Air pollution, UV irradiation and skin carcinogenesis: what we know, where we stand and what is likely to happen in the future?

Barbara Zegarska1, Katarzyna Pietkun1−2, Wojciech Zegarski1, Paulina Bolibok4, Marek Wiśniewski4, Katarzyna Roszek5, Joanna Czarnecka5, Maciej Nowacki3

1Chair of Cosmetology and Aesthetic Dermatology, Ludwik Rydygier’s Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Poland
2Chair and Department of Rehabilitation, Ludwik Rydygier’s Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Poland
3Chair and Department of Surgical Oncology, Ludwik Rydygier’s Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Oncology Centre – Professor Franciszek Łukaszczyk Memorial Hospital in Bydgoszcz, Poland
4Physicochemistry of Carbon Materials Research Group, Faculty of Chemistry, Nicolaus Copernicus University, Torun, Poland
5Department of Biochemistry, Faculty of Biology and Environment Protection, Nicolaus Copernicus University, Torun, Poland

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Abstract

The link between air pollution, UV irradiation and skin carcinogenesis has been demonstrated within a large number of epidemiological studies. Many have shown the detrimental effect that UV irradiation can have on human health as well as the long-term damage which can result from air pollution, the European ESCAPE project being a notable example. In total, at present around 2800 different chemical substances are systematically released into the air. This paper looks at the hazardous impact of air pollution and UV and discusses: 1) what we know; 2) where we stand; and 3) what is likely to happen in the future. Thereafter, we will argue that there is still insufficient evidence of how great direct air pollution and UV irradiation are as factors in the development of skin carcinogenesis. However, future prospects of progress are bright due to a number of encouraging diagnostic and preventive projects in progress at the moment.

Key words: air pollution, skin carcinogenesis, UV irradiation.

Introduction

The term carcinogenesis refers to the process by which tumors develop, including the different biological and pathological mechanisms which are conducive to it [1, 2]. To date, even though several publications have paid significant attention to this problem, there are still many unanswered questions, which means that it continues to be an area which requires further understanding [3-5]. For instance, only a few studies have been able to precisely detail how particular chemical substances, such as carcinogens, have a direct influence on neoplasm formation [6]. Those described more fully include asbestos, a carcinogen which causes lung mesothelioma; inorganic arsenic, a carcinogenic metalloid which is toxic to the liver; Zinc chromate which has been linked to lung cancer; and zalcitabine, a nucleoside analog reverse transcriptase inhibitor (NARTI) which the International Agency for Research on Cancer (IARC) lists as being possibly carcinogenic to humans [7-12].

Besides chemical agents, radiation and temperature levels are also considered important to carcinogenesis, these physical factors working alongside chemical ones. Notable examples include: how meat cooked at high temperatures can activate 2-amino-1-methyl-6-phenylimidazo[4,5-b] pyridine, a carcinogen associated with breast cancer; or the way in which air pollution combines with ultraviolet solar radiation to induce different types of cancer [13-15].

One area, though, which has been largely neglected and considered insignificant is the particular role that air pollution may play in cases of skin carcinogenesis [16, 17]. This, however, has changed in recent years as air pollu-
PM2.5, it has mainly been observed as inducing systemic respiratory infections [25–29]. Looking specifically at obstructive pulmonary disease, lung cancer, and various intensive pulmonary problems such as asthma, chronic related to birth weight (BW) and preterm birth (PTB); and ease and a higher cardiac risk; childbirth complications associated with adverse health effects such as: heart dis-

The five major soluble and insoluble components of PM2.5 [34–36]

| Soluble components | Insoluble components |
|--------------------|----------------------|
| Sulfate (SO$_4^{2-}$) | Organic carbon (OC) |
| Nitrate (NO$_3^{-}$) | Elemental carbon (EC) |
| Ammonium (NH$_4^{+}$) |                        |
samples drawing such conclusions are limited in scope to refinery, asphalt and other industrial workers [48, 49].

Air pollution and UV irradiation

To properly discuss the relationship between air pollution, UV irradiation and skin carcinogenesis, it is first important to outline the functions of the human skin as well as details about its structure. Its main role is to protect the body against the harmful effects of the surrounding environment [50] whilst preventing the excessive loss of various substances [51]. Paradoxically, it serves to connect the human organism with its surrounding environment [50] whilst providing a barrier against its negative effects, be they physical, chemical or mechanical [53]. When encountering UV radiation, the risk of cancer in the skin is greatly increased [54–59] and it is this interaction which makes it one of the most frequently diagnosed forms of cancer [60, 61]. Therefore, one of the best preventative measures is to limit the exposure of the skin to UV rays [61]. That is why it is so important to preserve the integrity of the epidermis which is no easy task [62]. For the simplest daily activities, even wearing clothes, make the stratum corneum exfoliate, meaning that new cells form to replace them as keratinocyte stem cells from the stratum basale undergo continuous proliferation [63, 64]. These new cells migrate to the stratum corneum [50, 64] where they build a so-called “bricks and mortar” structure. Here, the composition of skin lipids differs greatly from the lipid composition of cell membranes within living cells [51], the stratum corneum containing a high volume of ceramides, cholesterol and free fatty acids among other lipids. Their quantity and kind subsequently influences the strength and integrity of the semipermeable barrier [50].

Solar radiation

The sun is a source of light and heat which supports the metabolic processes of different organisms [65, 66]. It has a continuous spectrum and, at various wavelengths, consists of ultraviolet (UV), visible and infrared radiation [54, 66]. Of all these, UV radiation has the most detrimental effect on human health [67]. Depending on the source, this can be defined as radiation of 100–400 nm [55, 67–69] or 200–400 nm [54, 60, 65, 66] and is usually divided into three main ranges: UVA (400–324 nm), UVB (320–280 nm), and UVC (< 280 nm) [55, 68, 70]. Of which that reaches the Earth’s surface, UVA radiation is the most prevalent (90–99%), accompanied by a small amount of UVB radiation (1–10%) [60, 68, 71], which is largely absorbed by the ozone layer along with UVC radiation [52, 54, 55]. In terms of the total amount of UV radiation which reaches the Earth’s surface, this is dependent on the season, the time of a day, its latitude [52] and many other factors such as cloud cover or how thick the ozone layer is [72].

The impact of UV radiation on the skin

It continues to be difficult to describe how exactly different aspects of UV radiation affect the skin. The literature mostly refers to it without making a distinction between UVA and UVB radiation [55]. Meanwhile, studies which do have produced varying and inconsistent results, some concluding that UVB radiation is more mutagenic and cytotoxic to skin tissue [59, 69]. These argue that this only penetrates the epidermis whilst long-wave UVA radiation reaches the dermis layer (Figure 1) [65, 67, 73]. However, others claim that UVB radiation penetrates the epidermis in addition to part of the dermis and that UVA radiation extends to subcutaneous tissue [66].

UVA radiation

This radiation causes oxidative damage, penetrating deeply into the skin whilst also being able to interact with keratinocytes, melanocytes and fibroblasts [74]. The cytotoxic effect of UVA exposure is significantly less than that of UVB radiation due to the fact that DNA is not a chromophore for UVA [75], and its genotoxic effects occur via an indirect mechanism. It can, nonetheless, induce oxidative stress in keratinocytes and other cells through the formation of reactive oxygen species (ROS) when the skin is exposed to it [74, 76]. A result of this is irreparable damage to keratinocyte stem cells which is then transferred to “daughter cells” [64]. Moreover, many have suggested that skin exposure to this radiation at a range of 320–400 nm increases the risk of both melanoma and non-melanoma skin cancers [58, 67, 74, 77]. Others, though, argue that although UVA rays penetrate far deeper into the human skin than UVB ones, it has a weak carcinogenic effect and only primarily results in aging of the skin [78].

UVB radiation

It has been shown that radiation of 280–320 nm is the most damaging to cells [78]. This is because DNA, containing aromatic rings, is a UVB-absorbing chromophore which results in photoproducts such as 6,4-pyrimi-
Air pollution, UV irradiation and skin carcinogenesis: what we know, where we stand and what is likely to happen in the future?

includes enzymes such as glutathione peroxidase (GPx), work of antioxidant systems which are often classified dox equilibria, the human body is equipped with a net- radicals more generally [76, 77].

ing the main ROS responsible for the formation of lipid radicals, leading to cell mem-

Reactive oxygen species

Reactive oxygen species (ROS) are usually generated in the cell mitochondria during normal oxidative metabo-

lism [76]. Maintaining the appropriate ROS concentration is necessary for normal functioning such as destroying microorganisms [81]. However, excessive levels of ROS can disrupt the equilibrium between its levels and those of antioxidant defense, resulting in oxidative stress [76, 81]. Looking at ROS in more detail alone, they can be di-

vided into two main groups: oxygen molecules with un-

paired electrons or oxygen molecules in excited states [82]. The first group includes superoxide anion radicals (O$_2^-$), hydroxyl radicals (OH•), and lipid peroxide (LOO•) while the second group contains singlet oxygen (O$_2^*)$ [82]. Among the most significant reactive oxygen species is hydrogen peroxide which plays a role in the develop-

ment of many diseases as well as in the appearance of wrinkles and photo-aging of the skin [75]. Fundamen-
tally then, ROS and free radicals play an important role in the formation of lipid radicals, leading to cell mem-

brane damage [71, 83]. To prevent the formation of oxi-

dative stress, nature has equipped the human body with a

number of compounds such as enzymes which enable antioxidative action. One worth mentioning, at this stage, is superoxide dismutase which, along with anion super-

oxide, produces hydrogen peroxide which is usually neu-

tralized by catalase [76]. However, excessive exposure of

skin cells to UV radiation causes the immediate release of iron ions which can catalyze the production of toxic hydroxyl radicals due to the Fenton reaction, these be-

ing the main ROS responsible for the formation of lipid radicals more generally [76, 77].

The body’s defense against UV radiation and ROS

In order to prevent oxidative stress and maintain re-

dox equilibria, the human body is equipped with a net-

work of antioxidant systems which are often classified as enzymatic or non-enzymatic ones [84]. The first group includes enzymes such as glutathione peroxidase (GPx), glutathione reductase, superoxide dismutase (SOD), and catalase (CAT) [68, 84], being activated as a result of excessive ROS emission. Meanwhile, the second group consists of small molecular antioxidants [78] including ascorbic acid, α-tocopherol, uric acid and glutathione [84]. All in all, their task is to mitigate the adverse effects of UV radiation [78]. However, it is melanin, above all, which provides basic protection for the skin against its harmful effects, providing effective photoprotection by scattering radiation as a result of its pigment granules having a high refractive index relative to surrounding skin tissue [74, 85].

Is UV radiation purely harmful?

Ultraviolet radiation may also have a positive impact on the human skin [86] due to the fact that it causes the release of nitric oxide (NO) which has been suggested to lower blood pressure as well as having a positive effect on the cardiovascular system [86]. In addition, NO has the ability to protect against lipid peroxidation created as a result of exposure of the skin to UVB radiation [87]. Moreover, exposure of the skin to these rays is also said to enhance vitamin D$_3$ synthesis, 7-dehydroksycholes-

terol absorbing UV light most effectively at wavelengths between 290 and 320 nm and enabling its conversion to pre-vitamin D which isomerizes thermally into vitamin D$_3$ [57, 63].

Where we stand

From a dermatological point of view, air pollution can be linked to a lengthy list of pathological skin mani-

festations and disorders. This includes different allergic reactions, rashes, eczema, acne and the more rapid ag-

ing of the skin through a loss of moisture and elasticity [88–92]. The British surgeon, Percivall Pott was the first to describe a potential link between pollution and carci-

nogenesis, noting the scrotal squamous carcinomas in British chimney sweeps and directly attributing them to their continuous exposure to carcinogens [93, 94]. None-

theless, it is problematic to assert that any freshly diag-

osed skin lesion or recognized dermatosis is specifically due to air pollution. Doing so requires a demographical or local assessment of environmental impact [95, 96], which means that such etiology is easier corresponded to when the patient in question is from an area which is well-

known for its pollution such as a large urban agglomera-

tion where smog occurs or a recognized industrial and mining region [97–99]. This, subsequently, can result in medical omissions, errors and cases of wrong diagnosis [100, 101]. That is not to say that such methods are not useful with advances made related to clinical guidelines and recommendations continuing to enable the diagno-

sis and treatment of most malignant melanomas [102, 103]. At the same time, though, there is a lack of ade-

quate resources to enable proper diagnostic tracks and
their role as inhibitors being proved in a number of different pre-clinical and clinical studies. For example, it has been suggested that consuming food rich in antioxidants significantly enhances the natural biological production of melanin and other enzymatic antioxidants which help against UV radiation, examples along with their sources being listed in Table 4 [116–122]. Another initiative has involved the screening of people and groups at a higher risk of developing skin cancer such as those working in industry, though there is scope for improvement with indicators suggesting such programs have been limited in effect [123–131]. Perhaps this issue could be resolved by a more detailed study of existing skin cancer incidence reports and by focusing more on the role air pollution and UV irradiation may have played [132, 133].

What is likely to happen in the future?

Current literature indicates that there are broadly two paths of development. One is related to either building on the existing strategies or finding new ones, while the other focuses on the development and production of novel protective products such as sunscreens and dermocosmetics with an SPF filter [41, 134, 135]. One useful starting point, according to Fabbrocini et al., in building new strategies would be to try and foster greater general awareness of causative factors [136]. This is something the “European Code against Cancer 4th Edition: Environment, occupation and cancer” by Espina et al. looks to do, suggesting the use of legislative tools to further spread information about how individuals can protect themselves and the role pollution can have in carcinogenesis [137]. Likewise, at the 23rd World Congress of Dermatology in 2015, Dominique Moyal suggested the promotion of topical products which do not load the skin surface with particles, rinse-off products and high-quality sunscreens [138]. Elsewhere, more novel solutions include the further development and production of innovative protective products such as sunscreens and dermocosmetics which incorporate nanoparticles and nanosystems such as liposomes, nanoparticles, cyclodextrins and nanoemulsions. These could revolutionize cancer-prevention strategies and would rely on bioorganic materials including popular chitosan, lignosulfonate and others. However, as of yet, such solutions have only gone as far as the testing phase in both basic and pre-clinical studies, meaning there is still much work to be done [139–141].

Conclusions

Scientific understanding of the relationship between air pollution and skin carcinogenesis is something which

| List of antioxidants for prevention of skin cancer and their major natural sources [117–122] |
| --- |
| Antioxidants for skin cancer prevention | Major natural source |
| Vitamin C (ascorbic acid) | Blueberries, strawberries, grapes, plums, prunes, red beans, spinach, kale, broccoli |
| β-Carotene | Previously processed: carrots, spinach and sweet potato |
| Vitamin A (retinoic acid) | Fish oil, pork and beef liver, pumpkin |
| Coenzyme Q10 | Oily fish (salmon and tuna), whole grains |
| Glutathione | Onion, potatoes, bananas, apples |
| Tea | Mostly in green tea |
| Vitamin E (γ-tocopherol) | Canola oil, almonds, hazelnuts |

Table 3. Characteristics of the most popular physical and chemical UV protection filters [107–110]

| Type of UV filter used to protect the skin | Main substrates used in production | Spectrum of protection and time to take effect |
| --- | --- | --- |
| Physical filters | Titanium dioxide (TiO₂) | Stronger UVB protection than UVA, characterized by fast action just after topical application |
| Chemical filters | Sulisobenzone, oxybenzone, octyl dimethyl PABA, octyl methoxycinnamate, octyl salicylate, homosalate, helioplex, 4-MBC | Full protection and coverage against UVA and UVB approximately 15–25 min after application |

Table 4. List of antioxidants for prevention of skin cancer and their major natural sources [117–122]
continues to grow. This is in addition to greater knowledge about the role ultraviolet irradiation plays within this, facilitating pathological changes as it interacts with the many airborne chemicals and toxic particles inhaled daily by billions of people living around the world. Additionally, there are around 2800 different chemical substances emitted systemically into the air, our focus can be narrowed down to two chemical groups. These are namely particulate matter and polycyclic aromatic hydrocarbons, both of which should be assessed together with physical factors such as UV irradiation whereby they play a seemingly synergistic role in carcinogenesis. In this paper, alongside ways in which air pollution impacts upon skin cancer, we have also discussed a number of preventative measures currently used and, to a lesser extent, the role of screening. This is in addition to looking at what is likely to happen in the future whereby the large volume of unknowns about the role of air pollution in skin carcinogenesis will be subject to further scrutiny not only in dermatology, but also in medicine more generally.

Conflict of interest
The authors declare no conflict of interest.

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Air pollution, UV irradiation and skin carcinogenesis: what we know, where we stand and what is likely to happen in the future?

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Advances in Dermatology and Allergology 1, February / 2017

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