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Occupational skin carcinogens

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ABSTRACT

Occupational skin cancer may manifest when employees are under exposure to one specific carcinogenic substance or more in the workplace. Workplaces often have higher concentrations of carcinogens compared to any other setting. The most common causes of skin cancer in the workplace are ultraviolet radiation, ionizing radiation, polycyclic aromatic hydrocarbons, and arsenic. However, there is only a limited number of studies on skin cancer from occupational exposure. Skin cancers that are considered mainly work-related are non-melanoma skin cancers. Their most common variants are basal cell carcinomas, squamous cell carcinomas, and actinic keratosis. Two factors that reduced the risk of occupational carcinogen exposure are as follows: a better understanding of skin cancer risk factors involved in industrial processes and better control of the use of ionizing radiation. However, the exposure risk to ultraviolet radiation at dangerous levels remains. Worse still, this risk is often not considered. Yet, the prevention and risk reduction for occupational skin cancer requires the elimination of the contact of all carcinogens present in the workplace with the employees' skin. Additionally, to encourage and facilitate the early recognition and management of premalignant and malignant skin lesions, training should be given to those working under higher skin cancer risk, and periodic examinations should be performed.

Keywords: Cancer, occupation, skin, ultraviolet radiation

Especially in the last 30 years, skin cancers have become a significant public health concern following a rapid increase in their occurrence. According to data from the World Health Organization (WHO), approximately 2-3 million people worldwide are diagnosed with non-melanoma skin cancer (NMSC), and 132,000 people are diagnosed with malignant melanoma in a year. Furthermore, one out of every three people diagnosed with cancer is diagnosed with skin cancer [1]. Its occurrence has increased by 600% since the 1940s [2]. In addition to being the most diagnosed type of cancer in the Americas, one in five people has the risk of developing skin neoplasm [1]. In Australia, which is one of the countries with the highest incidence rate, 80% of newly diagnosed cancers are skin cancers [3]. According to the Public Health Agency of Turkey (2017), the age-standardized rate of C43-other skin cancers and C44-cutaneous melanoma skin cancers per 100,000 men were 1.7 and 25.5, respectively; for 100,000 women, they were 1.2 and 16.7, respectively [4].

Although human skin is resistant to the damage of many substances, it is the most frequently damaged organ in working life. Occupational skin cancer may develop when employees are under exposure to one or more specific carcinogenic substances in the work-

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place. Workplaces often have higher concentrations of carcinogens than any other setting. Moreover, there is only a limited number of studies on skin cancers from occupational exposure. While the exact number of work-related skin cancers is unknown, most observers agree that it is a considerably large number [5]. People with fair skin are more prone to develop NMSC [6]. It originates mainly from work-related exposure. Its most prevalent forms are basal cell carcinomas (BCCs), squamous cell carcinomas (SCCs), and actinic keratosis (AK). Until recently, AKs were considered precancerous due to their potential for SCC development. Currently, they are regarded as malignant intraepidermal neoplasms at an early stage [7]. Particularly for earlier stages of life, malignant melanoma results from intermittent ultraviolet radiation (UVR) exposure rather than cumulative sun exposure [8].

The list of skin carcinogens in humans with sufficient or limited evidence according to the International Agency for Research on Cancer (IARC) is listed in Table 1 [9].

Workers in the following jobs are at higher risk for occupational skin cancer: outdoor workers; coal tar workers; electrode production workers; dye industry workers; roof workers; workers in the production of arsenic-containing pesticides; workers in copper, lead, and zinc refining; uranium mine workers; and healthcare workers [10]. The most common causes of occupational skin cancer are UVR, polycyclic aromatic hydrocarbons (PAHs), arsenic, ionizing radiation, and trauma [5]. Chemicals carcinogenic to the skin were identified more than one hundred years ago, but they are not considered to contribute to the development of NMSC as much as UVR. Moreover, current studies propose that other potential factors (radon and air pollution) may also increase the risk of skin cancer [11, 12]. This manuscript discusses occupational skin carcinogens, such as UVR, ionizing radiation, arsenic compounds, and polycyclic aromatic hydrocarbons.

Table 1. Skin carcinogens with sufficient or limited evidence in humans

Skin cancer	Carcinogens with sufficient evidence in humans	Carcinogens with limited evidence in humans
Cutaneous malignant melanoma	Polychlorinated biphenyls	Oil refinery (occupational exposure)
	Sunlight	
	UVR-emitting tanning devices	
Non-melanomatous skin cancer	Arsenic and inorganic arsenic compounds	Creosotes
	Azothioprine	Human immunodeficiency virus type 1 (infection)
	Coal tar distillation	Human papillomavirus types 5 and 8 (in patients with epidermodysplasia verruciformis)
	Cyclosporine	Hydrochlorothiazide Merkel cell polyomavirus (MCV)
	Methoxsalen and UVA radiation	Nitrogen mustard
	Mineral oils, unprocessed or lightly processed	Oil refinery (occupational exposure)
	Shale oil	UVR emitting tanning devices
	Sunlight	
	Soot (e.g., chimney sweeps)	
	X-ray	
	Gamma radiation	

Ultraviolet Radiation and Ionizing Radiation

Exposure to UVR is usually through exposure to sunlight. Indeed, sunlight is a significant risk factor for occupational skin neoplasm development. Since 2012, the IARC and WHO have categorized UVR as "carcinogenic to humans" because it can result in both malignant melanoma and NMSC [13]. UVR causes mutations in the p53 tumor suppressor gene, and it may have a carcinogenic effect through this pathway. Among all employees, the ones working in an outdoor environment are under higher exposure to UVR from sunlight. There were studies investigating the frequency of skin neoplasms occurrence in outdoor employees. Recent European studies reveal that the risk of developing SCC and BCC in long-term outdoor employees is twice the frequency observed in the general population [14]. Nevertheless, skin cancer resulting from work-related exposure to UVR is not yet an occupational disease. According to the European Agency for Occupational Health and Safety, UVR is carcinogenic; about 14.5 million people working outdoors in 36 different employment sectors in the European Union are under UVR exposure for at least 75% of their working hours. This situation may further get worse by prolonged exposure to sunlight and the use of inappropriate sun protection equipment during working hours. Workers with the highest UVR exposure are in the agriculture, hunting, and construction industries. Other people with higher-risk occupations are farmers, forestry workers/gardeners, agricultural workers, garden and park workers, postmen/women, sorters, newspaper delivery workers, physical education trainers, and childminders [15]. In systematic meta-analysis studies, the risk of SCC and AK (i.e., intraepidermal SCC) development increased by 77%, and for BCC by 43%, compared to the general population [16, 17]. In a meta-analysis of 23 scientific articles, Bauer *et al*. [18] reported that outdoor employees are at a significantly higher risk for BCC (p = 0.014). A multi-center European case-control study compared the risk of occurrence of BCC, SCC, melanoma, and AK among 1416 outdoor and 1863 indoor employees. They found that 37.7% of outdoor employees versus 28.6% of indoor employees were diagnosed with skin cancers more than twice throughout their lives. The incidence of AK increased 1.55 times in outdoor employees and 2.58 times in agricultural and construction employees. On the other hand, for SCC, it is 1.32 times higher for outdoor employees and 2.77 times higher for agricultural and construction employees. For BCC, it is 1.53 times higher for outdoor employees and 1.83 times higher for agricultural and construction workers. The risk of skin cancer and AK was significantly higher for employees working outdoors for ≥ 5 years [19]. A cohort study based on the Norwegian Cancer Registry also asserts that exposure to UVR is a significant factor in having a higher risk of skin cancer (cutaneous melanoma and NMSC) among North Sea offshore employees [20]. The EPIDERM study covering the period from 1996 to 2012 in the United Kingdom revealed that 99% of described cases of occupational skin neoplasia resulted from sun/sunlight/ultraviolet radiation exposure [21]. In welders, UVR from the welding process is a potential factor in NMSC development [22]. According to recent studies, outdoor workers are under UVR exposure at an alarming rate, and the daily limit set by the International Commission on Non-Ionizing Radiation Protection (ICNIRP) was exceeded. This situation highlights the need for national and European health executives to take preventive measures [23].

The fact that ionizing radiation has the potential to cause SCC and premalignant changes are well-known since the experience of the first scholars to use X-rays and radiation devices. The first proof of the carcinogenic potential of ionizing radiation is in a case report in 1902 describing the occurrence of NMSC in the hands of radiation employees [24]. Since then, high incidences of skin cancer related to radiation exposure have been reported among various groups, including atomic bomb survivors, uranium miners, radiologists, interventional cardiologists, and individuals treated with radiation for childhood tinea capitis and malignant tumors. Nearly all of these reports suggest that exposure to radiation increases the incidence of basal cell carcinoma rather than melanoma or SCC. The mechanism behind the different effects of basal cells and squamous cells on radiation-mediated malignant transformation has not been clarified yet [25, 26]. Exposure to ionizing radiation devices is now sufficiently controlled and monitored. That's why skin cancer diagnosis is not expected in X-ray workers as frequently as before. However, a recent study highlighted that the risk of malignant melanoma is higher among radiological technologists who worked before 1950 and those who did not wear lead aprons, which are protective

against this radiation [27]. Wang *et al*. observed 27,011 X-ray employees (radiologists and technicians) in China and described that the relative risk for all cancers among X-ray workers was 4.1 times greater than among doctors working in the same hospitals. The highest relative risk for skin cancer was in those working for more than 15 years [28, 29].

A review by Wakeford [30] reported skin cancers associated with occupational ionizing radiation exposure in aircrew, uranium miners, nuclear weapon test participants, and employees from the nuclear industry. Air crews are under a greater degree of cosmic radiation exposure because of the reduced shielding of the atmosphere at higher altitudes. In another article, working as a pilot for more than 20 years was a risk factor for NMSC, as it increased exposure to ionizing radiation, especially for pilots with longer flight times at high altitudes [25]. A comprehensive review of studies about aircrews over the last 20 years reported a higher risk of melanoma [31]. A higher risk for skin cancer in pilots may result from exposure to excessive UVA radiation during flight operations. While most UVB radiation can be filtered by plastic and glass window protection, up to 54% of UVA radiation can enter planes and UVA radiation is 2 times higher at 9,000 meters compared to the ground [32]. Recently, some researchers have described a high prevalence of malignant melanoma among airline pilots and flight attendants exposed to cosmic radiation. However, some researchers argued that this is due to their lifestyle (e.g., sun exposure from sunbathing) rather than their relatively higher exposure to cosmic radiation [33, 34].

Another carcinogenic radiation is alpha particles. Hard rock miners (uranium, iron, tin, and gold) work in radon-rich environments. Yet, the risk of NMSC in radon-rich environments is not associated with inhalation of radon, but with contamination by the radon products composed of Po-218 and Po-214 on the epidermis exposed to alpha particles. Mechanistic studies of radon-associated carcinogenesis show that alpha particles produce complex biological responses. They involve mutations, chromosomal abnormalities, generation of reactive oxygen species, modification of the cell cycle, changes in cytokines, and carcinogenesis [35, 36]. Although epidemiological studies suggest a relationship between radon exposure and skin neoplasm risk among uranium miners, this relationship is not well-established [37]. The only research with a clear association between alpha radiation and skin cancer was in 1978, which was related to Czech uranium miners. A follow-up study with the same cohort by Sevcová *et al*. [38] described a significantly higher incidence of BCC with a 1-year attributable risk per 10,000 employees at the 1 Sv dose.

Arsenic and Inorganic Arsenic Compounds

Arsenic is a metalloid present in land, rocks, and water. Arsenic has been recognized as a group "A" carcinogen by the US Environmental Protection Agency (EPA) (corresponding to the sufficient evidence for cancer effect) and a group "I" carcinogen by the IARC that can induce cutaneous SCC, BCC, bladder, kidney, and lung cancers. Arsenic is a potent mutagen, as it causes a wide range of chromosomal mutations and acts as a carcinogen only with UVR. Arsenic suppresses DNA repair by inhibiting the PARP1 enzyme. Arsenic exposure increases the vulnerability of keratinocytes and melanocytes to UVR impairment. The cocarcinogenic consequences of UVR and arsenic may partially explain the higher risk of melanoma and keratinocyte carcinoma after arsenic exposure [39]. Prolonged exposure usually results in precancerous arsenic keratosis. However, carcinoma in situ (Bowen's disease and AK) and invasive BCC or SCC have also been detected [40]. Arsenic-related skin tumors occur after ingestion, injection, inhalation, and skin contact with arsenic. Among them, the most common exposure route is arsenic in drinking water. Detailed studies conducted in Taiwan revealed that using well water with a high arsenic concentration caused skin cancer in a dose-response correlated manner. An estimated 1.5 million workers in the United States are under inorganic arsenic exposure. They are from industries such as copper and lead smelting, the metallurgical industry, and pesticide production and use. Skin tumors attributable to occupational arsenic exposure were rare. The same conclusion was reached by studies on arsenic in pesticides as a possible skin neoplasm risk for farmers. Furthermore, some arsenic-induced skin cancer cases of agricultural workers might be from the carcinogenic effects of sunlight and other substances, such as tar [5, 41].

Polycyclic Aromatic Hydrocarbons (PAHs)

PAHs occur as a result of the incomplete combustion of organic compounds of both natural and human

origin. It naturally occurs due to forest fires or volcanic eruptions. Human-induced formations originate from industrial resources, motor vehicles, and cigarettes [42]. Industrial procedures, such as the pyrolysis or burning of coal, and the manufacture and use of coal tar and coal-derived goods, are the most significant sources of work-related exposure to PAHs [43]. Exposure is mostly by inhalation and skin contact. St. Percivall Pott, who was working as a surgeon at Bartholomew's Hospital, reported the relationship between PAHs and cancer for the first time. He observed that chimney cleaning workers had testicular cancer due to the exposure of their skin to soot. Then, 100 years later, Volkmann and Bell confirmed Pott's observation by detecting testicular skin cancer in people working in the paraffin industry in Germany and Scotland [42]. However, it was not until the 1940s that a carcinogenic PAH, benzo[a]pyrene, was shown to be a soot component. Several PAH types or their mixtures can increase the likelihood of cancer, and the carcinogenic effects of PAHs vary with the type or dose of PAHs. Most processes generate several different types of PAHs simultaneously. Among the PAHs, benzo[a]pyrene is the best-known carcinogen. Some professions are at higher exposure to PAHs that are human carcinogens (Group 1) by the IARC. These include coal gasification, coke production, coal tar distillation, chimney sweeping, asphalting, and coal tar roofing; jobs including mineral oils, petroleum oil manufacturing, and aluminum manufacturing [44]. There are several types of PAH in coal tar, bitumen, asphalt, soot, creosotes, anthracenes, paraffin waxes, and lubricating and cutting oils. There is an association between exposure to unprocessed or lightly processed mineral oil containing PAHs and skin and scrotal cancers in wax press workers, metal workers, and machine operators. The latent time between exposure to PAHs and skin neoplasms ranges from 20 (coal tar) to 50 years or more (mineral oil) [5]. In a cohort study found an association between exposure to crude oil or benzene and the risk of skin cancer on the hands and arms of offshore workers [45].

CONCLUSION

While UVR exposure is the most significant risk factor for occupational skin neoplasm development, other non-negligible carcinogens are polycyclic aromatic hydrocarbons, arsenic, and ionizing radiation exposure. The following jobs are at higher risk for occupational skin cancer: outdoor works, coal tar works, electrode production, dye industry, roof works, production of arsenic-containing pesticides, copper, lead, zinc refining, uranium mines, and healthcare works. A better understanding of skin cancer risk factors in industrial processes, cautious use of ionizing radiation, and taking necessary precautions, have resulted in a reduced risk of exposure to a chemical- and radiation-based carcinogens. However, the risk of exposure to UVR remains unsolved. Except in countries where skin cancer is a common public health problem (such as Australia), this risk is often overlooked as a predisposing factor for skin cancer.

The employees' skin contact with carcinogens in the workplace should be prevented to eliminate occupational skin cancer. For those working outdoors, taking protective measures is recommended. These are covering exposed skin with protective equipment (hat, long pants, long-sleeved shirt, sunglasses), and using sunscreen creams. Moreover, training should be organized, and periodic health examinations should be performed to support and facilitate the early recognition and management of premalignant and malignant skin diseases in those working at higher risk.

Authors' Contribution

Study Conception: SK, NG; Study Design: SK, NG; Supervision: SK, NG; Funding: SK, NG; Materials: SK, NG; Data Collection and/or Processing: SK, NG; Statistical Analysis and/or Data Interpretation: SK, NG; Literature Review: SK, NG; Manuscript Preparation: SK, NG and Critical Review: SK, NG.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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