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Review

THE EFFECT OF SMOKING ON CUTANEOUS MELANOMA

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SUMMARY – Melanoma has emerged as a significant global health issue in recent decades, especially in countries with a predominantly fair-skinned population. Well recognized risk factors for melanoma include exposure to ultraviolet radiation, fair skin phototypes and a familial predisposition to malignant skin conditions. Although smoking is a well-known carcinogen, its impact on melanoma has been under-researched and is not routinely assessed during melanoma patient examinations. Existing studies suggest a correlation between smoking and adverse prognostic factors in melanoma, such as increased tumor thickness, ulceration and lymph node metastasis, leading to higher mortality rates independent of age, sex and disease stage. Surprisingly, some studies report a negative correlation between smoking and melanoma incidence, particularly in men, highlighting the need for further investigation. In light of the detrimental effects of smoking on melanoma prognosis, it is recommended to routinely assess smoking status — including former smoking habits — during initial evaluation and follow-up, and offer the patient support in quitting. Recognizing smoking as one of the key modifiable risk factors for cutaneous melanoma could be useful in reducing the disease's impact and improving its outcome in these patients.

Keywords: *Melanoma*; *Smoking*; *Dermatology*

Introduction

There has been a steep and continuous increase in the incidence of cutaneous melanoma in recent decades[1]. Consequently, it has become an ever-present problem in healthcare on a global level, and especially in parts of the world where fair-skinned populations predominate. The most established risk factors for developing cutaneous melanoma are intermittent exposure to UV light, a fair skin tone and a family predisposition to malignant skin diseases[2].

Smoking is a well-known carcinogen for a multitude of malignant neoplasms[3]. On the other hand, the effect of smoking on cutaneous melanoma has not been investigated as much and has not been established as a routine part of the examination process in these patients. Furthermore, the analysis of smoking status is limited by the fact that all the data related to this habit are obtained from a self-reported smoking

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history, lacking a routine, systematized and objective method of evaluation[4].

Methods

In March 2024, a comprehensive literature search was conducted in the PubMed database to identify studies examining the relationship between smoking and cutaneous melanoma. The search covered publications from January 1994 up to March 2024. The search strategy used a combination of free-text terms and Medical Subject Headings (MeSH), including: ("cutaneous melanoma" [MeSH] OR "melanoma" [MeSH] OR "skin melanoma") AND ("smoking" [MeSH] OR "tobacco use" OR "cigarette smoking"). Reference lists of relevant articles and reviews were also manually screened to identify additional studies.

Two reviewers independently screened titles and abstracts for eligibility, followed by a full-text review of potentially relevant studies. Eligible articles included case-control, cohort and meta-analysis studies that evaluated either melanoma incidence or outcomes in relation to smoking status. Exclusion criteria were: (1) studies not available in English; (2) articles focusing on non-cutaneous melanoma (e.g., ocular or mucosal melanoma); and (3) studies primarily addressing other skin cancers. Data extraction was also performed independently by two reviewers. Extracted data included study design, population characteristics, smoking exposure assessment, melanoma outcomes and adjustment for confounders. Any discrepancies between reviewers were resolved through discussion and if a consensus was not reached, a third reviewer determined the final verdict. Factors known to influence melanoma risk and outcomes — such as sun exposure patterns, skin type, and number of nevi — were considered when interpreting the findings.

Cutaneous melanoma overview

Due to the considerable affinity of melanoma for early hematogenic and lymphogenic metastases, it is considered one of the most aggressive tumors of the skin and mucosa[5]. Hence, it is not so surprising that, with a continued increase in melanoma incidence worldwide, melanoma is becoming a prominent cause of cancer-related mortality[6]. An early diagnosis of melanoma is crucial for the survival of the patients, as statistics show that the patients treated with surgical excision of the lesion in the early stage of melanoma have an approximately 98% 5-year survival rate, while the survival rate of the more advanced stages is substantially lower, even in the era of new and promising adjuvant systemic treatments[7].

The risk factors for developing melanoma are classified into intrinsic (genetic) and extrinsic (behavioral, environmental) factors. Well known intrinsic factors are the phototype of the individual, genetic predisposition to skin tumors, personal history of skin tumors, and the number and type of nevi[8]. On the other hand, the most consequential extrinsic factor linked to melanoma is intermittent exposure to UV radiation from the sun[9]. Furthermore, studies indicate that childhood and adolescence are the most decisive periods for exposure to UV radiation in relation to the risk of developing cutaneous melanoma in the future[10]. Other external risk factors include immunosuppression, obesity and diet, including alcohol consumption and smoking[11,12].

Smoking and its multi-systemic impact

Smoking has been acknowledged as a serious health concern for a long time, as it has become one of the most prominent sources of preventable mortality worldwide. The damaging effects of smoking are not restricted to the smoker individually, as they additionally affect those who are exposed to second-hand smoke[13]. Tobacco smoke is a group I carcinogen that is known to be associated with a number of malignant diseases, including cancer of the oral cavity, pharynx, esophagus, pancreas, kidney, lungs, bladder, cervix, stomach, colon, rectum and liver[14,15].

In addition to its carcinogenic effects, smoking significantly reduces lung function, thereby increasing the risk of pulmonary infections[16]. It is also responsible for the development of chronic obstructive pulmonary disease, chronic bronchitis and emphysema[17]. In the cardiovascular system, it accelerates the process of atherosclerosis, resulting in an increased risk of stroke and myocardial infarction, and elevates blood

pressure, highly increasing the risk of developing cardiovascular conditions[18]. The endocrine system is also negatively affected, as smoking disrupts the regulation of hormones, causing dysfunction of the thyroid gland, and is linked with insulin resistance and increased risk of diabetes type 2[19]. Additionally, smoking decreases fertility in males and females[20]. Finally, from a dermatological point of view, it is also a known risk factor for psoriasis, untimely skin ageing and poor wound healing[21].

Quitting the habit has immediate and long-term health benefits. Within weeks of cessation, pulmonary function starts to improve and the risk of coronary disease decreases[22]. Long-term cessation greatly reduces the risk of chronic obstructive pulmonary disease, cancer and chronic diseases[23]. Consequently, smoking cessation improves quality of life and prolongs life expectancy[24].

Results – smoking and cutaneous melanoma

Smoking and Melanoma Outcomes and Prognosis

Most of the available studies divided their participants into 3 categories based on their smoking habits: never smokers, former smokers and current smokers[25]. The association between current smoking and an increased risk of melanoma-specific mortality was reported in several studies[21,26–28]. This increased risk was most pronounced in patients with negative sentinel lymph node biopsy (SLNB) after being diagnosed with primary melanoma. Among the patients who are SLNB-negative and who smoked at least 20 cigarettes per day, the risk of melanoma-specific mortality was doubled. In this population, smoking was identified as the second most significant risk factor for melanoma-specific mortality, following primary tumor ulceration[29].

A study by Jones et al. also showed a significant positive correlation between current smoking and sentinel lymph node metastases; its analysis of 4,231 patients from MSLT-I and MSLT-II trials revealed that current smoking was strongly linked to SLN metastasis ($P = 0.004$), increased ulceration ($P < 0.001$) and thicker tumors, with never smokers having a 0.25 mm decrease in Breslow thickness compared to current smokers ($P = 0.002$)[30]. Additionally, smoking was associated with other unfavorable prognostic indicators, such as increased Breslow thickness and ulceration of the lesion[31]. Several plausible mechanisms could explain the promotion of tumor metastasis and reduced survival rates in melanoma patients with a smoking habit. These potential mechanisms include endothelial damage, reduced blood flow through the skin and the procoagulant state induced by smoking[32,33]. Consequently, smoking should be explored as a feature contributing to early melanoma metastases and should be implemented in the available research databases.

A recent meta-analysis by Friedman et al. analyzed data from over 164,000 patients and found that current smokers had a 33% higher risk of melanoma-specific death compared to never-smokers (HR 1.33, 95% CI 1.14–1.55). Former smokers, however, had outcomes comparable to never-smokers (HR 1.04, 95% CI 0.94–1.14). Smokers were also more likely to have sentinel node positivity and postoperative complications following lymph node surgery[34].

Smoking and Melanoma Incidence

Surprisingly, there was an inverse relationship between smoking and the incidence of melanoma in multiple studies, which was more pronounced in the male population[21]. One hypothesis supporting the "protective" effect of smoking on melanoma incidence suggests that nicotine stimulates the production of anti-inflammatory mediators via cholinergic mechanisms whilst inhibiting pro-inflammatory markers (IL-8, IL-6, TNFA)[35]. This "protective" effect was more pronounced on parts of the body exposed to the sun, as smokers were more likely to be diagnosed with trunk melanoma and had the lowest incidence of head and neck melanoma[26,29]. The proposed mechanisms responsible for this occurrence include nicotine suppression of the skin's inflammatory response to UVB radiation and a downregulation of the Notch pathway in smokers[26]. This pathway, which largely affects cell fate, is crucial for linking the regulation of epidermal differentiation and proliferation[36]. It is hypothesized that women exhibit higher cytochrome P450 enzyme activity, leading to a faster nicotine metabolism and therefore a reduced protective effect of nicotine in relation to the incidence of melanoma[37]. Moreover, the use of oral contraceptives accelerates the metabolism

of nicotine and cotinine, which further supports the idea of a faster metabolism of nicotine in women compared to men[38].

A dilemma remains about whether this inverse association reflects a "protective effect" of smoking on melanoma development or whether other non-causal explanations are more plausible. On the one hand, melanoma would not be a disease unique in showing a favorable association with smoking – other conditions such as Parkinson's disease and ulcerative colitis show similar patterns[39]. Available studies investigating this potential association are subject to bias and confounding factors, leaving open the question of whether smoking increases or decreases the risk of melanoma. For example, detection bias can happen if smokers undergo fewer medical examinations than non-smokers, resulting in a supposedly lower incidence of melanoma among smokers. Additionally, the higher overall mortality rate among smokers could contribute to the apparently lower incidence of melanoma due to competing mortality risks[40].

A recent systematic review and meta-analysis by Friedman et al. found that smokers have a significantly lower incidence of melanoma compared to never-smokers. By analyzing 49 studies comprised of nearly 60,000 melanoma cases, the authors reported a 40% lower risk in male smokers (RR = 0.60, 95% CI 0.56–0.65) and a 21% lower risk in female smokers (RR = 0.79, 95% CI 0.73–0.86). While former male smokers retained a modest risk reduction (RR = 0.84), no such effect was seen in former female smokers. These findings support the paradoxical observation that cigarette smoking appears inversely associated with melanoma incidence, despite its established carcinogenicity in most other cancers[41].

Socioeconomic Status Context

Multiple studies found that individuals with higher socioeconomic status exhibited a higher incidence of melanoma, likely due to lifestyle factors, such as increased sun exposure from travel and recreational activities[21,28,42–44]. However, lower socioeconomic status has been associated with poorer prognosis and lower melanoma-specific survival, which may reflect disparities in healthcare access and comorbidities[28]. This aligns with the literature indicating that lower socioeconomic status is linked to premature mortality from numerous conditions, including cardiovascular and respiratory diseases, as well as certain malignancies[45]. Therefore, understanding socioeconomic disparities is relevant within this review's scope, as it helps contextualize how smoking behaviors and melanoma risk overlap across different populations.

Other Relevant Findings

A study by Kessides et al. evaluated the relationship between cigarette smoking and melanoma risk while controlling for key confounders including UV exposure, skin type and a history of sunburns resulting in blisters. Both former and current smokers showed a tendency for lower melanoma risk relative to never smokers, but these findings were not statistically significant. The study's limited sample size and the absence of data on nevi could have affected the precision of the findings. Overall, after a thorough adjustment for confounding factors, they found that smoking was not significantly associated with melanoma risk[46].

Table 1 provides a summary of key findings from the principal studies we reviewed, highlighting the relationship between smoking and cutaneous melanoma in terms of incidence, prognosis and outcomes. The gathered information is restricted by its dependence on self-reported smoking histories and the absence of objective and systematic quantitative smoking evaluations. Future studies and melanoma-related databases should incorporate more detailed quantitative smoking metrics, such as 'pack–year' data, the duration of smoking and time since cessation. Additionally, more precise information regarding the types of tobacco products used should be documented and compared in relation to the effect they have on cutaneous melanoma in the future.

Clinical and public health implications

Despite widespread public health campaigns and regulatory measures against smoking, it continues to pose a significant health risk to the general population. Effective public health interventions are key for reducing the prevalence of smoking. These interventions include preventive measures, such as tobacco product taxation, smoking bans in public places, advertising restrictions and thorough public education campaigns[47].

Table 1. Summary of Principal Studies

Study	Year	Design	Population	Key findings (with 95% CI)	Adjusted confounders	Reference number
Kessides et al.	2011	Case-control	246 participants	No significant link between smoking and melanoma incidence after UV adjustment. Current vs never: OR 0.65 (95% CI 0.19-2.24) / Former vs never: OR 0.43 (95% CI 0.18-1.04).	Age, sex, race, skin type, UV exposure, number of sunburns	(46)
Sondermeijer et al.	2019	Case-control	6752 participants	Slight inverse trend between smoking and melanoma incidence (not significant). Men: adjusted OR for current smoker 0.56 (95% CI 0.40-0.79); women: current smoker OR 0.96 (95% CI 0.74-1.26)	Age, marital status, education, skin type, sun-vacation, solarium use, time outdoors, sun protective measures	(21)
Mattila et al.	2023	Cohort	1359 participants	Smoking is an independent marker of poor prognosis. Persistent smokers vs never: HR 1.81 (95% CI 1.27-2.58); Former vs never: HR 1.75 (95% CI 1.28-2.40)	Age, sex, TNM stage, comorbidities	(27)
Jackson et al.	2024	Cohort	6279 participants	Smoking increased melanoma-specific mortality in patients with stage I and II melanoma. Current smokers vs never: HR 1.48 (95% CI 1.26-1.75); For SLNB-negative: HR 1.85 (95% CI 1.35-2.52)	Age, Breslow thickness, ulceration, primary site, SLN status (and likely other prognostic factors)	(29)
Friedman et al.	2024	Systematic review and meta-analysis	46 studies including 164,166 patients with melanoma	Smoking independently associated with poorer melanoma-specific survival; current smokers had higher mortality and postoperative complication rates. Current vs never: HR 1.33 (95% CI 1.14-1.55) for melanoma-specific death; Former vs never: HR 1.04 (95% CI 0.94-1.14)	Variable across component studies; adjustment typically for age, stage, other prognostic factors	(34)
Friedman et al.	2024	Systematic review and meta-analysis	49 studies including 59,429 patients with melanoma	Inverse association between smoking and melanoma incidence; lower risk in current male and female smokers; modest reduction in former male smokers only. Male current smokers: RR 0.60 (95% CI 0.56-0.65); Female current smokers: RR 0.79 (95% CI 0.73-0.86); Male former smokers: RR 0.84 (95% CI 0.77-0.93); Female former smokers: RR 1.00 (95% CI 0.92-1.08)	Most studies adjusted for age, sex, sun exposure/ skin type; the meta-analysis noted variation in adjustment sets.	(41)

Furthermore, support in smoking cessation — including behavioral therapy and pharmacotherapy — is essential, with youth-focused programs for smoking prevention being particularly crucial[48].

Public health initiatives should prioritize campaigns among high-risk groups. The strong evidence relating smoking with worse outcomes in melanoma patients emphasizes the need to integrate smoking cessation programs into melanoma treatment strategies[49]. Moreover, public health strategies must address the socioeconomic factors that contribute to elevated melanoma death rates in lower-income populations[50]. Ensuring equal access to health services is critical to improving clinical outcomes. Targeted interventions

aimed at decreasing the prevalence of smoking in socioeconomically disadvantaged communities could regulate the impact of this modifiable risk factor.

Conclusion

Considering the unambiguous negative impact of smoking on the severity of the disease and its outcome, it is advised to regularly ask about smoking status during the initial treatment of patients with melanoma and the ensuing follow-up, including making inquiries about former smokers (e.g. pack-year, years of smoking and time interval from smoking cessation). It is also imperative that physicians inform and educate patients on the grave dangers of this habit, while encouraging quitting and providing support for it. It is vital to continue the smoking prevention and cessation efforts, as well as scientific research to have a better understanding of the mechanisms behind the effects of smoking on melanoma in order to further decrease the occurrence of smoking, thus diminishing its impacts on health. By regarding the habit of smoking as a modifiable risk factor for cutaneous melanoma, we believe that significant progress in decreasing the burden of the disease and improving its outlook can be achieved.

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Sažetak

Utjecaj pušenja na melanom kože

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Melanom je posljednjih desetljeća značajan zdravstveni problem na svjetskoj razini, posebno u zemljama s pretežno svjetloputim stanovništvom. Dobro poznati čimbenici rizika za nastanak melanoma uključuju izloženost ultraljubičastom zračenju, svjetlije fototipove kože i obiteljsku predispoziciju za maligna stanja kože. Iako je pušenje dobro poznati kancerogen, njegov utjecaj na melanom nedovoljno je istražen i ne procjenjuje se rutinski tijekom pregleda pacijenata s melanomom. Postojeće studije ukazuju na korelaciju između pušenja i nepovoljnih prognostičkih čimbenika kod melanoma, kao što su veća debljina tumora, ulceracije i metastaze u limfnim čvorovima, što dovodi do viših stopa smrtnosti neovisno o dobi, spolu i stadiju bolesti. Iznenađujuće, neke studije pokazuju negativnu korelaciju između pušenja i incidencije melanoma, osobito kod muškaraca, naglašavajući potrebu za daljnjim istraživanjem. S obzirom na štetne posljedice pušenja na prognozu melanoma, preporučuje se rutinska procjena pušačkog statusa, uključujući prijašnje pušačke navike, tijekom početne procjene kao i tijekom praćenja tih pacijenata te pružanje podrške za prestanak pušenja. Bitno je prepoznati pušenje kao jedan od ključnih promjenjivih čimbenika rizika za melanom kože. Poticanje pacijenata s melanomom na prestanak pušenja moglo bi biti korisno za poboljšanje ishoda kod ovih pacijenata.

Ključne riječi: *Melanom*; *Pušenje*; *Dermatologija*