV-specific mutations, have strong similarities with *BRAF* mutations reported in skin melanomas in which the implication of UV is well accepted. Mutations occur at a CpA dinucleotide in either the codon 600 of *BRAF* gene in skin melanoma and the codon 209 of *GNAQ* and *GNA11* genes in uveal melanoma. Also, the tandem mutations, an extremely rare type of mutation, are reported in the CpA dinucleotide in codon 209 of *GNAQ* and *GNA11* genes of uveal melanoma as well as in codon 600 of *BRAF* gene of skin melanomas. Moreover, mutations found in codon 183 of *GNAQ* and *GNA11* are exclusively UV-related mutations (C:G→T:A).

In light of the C:G→T:A transition mutation obtained in *RAC1* gene of skin melanoma by Krauthammer et al. (46), we have investigated the occurrence of the same mutation in 15 uveal melanoma cell lines. We have determined that 3 of the cell lines (20%) harbor the aforementioned C:G→T:A transition. This is the first genetic alteration similitude shared between skin and uveal melanoma. However, this result has been obtained using cell lines derived from the tumors (78). Therefore, it has to be taken with caution and should be confirmed with primary tumors.

*DNA repair*

In human, UV-photoproducts (CPD and 6-4PP) are repaired by nucleotide excision repair in which the XP protein family (XPA-F and XPV) is the core of the repair system (79, 80). Xeroderma pigmentosum patients harbor defect in one or more XP proteins and are therefore deficient in UV-induced DNA photoproducts repair. Those patients have a 600- to 800-fold increased risk to develop a skin melanoma (81, 82). There are reported cases of ocular melanoma in xeroderma pigmentosum patients but they are rather of surface squamous origin (conjunctival melanoma) than uveal origin (83-85). Nevertheless, there are reported cases of uveal melanoma of the iris (86) and the choroid (87) and an overall 58-fold increased risk of developing uveal melanoma in xeroderma pigmentosum patients has been estimated (54). Thus, xeroderma pigmentosum disease is a significant risk factor for developing uveal melanoma even if that risk is less important than the one to develop skin melanoma.

## Discussion

Epidemiological and genetic data, as well as the optical properties of the ocular media, lead to controversial conclusions concerning the involvement of solar UV radiation as a risk factor for uveal melanoma. On one hand, UV light reaches the posterior structures of the eye (e.g. retina and choroid) only within the first decade of life. On the other hand, the adult cornea, aqueous humour, lens and vitreous chamber absorb all UV wavelengths, thus protecting the posterior segment of the eye. However, as sunburns at younger age have been established as a risk factor for skin melanoma, it can be hypothesized that overexposure to sunlight at a young age, when UV wavelengths are able to reach the

posterior segment of the eye, could be a risk factor for uveal melanoma. Nevertheless, this hypothesis has not been assessed and needs more investigation.

Epidemiological analyses have failed to clearly demonstrate that UV light is a risk factor for uveal melanoma. On the contrary, some case studies found a negative correlation between occupational exposure and uveal melanoma. Nonetheless, genetic analyses seem to validate the influence of UV light as a carcinogen responsible for the development of uveal melanomas. UV-hallmark mutations (CpG→TpA) are found in the codon 183 of *GNAQ* and *GNA11* and in the *RAC1* gene. On another hand, mutations found in codon 209 of *GNAQ* and *GNA11* seem not related to UV exposure. Those mutations however share homology with skin melanoma mutations reported in the codon 600 of *BRAF* gene. Since the role of UV light is accepted as a risk factor for skin melanoma, this mutational homology can be interpreted as a clue as to the implication of UV light in the etiology of uveal melanoma. Furthermore, a defective UV photoproduct repair in xeroderma pigmentosum patients is a moderate but significant risk for uveal melanoma.

With these information in hands, is it possible to conciliate contradictory epidemiological studies and genetic data on the uveal melanoma? It is well documented that vitamin D3 has a protective effect against several cancers, including skin melanoma (88-94) and that exposition of the skin to UVB wavelengths is essential for the conversion of 7-dehydrocholesterol into vitamin D3 (95). It has also been shown that skin melanoma cells can convert vitamin D3 to calcitriol, which causes growth inhibition and apoptotic cell death (94). To our knowledge, the protective effect of vitamin D3 on uveal melanoma

development has not been assessed so far. However, a strong protective effect of vitamin D3 would explain some of the data presented on uveal melanoma. It can be hypothesized that there is a balance between the protective effect of UVB via the formation of vitamin D3 and the genotoxic effect of UV light via the formation of mutagenic DNA photodamage. This premise could explain the fact that epidemiological studies have failed to establish a possible role for UV-light as a risk factor for uveal melanoma. In support to this hypothesis, we have highlighted a contradiction between epidemiological evidences showing that, as opposed to sunlight exposure, the use of sun-tanning devices is a risk factor for uveal melanoma. Lamps used for sun-tanning emit mainly short UVA wavelengths. Thus, artificial tanning is not a useful way to increase systemic level of vitamin D3 (96-98). Consequently, sun-tanning devices have the genotoxic effect of sunlight UV without the protective effect of UVB-induced vitamin D3. The fact that indoor occupation is a risk factor for uveal melanoma supports this hypothesis. In fact, it has been demonstrated that indoor solar UVA exposure (UVB being blocked by windows) depletes vitamin D3 (96).

In conclusion, there has been a tremendous amount of work done in the last decades to understand the etiology of uveal melanoma. However, it is still hazardous to establish UV exposure as a risk factor for uveal melanoma. There has been recent progress, especially in the determination of mutations that provide new insights on the implication of UV in uveal melanoma. New advances with the high throughput sequencing will undoubtedly bring some light in this controversy. Also, the influence of systemic levels of vitamin D3 may bring new avenues to understand the occurrence of uveal melanoma.

**ACKNOWLEDGMENTS**

The authors sincerely thank Nathalie Bastien for her valuable help in the preparation of this manuscript. This work was supported by a grant from the Natural Sciences and Engineering Research Council of Canada (NSERC) to P.J.R. P.J.R. is a research scholar from the Fonds de recherche du Québec – Santé (FRQ-S).

**REFERENCES**

1. Singh, A. D. and A. Topham (2003) Incidence of uveal melanoma in the United States: 1973-1997. Ophthalmology, 110**,** 956-961.
2. Singh, A. D., M. E. Turell and A. K. Topham (2011) Uveal melanoma: trends in incidence, treatment, and survival. Ophthalmology, 118**,** 1881-1885.
3. Chang, A. E., L. H. Karnell and H. R. Menck (1998) The National Cancer Data Base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society. Cancer, 83**,** 1664-1678.
4. Dutton, J. J., R. L. Anderson, R. L. Schelper, J. J. Purcell and D. T. Tse (1984) Orbital malignant melanoma and oculodermal melanocytosis: report of two cases and review of the literature. Ophthalmology, 91**,** 497-507.
5. Landreville, S., O. A. Agapova and J. W. Harbour (2008) Emerging insights into the molecular pathogenesis of uveal melanoma. Future Oncol, 4**,** 629-636.
6. Diener-West, M., S. M. Reynolds, D. J. Agugliaro, R. Caldwell, K. Cumming, J. D. Earle, B. S. Hawkins, J. A. Hayman, I. Jaiyesimi, L. M. Jampol, J. M. Kirkwood, W. J. Koh, D. M. Robertson, J. M. Shaw, B. R. Straatsma and J. Thoma (2005) Development of metastatic disease after enrollment in the COMS trials for treatment of choroidal melanoma: Collaborative Ocular Melanoma Study Group Report No. 26. Arch Ophthalmol, 123**,** 1639-1643.
7. Augsburger, J. J., Z. M. Correa and A. H. Shaikh (2009) Effectiveness of treatments for metastatic uveal melanoma. Am J Ophthalmol, 148**,** 119-127.
8. (2006) The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma: V. Twelve-year mortality rates and prognostic factors: COMS report No. 28. Arch Ophthalmol, 124**,** 1684-1693.
9. El Ghissassi, F., R. Baan, K. Straif, Y. Grosse, B. Secretan, V. Bouvard, L. Benbrahim-Tallaa, N. Guha, C. Freeman, L. Galichet and V. Cogliano (2009) A review of human carcinogens--part D: radiation. Lancet Oncol, 10**,** 751-752.
10. (2012) Radiation. IARC Monogr Eval Carcinog Risks Hum, 100**,** 7-303.
11. Armstrong, B. K. and A. Kricker (2001) The epidemiology of UV induced skin cancer. J Photochem Photobiol B, 63**,** 8-18.

12. Glickman, B. W., R. M. Schaaper, W. A. Haseltine, R. L. Dunn and D. E. Brash (1986) The C-C (6-4) UV photoproduct is mutagenic in Escherichia coli. Proc Natl Acad Sci U S A, 83, 6945-6949.
13. Pfeifer, G. P. and A. Besaratinia (2012) UV wavelength-dependent DNA damage and human non-melanoma and melanoma skin cancer. Photochem Photobiol Sci, 11, 90-97.
14. Song, Q., V. J. Cannistraro and J. S. Taylor (2011) Rotational position of a 5-methylcytosine-containing cyclobutane pyrimidine dimer in a nucleosome greatly affects its deamination rate. J Biol Chem, 286, 6329-6335.
15. Tu, Y., R. Dammann and G. P. Pfeifer (1998) Sequence and time-dependent deamination of cytosine bases in UVB-induced cyclobutane pyrimidine dimers in vivo. J Mol Biol, 284, 297-311.
16. Yoon, J. H., L. Prakash and S. Prakash (2009) Highly error-free role of DNA polymerase eta in the replicative bypass of UV-induced pyrimidine dimers in mouse and human cells. Proc Natl Acad Sci U S A, 106, 18219-18224.
17. Choi, J. H. and G. P. Pfeifer (2005) The role of DNA polymerase eta in UV mutational spectra. DNA Repair (Amst), 4, 211-220.
18. Kozmin, S. G., Y. I. Pavlov, T. A. Kunkel and E. Sage (2003) Roles of Saccharomyces cerevisiae DNA polymerases Poleta and Polzeta in response to irradiation by simulated sunlight. Nucleic Acids Res, 31, 4541-4552.
19. Jiang, N. and J. S. Taylor (1993) In vivo evidence that UV-induced C-->T mutations at dipyrimidine sites could result from the replicative bypass of cis-syn cyclobutane dimers or their deamination products. Biochemistry, 32, 472-481.
20. Hutchinson, F. (1994) Induction of tandem-base change mutations. Mutat Res, 309, 11-15.
21. Brash, D. E., J. A. Rudolph, J. A. Simon, A. Lin, G. J. McKenna, H. P. Baden, A. J. Halperin and J. Ponten (1991) A role for sunlight in skin cancer: UV-induced p53 mutations in squamous cell carcinoma. Proc Natl Acad Sci U S A, 88, 10124-10128.
22. de Gruijl, F. R. (1999) Skin cancer and solar UV radiation. Eur J Cancer, 35, 2003-2009.
23. Tatalovich, Z., J. P. Wilson, T. Mack, Y. Yan and M. Cockburn (2006) The objective assessment of lifetime cumulative ultraviolet exposure for determining melanoma risk. J Photochem Photobiol B, 85, 198-204.
24. Leiter, U. and C. Garbe (2008) Epidemiology of melanoma and nonmelanoma skin cancer--the role of sunlight. Adv Exp Med Biol, 624, 89-103.
25. Moan, J., Z. Baturaite, A. C. Porojnicu, A. Dahlback and A. Juzeniene (2012) UVA, UVB and incidence of cutaneous malignant melanoma in Norway and Sweden. Photochem Photobiol Sci, 11, 191-198.
26. Moan, J., A. C. Porojnicu and A. Dahlback (2008) Ultraviolet radiation and malignant melanoma. Adv Exp Med Biol, 624, 104-116.
27. Wang, S. Q., R. Setlow, M. Berwick, D. Polsky, A. A. Marghoob, A. W. Kopf and R. S. Bart (2001) Ultraviolet A and melanoma: a review. J Am Acad Dermatol, 44, 837-846.
28. Noonan, F. P., M. R. Zaidi, A. Wolnicka-Glubisz, M. R. Anver, J. Bahn, A. Wielgus, J. Cadet, T. Douki, S. Mouret, M. A. Tucker, A. Popratiloff, G. Merlino and E. C. De Fabo (2012) Melanoma induction by ultraviolet A but not ultraviolet B radiation requires melanin pigment. Nat Commun, 3, 884.

29. Cadet, J. and T. Douki (2011) Oxidatively generated damage to DNA by UVA radiation in cells and human skin. J Invest Dermatol, 131, 1005-1007.
30. Zhao, B., M. Ming and Y. Y. He (2013) Suppression of PTEN transcription by UVA. J Biochem Mol Toxicol, 27, 184-191.
31. He, Y. Y., J. L. Huang and C. F. Chignell (2004) Delayed and sustained activation of extracellular signal-regulated kinase in human keratinocytes by UVA: implications in carcinogenesis. J Biol Chem, 279, 53867-53874.
32. de Gruijl, F. R. (2002) Photocarcinogenesis: UVA vs. UVB radiation. Skin Pharmacol Appl Skin Physiol, 15, 316-320.
33. de Gruijl, F. R. (2000) Photocarcinogenesis: UVA vs UVB. Methods Enzymol, 319, 359-366.
34. Autier, P., J. F. Dore, A. M. Eggermont and J. W. Coebergh (2011) Epidemiological evidence that UVA radiation is involved in the genesis of cutaneous melanoma. Curr Opin Oncol, 23, 189-196.
35. Coelho, S. G. and V. J. Hearing (2010) UVA tanning is involved in the increased incidence of skin cancers in fair-skinned young women. Pigment Cell Melanoma Res, 23, 57-63.
36. Dore, J. F. and M. C. Chignol (2012) Tanning salons and skin cancer. Photochem Photobiol Sci, 11, 30-37.
37. Boniol, M., P. Autier, P. Boyle and S. Gandini (2012) Cutaneous melanoma attributable to sunbed use: systematic review and meta-analysis. BMJ, 345, e4757.
38. Davies, H., G. R. Bignell, C. Cox, P. Stephens, S. Edkins, S. Clegg, J. Teague, H. Woffendin, M. J. Garnett, W. Bottomley, N. Davis, E. Dicks, R. Ewing, Y. Floyd, K. Gray, S. Hall, R. Hawes, J. Hughes, V. Kosmidou, A. Menzies, C. Mould, A. Parker, C. Stevens, S. Watt, S. Hooper, R. Wilson, H. Jayatilake, B. A. Gusterson, C. Cooper, J. Shipley, D. Hargrave, K. Pritchard-Jones, N. Maitland, G. Chenevix-Trench, G. J. Riggins, D. D. Bigner, G. Palmieri, A. Cossu, A. Flanagan, A. Nicholson, J. W. Ho, S. Y. Leung, S. T. Yuen, B. L. Weber, H. F. Seigler, T. L. Darrow, H. Paterson, R. Marais, C. J. Marshall, R. Wooster, M. R. Stratton and P. A. Futreal (2002) Mutations of the BRAF gene in human cancer. Nature, 417, 949-954.
39. Thomas, N. E., M. Berwick and M. Cordeiro-Stone (2006) Could BRAF mutations in melanocytic lesions arise from DNA damage induced by ultraviolet radiation? J Invest Dermatol, 126, 1693-1696.
40. Thomas, N. E., A. Alexander, S. N. Edmiston, E. Parrish, R. C. Millikan, M. Berwick, P. Groben, D. W. Ollila, D. Mattingly and K. Conway (2004) Tandem BRAF mutations in primary invasive melanomas. J Invest Dermatol, 122, 1245-1250.
41. Thomas, N. E. (2006) BRAF somatic mutations in malignant melanoma and melanocytic naevi. Melanoma Res, 16, 97-103.
42. Besaratinia, A. and G. P. Pfeifer (2008) Sunlight ultraviolet irradiation and BRAF V600 mutagenesis in human melanoma. Hum Mutat, 29, 983-991.
43. Besaratinia, A., S. I. Kim and G. P. Pfeifer (2008) Rapid repair of UVA-induced oxidized purines and persistence of UVB-induced dipyrimidine lesions determine the mutagenicity of sunlight in mouse cells. FASEB J, 22, 2379-2392.
44. Hocker, T. and H. Tsao (2007) Ultraviolet radiation and melanoma: a systematic review and analysis of reported sequence variants. Hum Mutat, 28, 578-588.

45. Pollock, P. M., F. Yu, L. Qiu, P. G. Parsons and N. K. Hayward (1995) Evidence for u.v. induction of CDKN2 mutations in melanoma cell lines. Oncogene, 11, 663-668.
46. Krauthammer, M., Y. Kong, B. H. Ha, P. Evans, A. Bacchiocchi, J. P. McCusker, E. Cheng, M. J. Davis, G. Goh, M. Choi, S. Ariyan, D. Narayan, K. Dutton-Regester, A. Capatana, E. C. Holman, M. Bosenberg, M. Sznol, H. M. Kluger, D. E. Brash, D. F. Stern, M. A. Materin, R. S. Lo, S. Mane, S. Ma, K. K. Kidd, N. K. Hayward, R. P. Lifton, J. Schlessinger, T. J. Boggon and R. Halaban (2012) Exome sequencing identifies recurrent somatic RAC1 mutations in melanoma. Nat Genet, 44, 1006-1014.
47. Pleasance, E. D., R. K. Cheetham, P. J. Stephens, D. J. McBride, S. J. Humphray, C. D. Greenman, I. Varela, M. L. Lin, G. R. Ordonez, G. R. Bignell, K. Ye, J. Alipaz, M. J. Bauer, D. Beare, A. Butler, R. J. Carter, L. Chen, A. J. Cox, S. Edkins, P. I. Kokko-Gonzales, N. A. Gormley, R. J. Grocock, C. D. Haudenschild, M. M. Hims, T. James, M. Jia, Z. Kingsbury, C. Leroy, J. Marshall, A. Menzies, L. J. Mudie, Z. Ning, T. Royce, O. B. Schulz-Trieglaff, A. Spiridou, L. A. Stebbings, L. Szajkowski, J. Teague, D. Williamson, L. Chin, M. T. Ross, P. J. Campbell, D. R. Bentley, P. A. Futreal and M. R. Stratton (2010) A comprehensive catalogue of somatic mutations from a human cancer genome. Nature, 463, 191-196.
48. Greenman, C., P. Stephens, R. Smith, G. L. Dalgliesh, C. Hunter, G. Bignell, H. Davies, J. Teague, A. Butler, C. Stevens, S. Edkins, S. O'Meara, I. Vastrik, E. E. Schmidt, T. Avis, S. Barthorpe, G. Bhamra, G. Buck, B. Choudhury, J. Clements, J. Cole, E. Dicks, S. Forbes, K. Gray, K. Halliday, R. Harrison, K. Hills, J. Hinton, A. Jenkinson, D. Jones, A. Menzies, T. Mironenko, J. Perry, K. Raine, D. Richardson, R. Shepherd, A. Small, C. Tofts, J. Varian, T. Webb, S. West, S. Widaa, A. Yates, D. P. Cahill, D. N. Louis, P. Goldstraw, A. G. Nicholson, F. Brasseur, L. Looijenga, B. L. Weber, Y. E. Chiew, A. DeFazio, M. F. Greaves, A. R. Green, P. Campbell, E. Birney, D. F. Easton, G. Chenevix-Trench, M. H. Tan, S. K. Khoo, B. T. Teh, S. T. Yuen, S. Y. Leung, R. Wooster, P. A. Futreal and M. R. Stratton (2007) Patterns of somatic mutation in human cancer genomes. Nature, 446, 153-158.
49. Margo, C. E., Z. Mulla and K. Billiris (1998) Incidence of surgically treated uveal melanoma by race and ethnicity. Ophthalmology, 105, 1087-1090.
50. Singh, A. D., I. G. Rennie, S. Seregard, M. Giblin and J. McKenzie (2004) Sunlight exposure and pathogenesis of uveal melanoma. Surv Ophthalmol, 49, 419-428.
51. Egan, K. M., J. M. Seddon, R. J. Glynn, E. S. Gragoudas and D. M. Albert (1988) Epidemiologic aspects of uveal melanoma. Surv Ophthalmol, 32, 239-251.
52. Holly, E. A., D. A. Aston, D. H. Char, J. J. Kristiansen and D. K. Ahn (1990) Uveal melanoma in relation to ultraviolet light exposure and host factors. Cancer Res, 50, 5773-5777.
53. Rootman, J. and R. P. Gallagher (1984) Color as a risk factor in iris melanoma. Am J Ophthalmol, 98, 558-561.
54. Seddon, J. M., E. S. Gragoudas, R. J. Glynn, K. M. Egan, D. M. Albert and P. H. Blitzer (1990) Host factors, UV radiation, and risk of uveal melanoma. A case-control study. Arch Ophthalmol, 108, 1274-1280.
55. Tucker, M. A., J. A. Shields, P. Hartge, J. Augsburger, R. N. Hoover and J. F. Fraumeni, Jr. (1985) Sunlight exposure as risk factor for intraocular malignant melanoma. N Engl J Med, 313, 789-792.

56. Prota, G., D. N. Hu, M. R. Vincensi, S. A. McCormick and A. Napolitano (1998) Characterization of melanins in human irides and cultured uveal melanocytes from eyes of different colors. Exp Eye Res, 67, 293-299.
57. Sarna, T. (1992) Properties and function of the ocular melanin--a photobiophysical view. J Photochem Photobiol B, 12, 215-258.
58. Vajdic, C. M., A. Kricker, M. Giblin, J. McKenzie, J. Aitken, G. G. Giles and B. K. Armstrong (2003) Incidence of ocular melanoma in Australia from 1990 to 1998. Int J Cancer, 105, 117-122.
59. Gallagher, R. P., J. M. Elwood, J. Rootman, J. J. Spinelli, G. B. Hill, W. J. Threlfall and J. M. Birdsell (1985) Risk factors for ocular melanoma: Western Canada Melanoma Study. J Natl Cancer Inst, 74, 775-778.
60. Pane, A. R. and L. W. Hirst (2000) Ultraviolet light exposure as a risk factor for ocular melanoma in Queensland, Australia. Ophthalmic Epidemiol, 7, 159-167.
61. Ajani, U. A., J. M. Seddon, C. C. Hsieh, K. M. Egan, D. M. Albert and E. S. Gragoudas (1992) Occupation and risk of uveal melanoma. An exploratory study. Cancer, 70, 2891-2900.
62. Holly, E. A., D. A. Aston, D. K. Ahn and A. H. Smith (1996) Intraocular melanoma linked to occupations and chemical exposures. Epidemiology, 7, 55-61.
63. Lutz, J. M., I. Cree, S. Sabroe, T. K. Kvist, L. B. Clausen, N. Afonso, W. Ahrens, T. J. Ballard, J. Bell, D. Cyr, M. Eriksson, J. Fevotte, P. Guenel, L. Hardell, K. H. Jockel, A. Miranda, F. Merletti, M. M. Morales-Suarez-Varela, A. Stengrevics and E. Lynge (2005) Occupational risks for uveal melanoma results from a case-control study in nine European countries. Cancer Causes Control, 16, 437-447.
64. Monarrez-Espino, J., A. Stang, K. Bromen, H. Merzenich, G. Anastassiou and K. H. Jockel (2002) Occupation as a risk factor for uveal melanoma in Germany. Scand J Work Environ Health, 28, 270-277.
65. Swerdlow, A. J. (1983) Epidemiology of eye cancer in adults in England and Wales, 1962-1977. Am J Epidemiol, 118, 294-300.
66. Vagero, D., A. J. Swerdlow and V. Beral (1990) Occupation and malignant melanoma: a study based on cancer registration data in England and Wales and in Sweden. Br J Ind Med, 47, 317-324.
67. Vajdic, C. M., A. Kricker, M. Giblin, J. McKenzie, J. F. Aitken, G. G. Giles and B. K. Armstrong (2004) Artificial ultraviolet radiation and ocular melanoma in Australia. Int J Cancer, 112, 896-900.
68. Sliney, D. H. (1995) UV radiation ocular exposure dosimetry. J Photochem Photobiol B, 31, 69-77.
69. Lerman, S. (1980) Radiant energy and the eye. Macmillan Publishing Co., Inc., New York.
70. Norren, D. V. and J. J. Vos (1974) Spectral transmission of the human ocular media. Vision Res, 14, 1237-1244.
71. Mallet, J. D. and P. J. Rochette (2013) Wavelength-dependent ultraviolet induction of cyclobutane pyrimidine dimers in the human cornea. Photochem Photobiol Sci.
72. Dillon, J., R. H. Wang and S. J. Atherton (1990) Photochemical and photophysical studies on human lens constituents. Photochem Photobiol, 52, 849-854.
73. Krishna, C. M., S. Uppuluri, P. Riesz, J. S. Zigler, Jr. and D. Balasubramanian (1991) A study of the photodynamic efficiencies of some eye lens constituents. Photochem Photobiol, 54, 51-58.

74. Dillon, J. (1991) The photophysics and photobiology of the eye. J Photochem Photobiol B, 10, 23-40.
75. Van Raamsdonk, C. D., K. G. Griewank, M. B. Crosby, M. C. Garrido, S. Vemula, T. Wiesner, A. C. Obenauf, W. Wackernagel, G. Green, N. Bouvier, M. M. Sozen, G. Baimukanova, R. Roy, A. Heguy, I. Dolgalev, R. Khanin, K. Busam, M. R. Speicher, J. O'Brien and B. C. Bastian (2010) Mutations in GNA11 in uveal melanoma. N Engl J Med, 363, 2191-2199.
76. Van Raamsdonk, C. D., V. Bezrookove, G. Green, J. Bauer, L. Gaugler, J. M. O'Brien, E. M. Simpson, G. S. Barsh and B. C. Bastian (2009) Frequent somatic mutations of GNAQ in uveal melanoma and blue naevi. Nature, 457, 599-602.
77. Besaratinia, A. and G. P. Pfeifer (2011) Uveal melanoma and GNA11 mutations: a new piece added to the puzzle. Pigment Cell Melanoma Res, 24, 18-20.
78. Hu, D. N., S. A. McCormick, R. Ritch and K. Pelton-Henrion (1993) Studies of human uveal melanocytes in vitro: isolation, purification and cultivation of human uveal melanocytes. Invest Ophthalmol Vis Sci, 34, 2210-2219.
79. Yang, W. (2011) Surviving the sun: repair and bypass of DNA UV lesions. Protein Sci, 20, 1781-1789.
80. Sertic, S., S. Pizzi, F. Lazzaro, P. Plevani and M. Muzi-Falconi (2012) NER and DDR: classical music with new instruments. Cell Cycle, 11, 668-674.
81. Kraemer, K. H., M. M. Lee and J. Scotto (1984) DNA repair protects against cutaneous and internal neoplasia: evidence from xeroderma pigmentosum. Carcinogenesis, 5, 511-514.
82. Kraemer, K. H., D. D. Levy, C. N. Parris, E. M. Gozukara, S. Moriwaki, S. Adelberg and M. M. Seidman (1994) Xeroderma pigmentosum and related disorders: examining the linkage between defective DNA repair and cancer. J Invest Dermatol, 103, 96S-101S.
83. Aoyagi, M., N. Morishima, Y. Yoshino, N. Imagawa, M. Kiyosawa, M. Ito, S. Kondou and O. Matsubara (1993) Conjunctival malignant melanoma with xeroderma pigmentosum. Ophthalmologica, 206, 162-167.
84. Mehta, C., C. N. Gupta and M. Krishnaswamy (1996) Malignant melanoma of conjunctiva with xeroderma pigmentosa--a case report. Indian J Ophthalmol, 44, 165-166.
85. Benatiya Andaloussi, I., M. Abdellaoui and H. Tahri (2012) [Conjunctival melanoma and xeroderma pigmentosum, a rare association]. Bull Soc Belge Ophtalmol, 17-21.
86. Johnson, M. W., G. L. Skuta, M. C. Kincaid, C. C. Nelson and J. R. Wolter (1989) Malignant melanoma of the iris in xeroderma pigmentosum. Arch Ophthalmol, 107, 402-407.
87. Kraemer, K. H., M. M. Lee and J. Scotto (1987) Xeroderma pigmentosum. Cutaneous, ocular, and neurologic abnormalities in 830 published cases. Arch Dermatol, 123, 241-250.
88. Garland, C. F., E. D. Gorham, S. B. Mohr and F. C. Garland (2009) Vitamin D for cancer prevention: global perspective. Ann Epidemiol, 19, 468-483.
89. Giovannucci, E., Y. Liu, E. B. Rimm, B. W. Hollis, C. S. Fuchs, M. J. Stampfer and W. C. Willett (2006) Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. J Natl Cancer Inst, 98, 451-459.
90. Grant, W. B. and C. F. Garland (2006) The association of solar ultraviolet B (UVB) with reducing risk of cancer: multifactorial ecologic analysis of geographic variation in age-adjusted cancer mortality rates. Anticancer Res, 26, 2687-2699.

91. Boscoe, F. P. and M. J. Schymura (2006) Solar ultraviolet-B exposure and cancer incidence and mortality in the United States, 1993-2002. BMC Cancer, 6, 264.
92. Grant, W. B. (2007) An ecologic study of cancer mortality rates in Spain with respect to indices of solar UVB irradiance and smoking. Int J Cancer, 120, 1123-1128.
93. Tang, J. Y., T. Fu, E. Leblanc, J. E. Manson, D. Feldman, E. Linos, M. Z. Vitolins, N. C. Zeitouni, J. Larson and M. L. Stefanick (2011) Calcium plus vitamin D supplementation and the risk of nonmelanoma and melanoma skin cancer: post hoc analyses of the women's health initiative randomized controlled trial. J Clin Oncol, 29, 3078-3084.
94. Godar, D. E., R. J. Landry and A. D. Lucas (2009) Increased UVA exposures and decreased cutaneous Vitamin D(3) levels may be responsible for the increasing incidence of melanoma. Med Hypotheses, 72, 434-443.
95. Lehmann, B. (2009) Role of the vitamin D3 pathway in healthy and diseased skin--facts, contradictions and hypotheses. Exp Dermatol, 18, 97-108.
96. Levine, J. A., M. Sorace, J. Spencer and D. M. Siegel (2005) The indoor UV tanning industry: a review of skin cancer risk, health benefit claims, and regulation. J Am Acad Dermatol, 53, 1038-1044.
97. Weinstock, M. A. and D. E. Fisher (2010) Indoor ultraviolet tanning: what the data do and do not show regarding risk of melanoma and keratinocyte malignancies. J Natl Compr Canc Netw, 8, 867-872; quiz 873.
98. Diffey, B. (2011) Ultraviolet A sunbeds and vitamin D. J Am Acad Dermatol, 65, 1059-1060.