

Photocarcinogenesis and Skin Cancer Prevention Strategies

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Abstract. *In this review the basic principles of UV-induced carcinogenesis are summarized and the state of the art diagnosis and therapeutic strategies are discussed. The prevalent keratinocyte-derived neoplasms of the skin are basal cell and squamous cell carcinomas. Cutaneous melanoma is less frequent but associated with high mortality. Common risk factors for all three tumor entities include sun exposure and DNA-repair deficiencies. Photocarcinogenesis follows a multistep model of cancer development in which ultraviolet-induced DNA damage leads to mutations resulting in activation of oncogenes or silencing of tumor-suppressor genes. This ends in a cellular mutator phenotype even more prone to mutation acquisition. DNA repair, especially the nucleotide excision repair (NER) pathway, counteracts mutation formation and skin cancer development. This is vividly demonstrated by the NER-defective disorder xeroderma pigmentosum. Primary skin cancer preventative strategies, therefore, include reduction of DNA photodamage by protection from the sun. Secondary preventative strategies include skin cancer screening. This implies standard examination techniques with the naked eye, an epiluminescence microscope, or digital epiluminescence microscopy. More advanced techniques include confocal laser scan microscopy.*

Carcinogenesis of UV-induced Skin Tumors

The electromagnetic spectrum encompasses a wide range of all possible electromagnetic fields, and is conventionally categorized into an ionizing and a non-ionizing part. Ionizing

radiation carries enough energy to break chemical bonds in molecules, thereby creating ions. In contrast, non-ionizing radiation does not offer sufficient energy to form charged ions but can lead to excitation of molecules. Non-ionizing radiation is known to cause potential health risks and is especially associated with a number of skin disorders, such as cancer [reviewed in (1)].

The non-ionizing spectrum is divided into two main regions, optical radiation and electromagnetic fields, the latter being further divided by radiofrequency (microwave, very high frequency and low frequency radiowave). The optical region can be further subdivided into ultraviolet (UV), visible, and infra-red. In this review, we focus primarily on the effects of UV radiation in photocarcinogenesis.

UV Spectrum

The UV spectrum ranges from 100 nm to 400 nm, whereas 100 nm has been defined as the boundary between non-ionizing and ionizing radiation (UV photons fall between the wavelengths of visible light and gamma radiation) (2). Solar UV radiation can further be subdivided into UVA (315-400 nm), UVB (280-315 nm) and UVC (100-280 nm). UVC has the shortest wavelength of visible light and the highest energy, while UVA has the longest wavelength accompanied by the least energy and UVB falls between [reviewed in (3)]. The optimal absorption of UV light by DNA is 254 nm (4, 5). Despite representing only a fraction of the solar spectrum, UV radiation has a high carcinogenic activity and gives rise to a long-term risk of skin cancer.

Skin Penetration

UVC is strongly mutagenic but does not reach the earth's surface because it is almost completely blocked by the stratospheric ozone layer. Therefore, the UV light reaching the earth's surface is predominantly UVA (90-95%) and to a minor extent UVB (5-10%), with UVA penetrating the ozone layer, while this layer absorbs most UVB radiation (6).

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UV light penetrates the skin in a wavelength-dependent manner, with longer wavelengths reaching deeper skin layers [reviewed in (3)]. Concordantly, the less energetic UVA rays penetrate deeper into the dermal compartments compared to UVB, which is almost completely absorbed by the epidermis (7) (Figure 1).

Although UVA is the most prevalent component of solar UV radiation reaching the earth's surface, it mainly causes skin photoaging (solar elastosis) by dermal fiber deterioration, and it is far less carcinogenic compared to UVB radiation [reviewed in (8)]. In contrast, although UVB radiation only constitutes a minor part of the solar radiation it is far more carcinogenic at significantly lower doses than UVA radiation. UVB has a direct mutagenic effect on DNA as it is maximally absorbed by this primary chromophore [reviewed in (9)]. UV photon energy absorption by DNA decreases constantly at longer wavelengths (in the UVA range); therefore, UVB radiation is considered the major cause of skin cancer. However, UVA radiation also has a particular significance in photocarcinogenesis, leading to DNA lesions through indirect effects (10, 11).

In conclusion, UV radiation can give rise to cellular DNA damage by either direct excitation of DNA (dimer formation) or by the indirect excitation of other endogenous non-DNA chromophores (endogenous photosensitizers), both contributing to a long-term skin cancer risk [reviewed in (12)].

UVA Photocarcinogenesis

At the molecular level, low-energy UVA radiation is not directly absorbed by DNA but leads to indirect photo-oxidative DNA damage. UVA is absorbed by other endogenous non-DNA chromophores, contributing to generation of reactive oxygen species (ROS) through an indirect photosensitizing reaction [reviewed in (13)]. The main target of ROS within DNA is guanine, and 8-oxo-7,8-dihydro-2'-deoxyguanosine has been considered as the most frequent oxidative UVA-induced DNA lesion (14). More recently, it was shown that UVA also induces pyrimidine dimer-type DNA damage, as well as immunosuppressive effects and reduced cell-cycle arrest. Such inhibition of the DNA damage response may render UVA-induced dimers more mutagenic than UVB-induced dimers (15, 16).

UVB Photocarcinogenesis

UVB radiation is directly absorbed by DNA, leading to the formation of DNA photoproducts, such as cyclobutane pyrimidine dimers (CPDs) and 6-pyrimidine-4-pyrimidone photoproducts (6-4 PPs), which are of principal importance for the cancerogenic effect of UVB (Figure 2) (17, 18). CPDs are formed between two adjacent thymine (T) or cytosine (C) residues forming a cyclobutane ring, whereas 6-4 PPs are

produced by a single non-cyclic bond between carbon 6 of the 5' pyrimidine and carbon 4 of the 3' pyrimidine residues (19, 20). CPDs are formed in higher proportions (66%) compared to 6-4 PPs (33%) [reviewed in (21)] and both lesions cause bulky distortion of the DNA backbone. These distortions inhibit polymerases during transcription or DNA replication during cell division because they cannot pass these lesions. When unrepaired, these lesions can lead to characteristic mutations in DNA sequences, namely C to T base changes and CC to TT tandem mutations, the so-called UV-signature mutations as virtually no other mutagen induces such mutations.

Notably, it is now generally acknowledged that UVA radiation can also induce CPDs to a similar extent to oxidative DNA damage, as indicated above (15, 22).

Signature Mutations

If the cell encounters unrepaired UV-induced lesions in DNA during the S-phase of the cell cycle, mutations may occur. Most commonly pyrimidine dimers lead to single C-T transitions which represent signature mutations of exposure to UVB irradiation. The so-called A-rule (23) predicts that DNA polymerase-eta (a translesion polymerase) is error-prone because of a lack of proofreading ability and mainly substitutes non-informative bases (bulky lesions such as dimers) on the template strand by two adenines on the opposite strand (24). This means that photoproducts (CPDs and 6-4 PPs) generate a characteristic C-T transition mutation, including the CC-TT tandem mutation, by misincorporation of adenine opposite cytosine. These signature mutations are found almost exclusively in UVB-induced skin cancer and can, therefore, be called UVB-fingerprint or -signature mutations (5, 17, 25).

Mutations typically found in UVA-induced tumors are comparable to the mutation spectrum of UVB (C to T transitions) arising from photodimers. Only a very minor proportion (8%) of UVA-generated mutations include G-T transversions, presumably arising through mechanisms involving oxidized DNA bases (8-oxo guanine) and indirect energy transfer (15). Hence, UVA-induced CPDs are much more carcinogenic than oxidative DNA damages.

Multistep Skin Cancer Development

Skin cancer development is a multistep process involving tumor initiation, tumor promotion, and tumor progression, ultimately resulting in visible skin cancer. Damage to DNA lead to mutations in key cellular regulators such as the *p53* tumor-suppressor gene, which is commonly referred to as the guardian of the genome (26). However, other essential genes may also be mutated as early events in tumorigenesis including rat sarcoma (*RAS*), *p16INK4A*, epithelial growth factor (*EGFR*), and the proto-oncogene *FYN* [reviewed in (27)].

Subsequently due to failure of key regulatory genes, a cellular mutator phenotype may occur with even more mutations accumulating. These events then lead to uncontrolled cell differentiation and growth, finally resulting in skin cancer.

The unique features of UV-induced mutations can be exploited for the analyses of different skin cancer types, *e.g.* basal cell (BCC) and squamous cell (SCC). Mutations in the tumor-suppressor gene *p53* have been found in more than 90% of all SCCs and in approximately 50% of all BCCs, representing early events in non-melanoma tumorigenesis (27-29). Most of these mutations exhibit the UV-typical mutation pattern C-T (17, 30-34).

During multistep carcinogenesis of white skin cancer, multiple cell functions are gained or lost. Other genes besides *p53*, such as *RAS*, *p16INK4A*, epithelial growth factor receptor (*EGFR*) and *FYN*, with important cell regulatory functions in signaling pathways are also involved in early cancer development [reviewed in (27)]. *p53* mutations confer a survival benefit on cells during tumor promotion (reduced apoptosis) and resistance to further UV exposure (mutator phenotype) (34).

Nucleotide Excision Repair and Associated Disease

UV-induced pyrimidine dimers are almost exclusively repaired by the NER pathway, which removes bulky DNA damage and protects from skin cancer. Malfunctions in this repair pathway lead to the rare human autosomal recessive disorder *xeroderma pigmentosum* (XP) [reviewed in (35)]. XP is very rare with an estimated incidence of 1 in 1,000,000 in North America and Europe (36). Clinical signs of XP usually appear in early infancy or childhood, with patients exhibiting sun sensitivity, freckling in sun-exposed skin, and development of skin cancer early in life. Patients with XP exhibit a >1,000-fold increased skin cancer risk in comparison to the general population (37, 38). This risk extends to all forms of UV-induced skin cancers, including BCC and SCC, as well as melanoma.

Seven NER complementation groups (XP-A to XP-G) exist corresponding to the affected gene (*XPA* to *XPG*) and a variant form (XP-V) with mutations in DNA polymerase eta (*POLH*) (38). With these defects in NER, XP presents a model disease for skin tumorigenesis, showing accelerated generation of skin tumors compared to the normal population.

Skin Cancer Entities

Skin cancer development represents a multistep process in which cellular events lead to accumulation of DNA mutations, resulting in loss of cellular growth control [reviewed in (39)]. Mutations in the DNA result in different skin cancer entities which can be divided into cutaneous melanoma (malignant transformation of melanocytes) and

non-melanoma skin cancer. The latter is further subdivided into BCC and SCC of the skin, both resulting from malignant transformation of keratinocytes [reviewed in (40)].

BCC is the most common type of skin cancer (ratio between BCC and SCC is about 4:1) (41), being a cancer of the elderly, as the risk increases with age (60-70 years) (42). However, a tendency towards a younger age for first tumor manifestation has been observed. In Germany, the incidence of BCC is estimated as 100 per 100,000 inhabitants (43). BCCs are subdivided according to their different morphological growth pattern (44, 45) (nodular, sclerosing and multicentric-superficial) and several rare growth forms are described (*e.g.* metatypic BCC, *ulcus rodens*). BCCs rarely metastasize and the local growth pattern results in a rather benign course of the disease (27, 46).

An early warning sign of skin cancer is the development of actinic keratosis (AK), which is *in situ* SCC. It presents the earliest clinically recognizable manifestation of cutaneous SCC. Approximately 0.025-16% of AKs transform into invasive SCCs within one year (47, 48); however, about 26% of AKs spontaneously regress within one year (48). In general, AKs are a typical phenomenon of aging skin, with a prevalence of 11-25 per 100 in patients over 40 years of age, compared to a higher prevalence (18-34 per 100) in patients over 70 years of age. Notably, AKs are not covered in tumor registries. Treatment of AKs can prevent the development of SCC, which comprise the second most common human cancer following BCCs, with an incidence of approximately 20-30 per 100,000 inhabitants in Europe. SCC prevalence also increases with age and the mean age of first occurrence is 70 years, accompanied by a preponderance of men [reviewed in (27)]. Compared to BCCs, SCCs can be highly invasive and have a higher potential to metastasize. However, only about 5% of SCCs metastasize, particularly to local lymph nodes (49, 50). Both non-melanoma skin cancer entities (BCC and SCC) develop predominantly in sun areas of the skin exposed to the sun, particularly on the face, lips and ears. In contrast, cutaneous melanomas are rather homogeneously distributed all over the body (51).

Epidemiological studies have demonstrated that the incidence of non-melanoma skin cancer has been increasing alarmingly. Professor Alexander Katalinic (Institute for Cancer Epidemiology e.V. University Luebeck) estimated the number of new cases to approximately 180,000 per year in Germany (52). However, the number is not precisely known since the incidences of BCC and SCC are not usually reported to cancer registries (53).

In contrast, melanomas only account for 2% of all skin cancer; however, they are the most deadly type of skin cancer because they often metastasize [reviewed in (54)]. Clinically, cutaneous melanoma can be divided into four growth subtypes: superficial spreading melanoma, nodular melanoma, *lentigo maligna* melanoma and acro-lentiginous melanoma (55). The growth pattern of melanoma is divided

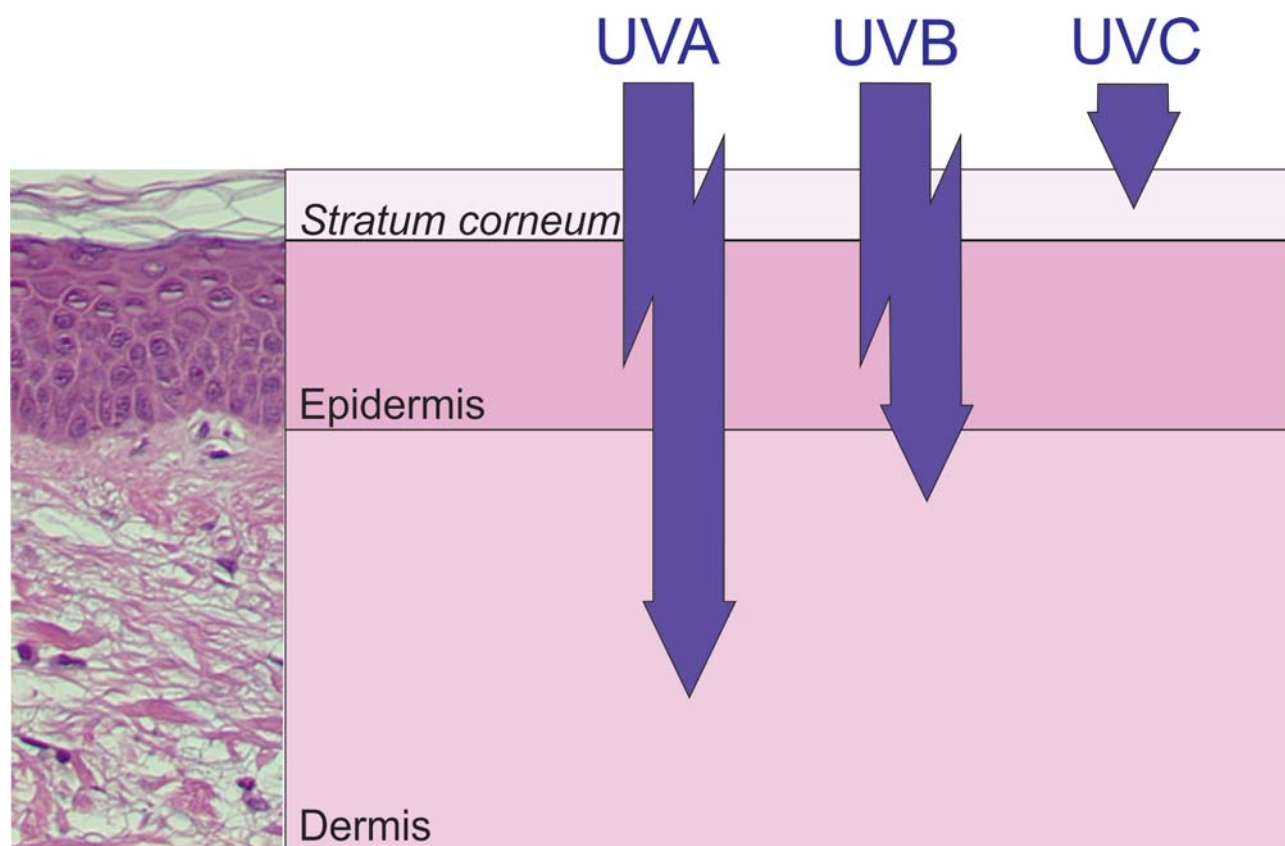


Figure 1. A histological skin section (hematoxylin and eosin staining, magnification $\times 40$) is depicted on the left and the corresponding penetration depth of the different UV wavelengths on the right. UVC, although highly mutagenic to DNA, only reaches the corneal layer consisting of dead keratinocytes. UVB reaches the stratum basale of the epidermis, i.e. the epidermal stem cell layer. Due to its shorter wavelength, higher energy and smaller depth of penetration, the energy deposition per cell volume and, thus, mutagenicity of UVB is the highest. UVA can reach dermal structures including elastic and collagen fibers and leads to skin aging, as well as DNA damage.

into a radial growth phase and a vertical growth phase, which is prognostically unfavorable because of the infiltration of tumor cells into the dermis (56). Therefore, diagnosis of early stages of melanoma significantly improves the relative survival rate of patients. In Germany (80 million inhabitants), the incidence of melanoma for 2014 was estimated at 15,000, and approximately 2,500 deaths were recorded (57). In contrast to non-melanoma skin cancer, melanoma is more common in young adults, referred to as the cancer of the young (58). However, the incidence of non-melanoma skin cancer is also rising in the younger population (59).

Skin Cancer Prevention

As mentioned above, skin cancer incidences have been increasing dramatically over the past few years; therefore primary prevention has become highly important. Since solar UV irradiation represents the most important environmental

risk factor for the development of skin cancer (60), skin protection against UV exposure is a fundamental part of cancer prevention. Approaches commonly used in order to prevent skin cancer include avoiding direct exposure to midday sun (between the hours of 10 am and 2 pm), textile protection with appropriate clothing and the use of sunscreens with a minimum sun protection factor of 15-20, collectively leading to a reduced UV exposure (61). Currently, a broad spectrum of sunscreen products protects against both UVA and UVB radiation. Furthermore, regularly performed self-examinations increase the likelihood of detecting any skin changes, e.g. AK or other skin tumors. Complemented by an annual full-body skin examination performed by a dermatologist, skin changes can be diagnosed at an early and curable stage. Given that almost 80% of all skin cancers can be prevented by reasonable behavior, the American Cancer Society promoted an awareness campaign with the slogan “Slip! Slop! Slap! and

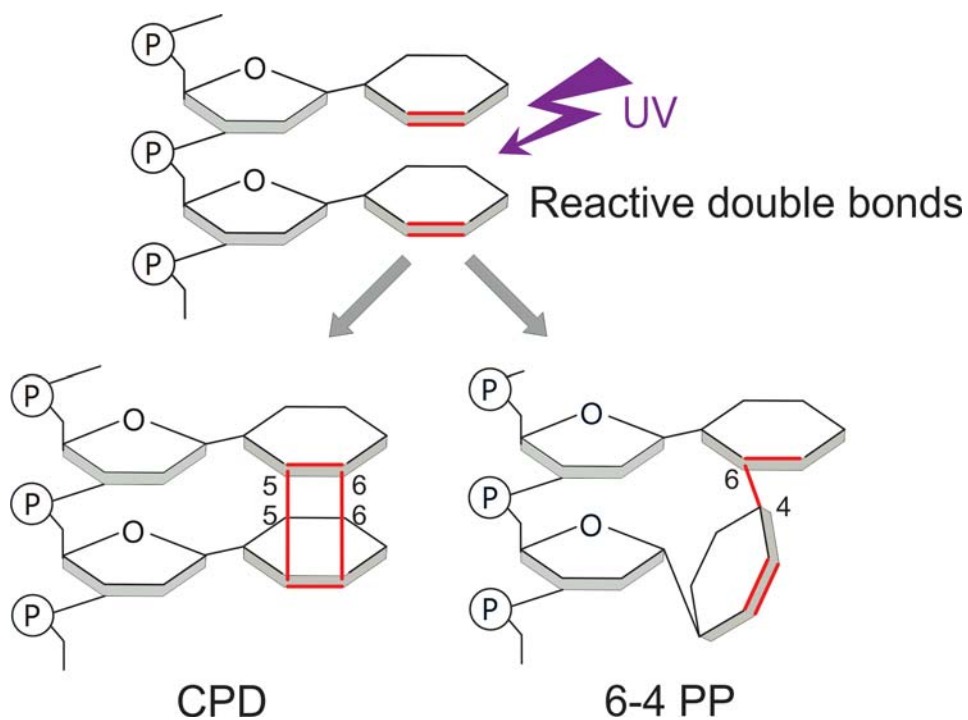


Figure 2. DNA molecules can directly absorb UV photon energy at UVC and UVB wavelengths, which induces the formation of cyclobutane-pyrimidine dimers (CPDs) or 6-pyrimidine-4-pyrimidone photoproducts (6-4 PPs) at a constant ratio of about 2:1.

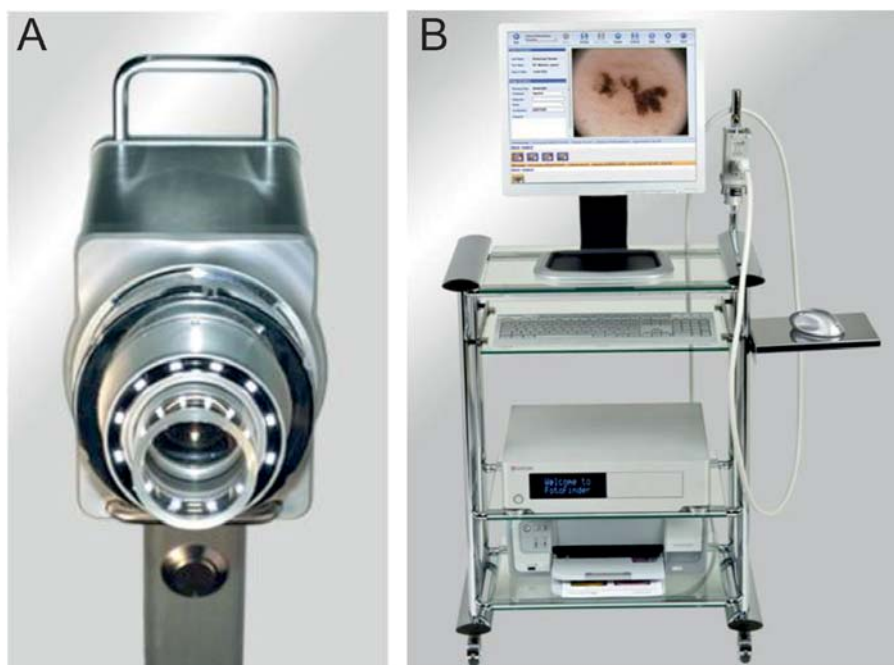


Figure 3. The detection head (A) and a complete digital epiluminescence microscopic device (B) are depicted (Fotofinder®). Images of moles can be stored at 20-fold or higher magnification and then compared to each other over time, adding dynamic criteria to mole assessment.

Wrap”, reminding people of the four easy ways to protect themselves against UV radiation: to slip on a shirt, to slop on sunscreen, to slap on a hat and to wrap on sunglasses.

Skin Cancer Diagnosis and Screening

Generally, the gold standard for the treatment of skin cancer is still the surgical excision of all tumor cells with histological control of the margins. The survival prognosis of patients with skin cancer, especially with melanoma, is inversely correlated with the tumor thickness. Early diagnosis and treatment are pivotal in reducing morbidity associated with these malignancies.

Since the worldwide incidence of melanoma as well as non-melanoma skin cancer has increased dramatically in recent years, skin cancer screening plays an important role in skin cancer treatment (healing by early detection) and the prognosis of the patient improves substantially with early detection (62). Accordingly, the evolution of new screening techniques represents a weapon in the fight against skin cancer. The development of optical techniques (63), such as dermoscopes, is superior to naked-eye examinations and leads to a higher efficacy in early skin cancer diagnosis [reviewed in (64)]. Dermoscopy (also referred to as dermatoscopy, epiluminescence microscopy, incident light microscopy, or skin-surface microscopy) significantly improves the diagnostic accuracy of discriminating melanoma from benign melanocytic lesions compared to routine naked-eye examinations (65, 66). A number of instruments are used in the screening process, including widely applied, inexpensive, handheld instruments such as an epiluminescence microscope (*e.g.* Welch Allyn Inc., Skaneateles Falls, NY, USA), which provides a high quality lens with a 12-fold magnification, digital epiluminescence light microscopes (DELMs), and more recently, confocal laser scan microscopy.

These devices represent a non-invasive diagnosis technique, preventing excessive surgical excision of benign skin lesions. Handheld dermoscopes are especially cost-effective and easy to use. Nevertheless, diagnostic accuracy is only guaranteed if performed by dermatologists experienced in this technique (67, 68).

DELM can also be used for a surveillance program regarding patients at high melanoma risk, *e.g.* with a family background of melanoma, lighter skin type, or an increased number of dysplastic nevi. It was demonstrated that melanoma detected by DELM had significantly thinner Breslow thickness (better prognosis), therefore increasing the sensitivity for detection of early cutaneous melanoma that has not yet acquired melanoma-typical ELM features (69) compared to other techniques (70). With this technique, images of a mole can be compared sequentially over time, adding dynamic features to the criteria of mole assessments (71). In conclusion, DELM is valuable tool in improving early

detection of cutaneous melanoma, especially of atypical melanocytic lesions primarily not suspicious for melanoma.

Applying up to 50-fold magnification, DELM images can be recorded and saved (*e.g.* using the FotoFinder®; TeachScreen Software GmbH, Bad Birnbach, Germany). Automatic measurement of maximum lesion diameter can be obtained. This has a great advantage for follow-up studies regarding the sensitivity and specificity of melanoma detection over time (72) (Figure 3).

More recently, the introduction of reflectance confocal microscopy (RCM), also known as confocal laser scanning microscopy, has been used as link between dermoscopy and histopathological analysis (73) in order to provide more accurate diagnosis and to reduce the number of benign excised lesions (74). The most valuable advantage of RCM is its high resolution, allowing the assessment of single cells and cell nests, as well as its ability to monitor dynamic changes in the architecture of the skin over time (75).

Taken together, avoidance of mutations due to UV-induced DNA lesions is the best strategy for cancer prevention. One can rely on DNA repair to reduce the number of lesions, but it is wise to reduce lesion formation by sun protective measures in the first place. As effective secondary preventative measures, several techniques for early skin cancer detection have been developed.

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