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Multiple factors influence skin cancer development: A comprehensive review

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Abstract
Any human malignancies have mutations in the tumor suppressor gene p53. They are typically prevalent in actinic keratoses (AKs) and over 90% of squamous cell carcinomas (SCCs) have them. In the US and many other nations, skin cancer is becoming more common and killing more people. Many groups are considering public and professional health programs as a potential solution due to concerns that stratospheric ozone depletion is exacerbating the issue. Since melanoma mortality is directly correlated with the degree of tumor invasion at the time of removal, early diagnosis can mitigate the issue in the short run. This is the element that can be altered in an early detection education program. There is little doubt that exposure to sunlight increases the chance of developing skin cancer, both melanoma and nonmelanoma types. This is the part of the equation that combines exposure to environmental risk factors with constitutional predisposition. Light-skinned, easily sunburned people and those who are exposed to the sun the most whether for work-related or socially purposeful reasons are more likely to develop skin cancer. Moreover, non-melanoma skin malignancies mostly develop on areas exposed to sunlight. The incidence of skin cancer could rise sharply in the future due to the recent, notable decline in stratospheric ozone, which raises transmitted short-wavelength UV light. We'll talk about the epidemiologic characteristics and dose-response relationships of UV-induced skin cancers. Chemical exposure (Polycyclic hydrocarbons from incomplete coal or petroleum distillation or combustion; inorganic arsenic; and photosensitizing compounds like psoralens) is another environmental factor that contributes to the development of skin cancer. Since UV radiation is recognized to be the primary risk factor for skin cancer and may be successfully cured when found early, this trend can be reversed through primary and secondary prevention. Appropriate risk (group) indicators must be utilized to identify those at risk in order to detect skin cancer early. In the future, the science of molecular epidemiology should employ new molecular markers or biomarkers to improve the sensitivity and specificity of early detection efforts (Screening programs).

Keywords: Skin, cancer, BCC (Basal cell carcinoma), SCC (Squamous cell carcinoma), melanoma, radiation

Introduction
In India, and in several other nations, skin cancer is becoming more common and more deadly. Many groups are considering public and professional health programs as a potential solution due to concerns that stratospheric ozone depletion is exacerbating the issue. There is little doubt that exposure to sunlight increases the chance of developing skin cancer, both melanoma and nonmelanoma types. This is the part of the skin cancer equation that can be altered by educational initiatives. It consists of exposure to environmental risk factors and constitutional predisposition (Marks, 1995) [37]. Malignant melanoma and NMSC are the two most prevalent forms of skin cancer, with BCC and SCC being the main subtypes of the latter. Since BCC and SCC cases are exempt from reporting requirements to national cancer registries, it is challenging to determine the precise number of NMSC. Researchers from the US and a number of other nations support changes to NMSC registration requirements (Gordon, 2013) [24]. Globally, there are an estimated 91,998 new instances of melanoma and 2,749,998 new cases of nonmelanocytic skin cancer each year. These cancers vary in occurrence by more than 100 times, with low rates among Asians and highly high rates among white people in Australia. The incidence of melanoma has been increasing by roughly 3% to 7% per year in white communities over the last 30 years; recent, exceptionally high increases in some populations are probably due to early and more frequent diagnosis of pre-existing cancers. Additionally, nonmelanocytic skin malignancies are probably on the rise. The main cause of skin cancer is sun exposure, which is responsible for at least 65% of

melanomas globally and a far higher percentage among white people (Armstrong & Kricker, 1995) [4]. Epidemiological research demonstrates the impact of pesticides, particle matter in air pollution, poisons (like arsenic) in water, certain diets, and various forms of radiation (Like ionizing radiation) on the incidence of skin cancer. Intense UV exposure throughout childhood and adolescence is the primary cause of BCC formation, but chronic, cumulative UV exposure over decades is linked to SCC growth. The geographic zone and the skin's constitutive color are directly related to how frequently it occurs. An key contributing reason to the rising incidence of melanoma over the past 70 years is changes in outdoor activity and sun exposure (Leiter *et al*. 2020) [8].

In this paper let's discuss in detail about the types of the skin cancer and the factors affecting it in detail. There are two types of factors affect the skin cancer and these are the external and the internal factors. The external factors are sunlight, UV rays, etc, & the internal factors are oxidative stress, vitamin D, genetics, etc.

Types of Skin Cancer

Melanoma

In all Caucasian groups, the greatest risk factor for melanoma is a high number of nevi. Heritable is the number of nevi, with additive genetic influences accounting for 60% of the diversity in their number. Although fair skin and hair can also be inherited, the risk is far lower than for nevi. The "at-risk" characteristics that lead to melanoma are diverse. Melanoma and sun exposure are related, with the incidence of melanoma rising as latitude decreases (Bataille, 2009) [7]. With an anticipated yearly growth of 3-7% over the last decades, cutaneous melanoma is quickly rising in White populations. As opposed to SCC, melanoma risk is linked to both chronic and sporadic sun exposure. The rising incidence of melanoma is mostly due to changes in outdoor activity and sun exposure during the past 70 years (Leiter *et al*. 2020) [8]. Melanoma is the sixth most frequent cancer, and by the end of 2020, it is expected that over 100, 640 new cases would be diagnosed in the US. Almost 8290 individuals are predicted to lose their lives to melanoma by the end of the year, despite the fact that it only makes up 1% of all skin malignancies. Over 3.3 million persons in the US receive treatment for more than 5.4 million instances of NMSC annually (Trager *et al*. 2022) [42]. Melanoma is considered the fastest growing cancer and rates of non-melanoma skin cancer have also increased over the last decade.

Non-Melanoma

Although skin malignancies can develop from any host cell in the skin, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) account for 70% and 25% of NMSC, respectively. Although the behavior, development, and metastatic potential of NMSC vary, both BCC and SCC have favourable prognoses, particularly when discovered early. In fact, the incidence of metastatic BCC is 1 case per 14,000,000, and the mortality rate from locally advanced BCC is 2 cases per 14,000,000. Consequently, one should anticipate an MR of 0.02 per 10,000 (Didona *et al*. 2018) [20]. They often grow quickly, experience more local recurrences, and spread to 5-8% of patients (Boukamp, 2005) [12].

External Factors contribute to the development of skin cancer

Skin cancer is a common form of cancer caused by genetic predispositions and external factors. The most significant contributor to DNA damage is ultraviolet radiation (UV) from the sun or artificial sources such as tanning beds. UV radiation damages DNA directly and impairs the ability of skin cells to repair themselves. As a result of prolonged exposure to environmental pollutants, certain chemicals, and lifestyle choices such as smoking, the risk increases. Furthermore, factors such as geographic location, ozone depletion, and cultural practices play an important role in determining sun exposure.

Sunlight: A general model for environmental carcinogenesis, the multistage theory of carcinogenesis is based on experimental research in rats. In the initial phase, known as initiation, a carcinogen causes a target gene to change. Promotion, a process in which a single injured cell grows into a clone of damaged cells, comes after initiation in skin that appears to be normal. As these alterations worsen, precancerous skin becomes clinically abnormal, and eventually, cancer. Numerous experimental investigations have been planned to analyse the molecular and cellular mechanisms underlying this process. (Kraemer, 1997) [34]. The below mention figure explains the effect of sun rays or the sun exposure on the tumor. Sunlight's ultraviolet (UV) radiation causes the development of skin cancer. In humans, skin cancer is the most prevalent type of neoplasia. There are thought to be more than 1.5 million new instances of skin cancer, Skin cancers are easier to cure and can be identified more quickly than other malignancies (Ullrich, 2007) [46].

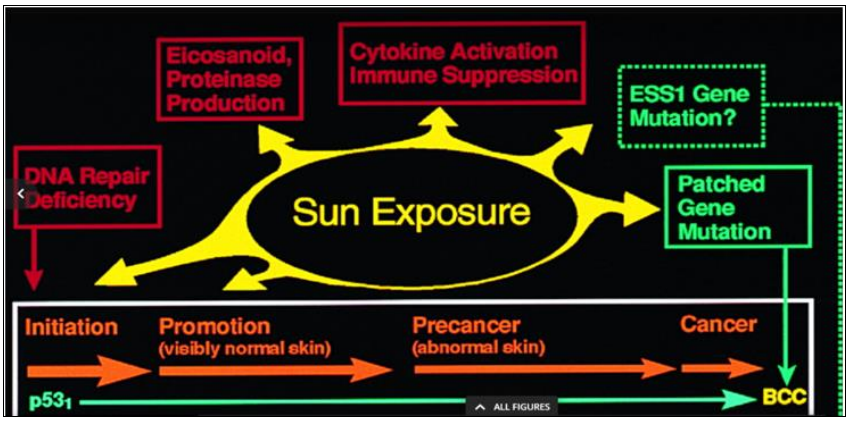

Fig 1: Effect of sun exposure on the tumor suppressor gene, p53 (Kraemer, 1997) [34].

UVB Radiation: Traditional outdoor jobs like farming and forestry did not raise the risk of NMSC, but jobs requiring a high level of education or mandatory health controls, like pilots, engine drivers, and medical care workers, did raise the risk of BCC, in highly educated populations, this would indicate more frequent consultation for skin problems (Ramirez *et al*. 2005) [39]. DNA absorbs UV radiation most efficiently between 245-290 nm (10); UV can cause mutagenic photoproducts or lesions in DNA between neighbouring pyrimidines in the form of dimers, UV-induced DNA lesions have the potential to permanently alter the DNA sequence if they are not repaired. The below mention figure explains about the role of genes in leading to risk of skin cancer. These mutations, which are referred to as UV "signature" mutations, manifest as CT and CCTT transitions (Soehnge *et al*. 1997) [41].

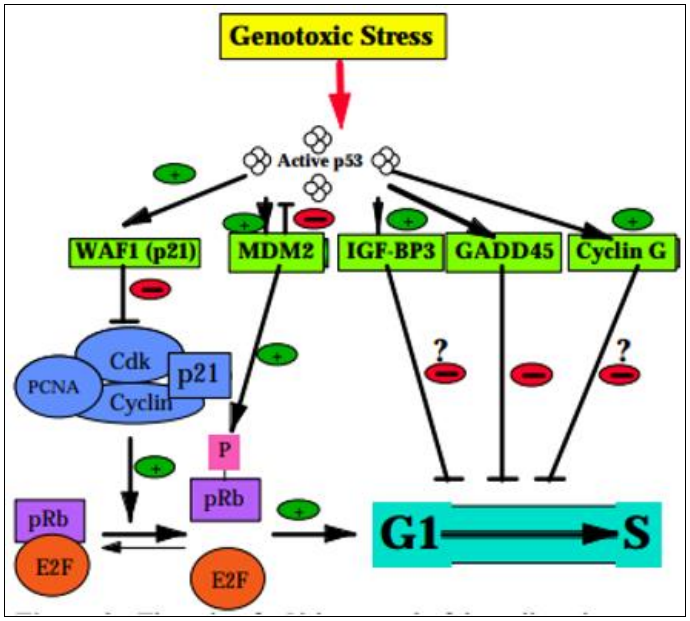

Fig 2: The role of p53 in control of the cell cycle (Soehnge *et al*. 1997) [41].

Enivornmental Pollutants

The skin serves as a barrier between an organism and its sur roundings, pollution is often immediately exposed to it.It ser ves as an entrance to other tissues and is frequently broken d own by pollutants. Several human investigations have identified and proven the carcinogenic potential of specific contaminants in the respiratory and digestive systems. UV light, polycyclic aromatic hydrocarbons (Like benzo [a] pyrene), volatile organic chemicals (Like benzene), heavy metals, and ozone are the "pollutants" that react with the skin the most specifically. The fig.3 shows the cellular targets of the arsenic trioxide action. The majority of human skin malignancies have been attributed to ultraviolet radiation, a "physical" pollutant (Baudouin *et al*. 2002) [9].

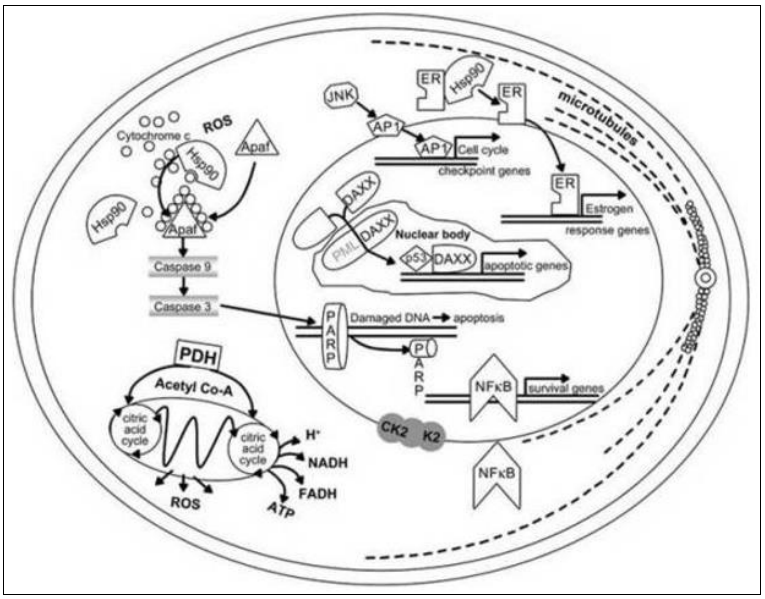

Fig 3: Cellular targets of arsenic trioxide action, with multiple pathways in malignant cells resulting in apoptosis (Baudouin *et al*. 2002) [9].

Environmental Factors

Different diseases spread in different geographical regions based on their climatic circumstances. One of the most prevalent cancers in many geographical areas is skin cancer, One in five persons is at risk of getting some form of skin cancer, Modern human migration and the mismatch between

skin pigmentation and location or lifestyle are the main causes of skin cancer (Maghsoudi *et al*. 2022) [28]. It is anticipated that this behavioural adaptation will have a detrimental effect on the incidence of skin cancer and other health aspects of solar UVR exposure, even though it may have advantages for vitamin D synthesis (Fabbrocini *et al***.** 2010) [21].

Smoking

The development of melanoma cancer seems to be affected with long term smoking (Grant, 2008) [26]. In adult participants at risk of developing any kind of skin cancer, the study aimed to investigate the relationship between smoking and cutaneous photoaging, actinic keratosis (AK), skin malignancies, and pigment cell nevi. However, compared to non-smokers, ever smokers had a higher crude odds ratio (OR=1.99; 95% CI: 1.02–3.88, p=0.043) for squamous cell carcinoma (SCC) (Uotila *et al*. 2024) [47]. Present smoking was linked to a lower risk of BCC (pooled RR = 0.85, 95% CI 0.75, 0.96) and MM (pooled RR = 0.72, 95% CI 0.64, 0.82) but a greater risk of SCC (pooled RR = 1.32, 95% CI 1.15, 1.52). There was no evidence of publication bias, and the combined results were not significantly influenced by any one study. But the risk of skin cancer was unrelated to prior smoking (Arafa *et al*. 2020) [3].

Internal factors

Vitamin D

The fat-soluble vitamin D is necessary for the immune system, bone growth, and the processing of antiproliferative actions, the conversion of 7-dehydrocholesterol to pre-Vitamin D3 occurs when sunlight strikes the skin. 25-hydroxyvitamin D (25(OH)D), the best indicator of vitamin D status, is produced in the liver by the metabolism of vitamin D3 from the skin, vitamin D2, and vitamin D3 from the diet. The kidney then hydroxylates this to create 1, 25-dihydroxyvitamin D (1, 25(OH)2D3), the physiologically active form of vitamin D (Gandhi *et al*. 2009) [51]. There are some negative consequences even if getting vitamin D via UVB radiation is less expensive than buying supplements or eating meals high in vitamin D all the time. Both short-term, high-intensity UVB radiation and long-term UVB exposure have been shown to cause DNA damage and cutaneous inflammation, which can aid in the development of skin cancer (Burns *et al*. 2015) [15]. Vitamin D3's photosynthesis 7-dehydrocholesterol in the epidermis and dermis absorbs ultraviolet B radiation (UVB), which can pass through the ozone layer with energies between 290 and 315 nm, when the skin is exposed to sunlight (Holick, 2008) [30].

Dietary Fats

The impact of a low-fat diet on the incidence of non-melanoma skin cancer was investigated. A total of 101 patients with skin cancer were randomly assigned to one of two groups: the low-fat dietary-intervention group, which instructed patients to limit their intake of fat to 20% of total calories, or the control group, which consumed, on average, 38% of calories as fat and in which no dietary changes were made (Black *et al*.1995) [10]. Low-fat diets have been shown to inhibit the development of skin tumours in animals (Gamba *et al*. 2013) [22]. Patients with skin cancer were taught fat-loss techniques to fit their unique dietary habits and lifestyles (Jaax *et al*. 1997) [31]. Watson and Mellanby found that adding butter to the diet increased the incidence of tar-induced skin tumours (Bojková *et al*. 2020) [11]. Saturated fats and polyunsaturated fish oils either have no effect or are inhibitory, while dietary polyunsaturated vegetable oils encourage the development of tumours in animals (Carroll *et al*. 1986) [16].

Obesity

Roughly 20% of all cancers are thought to be caused by being overweight, and the Million Women Study, the biggest study of its kind on women, has revealed that roughly half of postmenopausal women's cancers are related to obesity (Pergola & Silvestris.2013) [19]. Being overweight is thought to be the second biggest risk factor for developing cancer, behind tobacco use. IARC statistics indicates that a high BMI may contribute to nearly half a million cancer cases annually. Approximately 3.6% of all confirmed cancer cases in 2012 were caused by high bogy weight, according to an IARC study. Being overweight or obese is thought to be responsible for 14% of male deaths and 20% of female deaths (Kotara *et al*. 2021) [35]. The available epidemiologic data, the obesity paradox in cancer risk and mortality, the influence of weight gain and reduction on cancer risk (Avgerinos *et al*. 2019) [6]. The United States is seeing a growing recognition of obesity as a serious public health issue. Over the past three decades, the number of Americans who suffer from obesity-defined as having a body mass index (BMI) of 30 kg/m2 or higher-has dramatically climbed and showed the increasing risk of cancer (Yosipovitch *et al*. 2007) [49].

Melanin

In human skin of various racial/ethnic groups, melanin levels are inversely correlated with the amount of UV-induced DNA damage. Melanin plays a significant role in protecting the skin from UV radiation. Incidence of cancer among skin types, especially between Black and white skin. The darker skin is better at preventing UV-induced DNA damage to the lower epidermis, including keratinocyte stem cells and melanocytes (Yamaguchi *et al*. 2008) [48]. Due to interactions with UV light, white skin's low melanin content causes several genetic changes that trigger oncogenes to produce metastatic melanomas. Those who have a personal or family history of melanoma are at a heightened risk of developing the disease, the treatments include sentinel lymph node biopsies, immunotherapy, radiation, and surgery (Abbas *et al*. 2019) [1]. Skin pigmentation is the most significant photoprotective feature because melanin contains antioxidant and radical scavenging qualities in addition to being a broadband UV absorber. In addition, skin cancer incidence is lower in people with darker skin than in people with lighter skin, according to numerous epidemiological research (Brenner & Hearing, 2008) [13]. The behavior of both healthy and malignant melanocytes is influenced by melanogenesis and melanin pigment, which may have consequences for melanoma diagnosis and treatment (Slominski *et al*. 2015) [40].

Oxidative Stress

The environment and the skin itself are the sources of reactive oxygen species (ROS), which make the skin a prime target for oxidative stress. Normal metabolism produces ROS, which are essential for regular cellular activity and are typically harmless due to intracellular

processes that lessen their harmful effects (Trouba *et al*. 2004) [43]. Skin cancers that are not melanoma mostly include cutaneous squamous-cell carcinoma (SCC) and basal-cell carcinoma (BCC), with a few less common skin tumors included. SCC results from the unchecked proliferation of atypical epidermal keratinocytes, while BCC is derived from the basal layer of the epidermis and its related components (Karampinis *et al*. 2023) [32]. About 90% of all human malignancies are environmental (non-genetic) in origin, primarily from lifestyle choices like smoking, food, and UV radiation, with the remaining percentage coming from infections and chemical exposure. The multistage process of cancer includes unchecked cell proliferation and mutational alterations. Studies have conclusively demonstrated that oxidative stress and oxidative damage play a causal and contributing role in the development and spread of cancer.

Genetics

The biology behind the development of skin cancer is now better understood because to recent developments in molecular genetics. The RB, p53, and RAS pathways seem to be important in the pathophysiology of a number of skin cancer forms, as they are in the majority of malignancies (Tsai & Tsao, 2004) [44]. In contrast to typical genetic disorders, where the disturbed phenotype is often determined by a single inherited mutation, most malignancies, particularly solid tumors, emerge after a number of genetic lesions have accumulated. Germline mutations are those that are inherited and make a person more likely to get cancer, whereas somatic mutations are acquired and help produce tumours (Tsao, 2001) [45]. Thekidney transplant recipients (KTRs) are 65-250 times more likely to acquire nonmelanoma skin cancer. The most modifiable risk factors for the development of skin cancer in transplant recipients are immunosuppressive medications in conjunction with conventional risk factors like exposure to UV radiation (Burke *et al*. 2015) [14].

Rheumatoid Arthritis

Risk factors for the formation of NMSC in patients with RA, rheumatoid arthritis (RA) was linked to a higher risk for NMSC development compared to individuals with osteoarthritis (OA) (Chakravarty *et al*. 2005) [18]. People with rheumatoid arthritis (RA) are known to have a higher risk of lymphoproliferative diseases than people in the general population. Uncertainty surrounds whether this risk results from immunological dysregulation and underlying inflammation, the side effects of disease-modifying drugs, or a combination of the two. As targeted biologic therapies-including those that could potentially disrupt innate tumor surveillance-become more widely used, there is growing fear that other cancers may emerge (Chakravarty & Farmer, 2008) [17]. Rheumatoid arthritis patients had a greater incidence of non-melanoma skin malignancies than the general population, according to epidemiological studies. Inhibitors of tumor necrosis factor (TNF) are the most often utilized biological immunosuppressive drugs to treat rheumatoid arthritis (Assassi, 2016) [5]. When compared to the general population, rheumatoid arthritis (RA) is known to be linked to a higher incidence of lymphoproliferative disorders. There were not enough melanomas reported to make any inferences about whether underlying RA or commonly used medicines enhanced or lowered risk. There is currently no known safety signal for skin cancer associated with RA or its treatments (Chakravarty & Farmer, 2008) [17]. Here the below flow chart figure explains the cycle of getting risk of skin cancer due to rheumatoid arthritis.

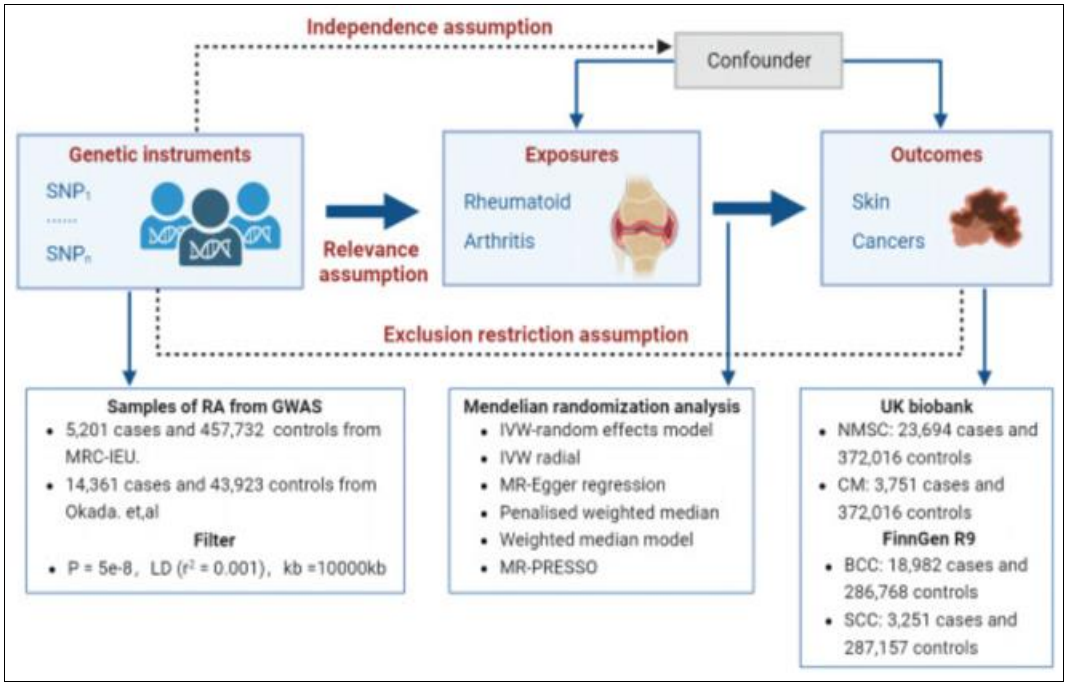

Fig 3: Mendelian randomization concept and assumptions (Yu *et al*. 2024) [50].

Inflammation

Study on skin cancer has been sparked by the discovery in 1828 that tumors form in areas of persistent irritation and inflammation (Hensler *et al*. 2013) [29]. Numerous animal models have been created to clarify these processes, and they have been very helpful in determining how the

inflammatory process contributes to the development and spread of tumors. The conventional tumor initiation and promotion scheme for the creation of mouse skin tumors is one of the most well-established and possibly most thoroughly examined animal models that links inflammation to the development of skin cancer (Muller, 2006) [37]. Dense inflammation can serve as a sign of additional tumors beyond a specimen's edge in addition to hiding a tumor. It is unclear how the placement of the new tumor and the microscopic location of the inflammation are related (Alam *et al*. 2016) [2]. Both acute and chronic inflammatory processes have been demonstrated to have a significant impact on the development of cancer. Advances in inflammation research have shown a link between inflammatory processes and the development of metastases and recurrences, tumor progression, and neoplastic transformation (Piotrowski *et al*. 2020) [38].

Conclusion

With millions of cases worldwide, skin cancer is the most prevalent type of carcinoma. Since the incidence is rising every year, it is the biggest hazard to public health. Numerous factors may be significant prognostic indicators for skin cancer and raise the risk of the disease. Millions of individuals worldwide suffer from skin cancer, the most prevalent type of carcinoma. Skin cancer is a major public health concern due to its rising occurrence. The chance of developing skin cancer is increased by a number of endogenous and external risk factors. Numerous risk variables could be crucial prognostic markers for the illness. Clinicians should be urged to: 1) maintain a high index of suspicion, 2) stay alert when visually monitoring patients' skin. Often, changing moles are thought to be insignificant and do not indicate the possibility of skin cancer. The elements that can cause or act as obstacles to seeking treatment are highlighted in this study, which supports existing national programs to increase patient awareness and early cancer diagnosis. The site of the inflammation and the eventual tumor are somewhat correlated when dense inflammation alone occurs before the tumor is discovered in frozen sections. When inflammation is absent, peripheral tumors are unlikely to be detected.

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