Sančanin, B., & Penjišević, A. (2024). The critical role of detection in effective melanoma treatment, *MEDIS - Medical Science and Research, 3*(3), 7-12.
doi: 10.35120/medisij030307s UDK: 616.5-006.81-084

THE CRITICAL ROLE OF DETECTION IN EFFECTIVE MELANOMA TREATMENT

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Abstract: The global incidence of skin cancer is continuously rising, particularly among the white population. Uncontrolled UV radiation exposure, combined with genetic factors, leads to various health risks, including wrinkles, pigment changes, and malignancies. This paper aims to highlight the increasing trend of skin melanoma and emphasize the necessity for ongoing education and preventive measures to detect potential changes early. Early diagnosis and disease assessment are crucial for successful treatment. High mortality rates are associated with late detection of malignant melanoma, making the development of new, more efficient detection methods essential. Additionally, efforts must be made to develop minimally invasive, safe, and effective therapies with fewer side effects. Lack of timely information for the population and the absence of continuous, targeted education for health personnel are significant factors contributing to the advanced-stage recognition and diagnosis of these diseases.

Keywords: skin cancer, melanoma, UV radiation, metastases, early diagnosis.
Field: Medical Sciences and Health

1. INTRODUCTION

Melanoma arises from malignant changes in melanocytes, primarily on the skin but also on mucous membranes in regions such as the head and neck, eyes, urogenital tract, and gastrointestinal tract (Grozdić Milojević et al., 2023). The development of melanoma skin cancer is predominantly attributed to exposure to ultraviolet (UV) radiation. Preventive measures include minimizing sun and tanning device exposure, using sunscreen, and wearing protective clothing like hats. The pattern and timing of UV exposure significantly influence melanoma development; frequent sunburns, especially in childhood, correlate with melanomas on the chest, back, and legs, areas intermittently exposed to UV radiation. Conversely, melanomas on the face, neck, and hands, which receive more consistent sun exposure, exhibit different characteristics (American Cancer Society, 2023).

Regularly monitoring moles for changes in size and texture enhances early detection of suspicious developments. Lighter skin tones pose the greatest risk for melanoma, with white individuals facing a lifetime risk of approximately 3% (1 in 33), compared to 0.1% (1 in 1,000) for black individuals and 0.5% (1 in 200) for Hispanics (American Cancer Society, 2024). Additional risk factors identified by Antonijević et al. (2018) include the presence of common and atypical nevi, skin type, family history of melanoma (found in 8-12% of patients), actinic damage, age over 65, history of sunburns and sporadic sun exposure, particularly during childhood, and geographic location.

In Germany and France, the two most populous countries in the European Union, 31.4 thousand and 16.4 thousand cases of melanoma skin cancer were reported in 2022, respectively. Italy followed with 12.5 thousand cases of this cancer type (Gagliardi, 2024). In England, there were over 8 thousand newly diagnosed melanomas in men and 7.7 thousand in women in 2021 (Gagliardi, 2023). According to the American Cancer Society, it is projected that in 2024 there will be 100,640 new cases of skin melanoma out of a total of 108,270 skin cancer cases, resulting in 8,290 deaths from melanoma (American Cancer Society, 2024).

Residents of Australia and New Zealand face the highest risk of skin cancer. In 2020, Australia recorded 37 cases per 100,000 inhabitants, while New Zealand had 32 cases per 100,000. Denmark followed closely with just under 30 cases per 100,000 inhabitants. New Zealand reported the highest mortality rate at 4.7 deaths per 100,000 inhabitants, followed by Norway (3.2) and Montenegro (3.0) (Fleck, 2024). Malignant melanoma is a deadly form of skin cancer, accounting for over 20,000 deaths in Europe annually, with nearly 100,000 new cases registered each year. Recent studies emphasize that early detection is the most crucial factor for improving survival rates in this disease.

(Fleck, 2024) In routine clinical practice, visual examinations are predominantly relied upon, but

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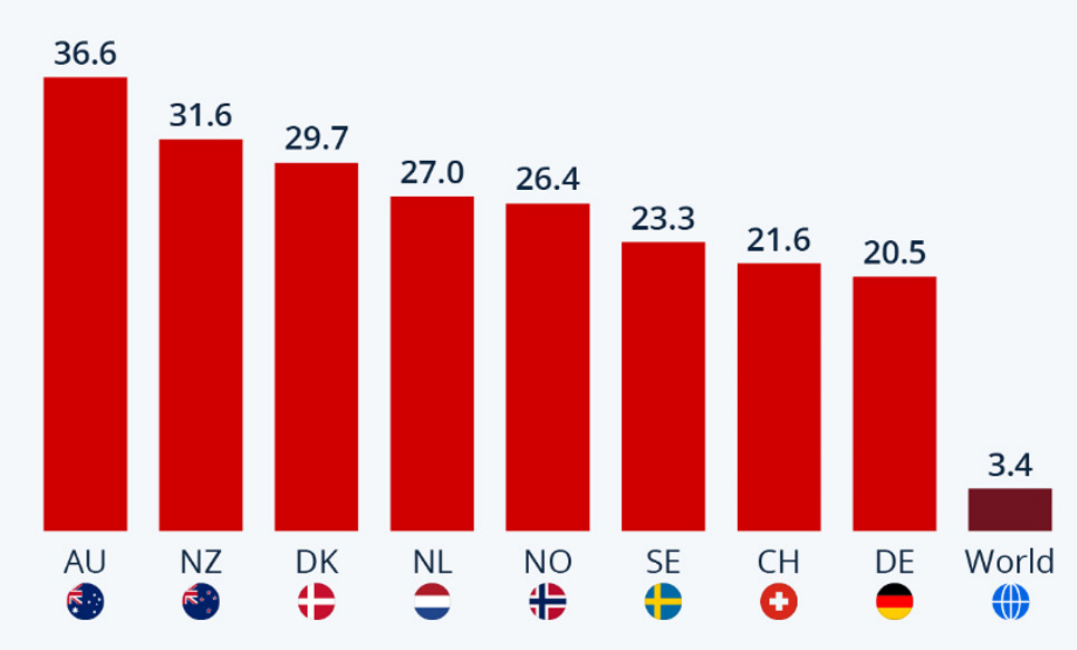
their sensitivity in recognizing melanoma via dermoscopy is often less than 80%. Therefore, Abayomi-Alli et al. (2021) advocate for the enhancement of computer-assisted methods to improve the diagnosis of skin melanoma, potentially leading to higher survival rates.

UV radiation is epidemiologically and molecularly linked to the three most common types of skin cancer: basal cell carcinoma, squamous cell carcinoma, and malignant melanoma. Genetic factors also significantly influence the risk of UV radiation-induced skin diseases, with particular emphasis on polymorphisms of the melanocortin 1 receptor (MC1R) gene. These variants are associated with fair skin, increased UV sensitivity, and elevated cancer risk (D'Orazio et al., 2013).

Figure 1. Countries with the highest rates of skin cancer in 2020 (per 100.000 population)



Source: Fleck, 2024

2. LEADING RISK FACTORS

Approximately 80% of skin aging is attributed to sun exposure. Individuals using sunscreen with SPF 15 or higher demonstrate 24% less skin aging compared to those who do not use sunscreen. Sun damage accumulates over time: Table 1 illustrates the average cumulative sun exposure over a lifetime of 78 years.

Table 1. Average lifetime sun exposure

Age¤	Accumulated·sun·exposure¤	¤
1-18¤	23%¤	¤
19-40¤	47%¤	¤
41-59¤	74%¤	¤
60-78¤	100%¤	¤

Source: Skin Cancer Foundation, 2024.

The depletion of the ozone layer has led to an increase in skin cancer cases. According to estimates from the World Health Organization, every 10% reduction in the ozone layer results in three million additional cases of non-melanoma skin cancer and 4,500 cases of melanoma skin cancer. The ozone layer acts as a barrier in the stratosphere, absorbing harmful ultraviolet radiation and thereby providing protection against skin cancer. These radiations can induce severe mutations and genetic alterations in skin cells, leading to uncontrolled cell growth (Vishwakarma et al., 2024).

Medenica (2008) emphasizes that skin cancer is potentially the most serious consequence of

excessive sun exposure, serving as a lasting reminder of past sun exposure behaviors. Therefore, it is crucial to adopt preventive measures from a young age to safeguard against sun exposure.

The World Health Organization has classified tanning beds as a Class 1 carcinogen. Countries like Brazil and Australia have banned the use of tanning beds since 2014. In Serbia and most European nations, tanning beds are prohibited for individuals under 18 years old, while older individuals are permitted use only with signed informed consent (Ministry of Health of the Republic of Serbia, 2019).

Table 2. Recommendations for protection against ultraviolet radiation and skin self-examination in adults

1.	Avoid unnecessary sun exposure from 10 a.m. to 5 p.m. during the summer, from June to October, including cloudy days. Be especially cautious near water, sand, and snow, as these surfaces reflect UV rays, increasing their harmful effects.
2.	It is recommended to check the UV index via media or web applications before spending time outdoors during sunny periods of the year.
3.	Wear protective clothing, a hat, and UV-blocking sunglasses.
4.	Apply sunscreen with a high protection factor (SPF 50+) that protects against both UVA and UVB rays. Use it 30 minutes before sun exposure and reapply every two hours while outdoors.
5.	Skin self-examination is necessary once a month
6.	Examination of the skin of partners and family members once a month
7.	Completely avoid using tanning beds.
8.	Visit a dermatologist annually if you have a medium or high risk of skin cancer.
9.	People advised to strictly avoid sun exposure should supplement vitamin D through diet and supplements.

Source: Ministry of Health of the Republic of Serbia, 2019.

Various risk factors contribute to the development of all types of skin cancer, although their interactions are not fully understood. Key endogenous factors include phototype, skin and eye color, the presence of melanocytic nevi (moles), dysplastic nevi, and personal or family history of skin cancer. Exogenous factors relevant to skin cancer development include the type and extent of cumulative sun exposure, history of sunburns, and adherence to protective measures. While malignant melanoma constitutes only 4% of skin cancer cases, it is responsible for 65% of all skin cancer-related deaths. (Gordon, 2013)

3. NEW MODELS IN DIAGNOSIS AND TREATMENT

The pathological diagnosis of cutaneous melanoma, recognized as one of the most metastatic cancers in humans, has traditionally relied on pathohistological characteristics and a straightforward set of immunohistochemical markers over the past few decades. However, Tímár and Ladányi (2022) note a shift in approach, with widespread dermatological melanoma screening programs now detecting premalignant lesions more frequently. This necessitates highly sensitive molecular tests to confirm malignancy.

For patients with advanced melanoma, Grozdić Milojević et al. (2023) stress the importance of utilizing multi-detector computed tomography or magnetic resonance imaging. They further highlight that numerous international studies and guidelines advocate for the utility of positron emission tomography combined with computed tomography using fluorodeoxyglucose in these cases. (18F-FDG PET/CT).

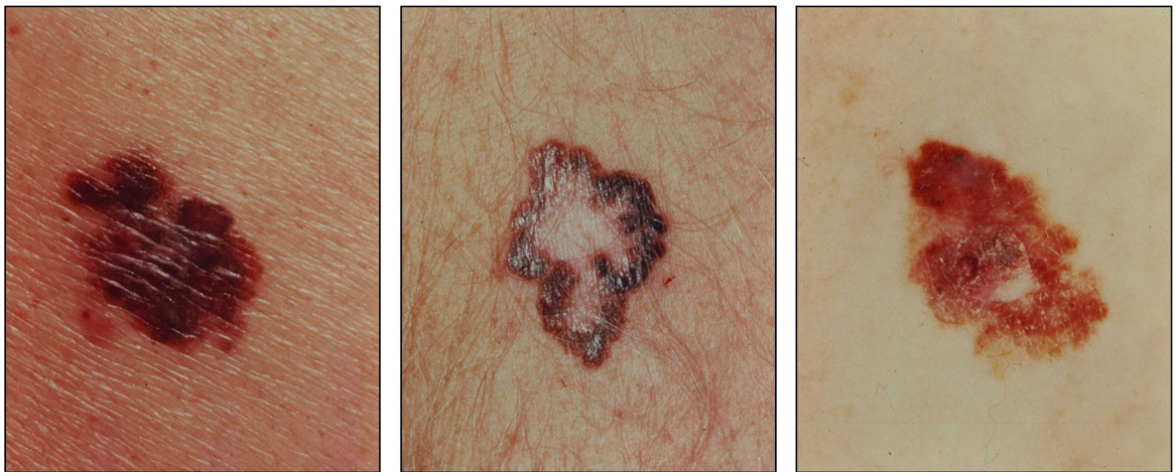
Numerous studies examining somatic mutations in melanoma at the single-gene level have provided valuable insights into critical pathways controlling the initiation and progression of the disease. Advances in next-generation sequencing have further enhanced mutational screening across multi-gene panels, exomes, and genomes. Zhang et al. (2016) argue for a reassessment of the melanoma mutational landscape to identify key genes and cellular pathways driving this cancer.

In their research on skin melanoma, Hosny et al. (2020) propose an automated classification method for color skin images. This method employs deep convolutional neural networks (DCNNs) and involves three primary steps: preprocessing of input color skin images by segmenting the region of interest (ROI), followed by image augmentation through rotation transformations and translations of the segmented image. The final step utilizes a DCNN architecture, particularly a modified GoogleNet, achieving a classification accuracy of 99.29%. The researchers highlight significant improvements in the classification process with their approach.

Melanoma primarily affects adults, with over half of cases originating in seemingly normal skin areas. While melanoma can develop anywhere, it typically occurs on the trunk or head and neck in men,

and on the extremities in women. Early signs of malignant transformation in a nevus include darker or variable discoloration, itching, size increase, development of satellites, and ulceration or bleeding (late signs).

Figure 2. Melanomas with characteristic asymmetry, border irregularity, color variation, and large diameter



Source: National Cancer Institute, 2024.

To comprehensively understand the impact of diseases on populations, it is essential to utilize metric data beyond just incidence and mortality rates. One such approach involves assessing Disability-Adjusted Life Years (DALYs), where each DALY represents one year of healthy life lost. Previous studies have employed DALYs to examine the burden of melanoma globally and within specific countries, alongside traditional metrics like incidence, mortality, and prevention efforts.

DALYs are integral to initiatives such as the Global Burden of Disease (GBD) study, which evaluates multiple diseases including melanoma. The GBD study utilizes a systems science approach to quantifying the comparative health loss due to diseases, injuries, and risk factors across different age groups, genders, and geographic regions over time. (Karimkhani et al., 2017)

Several treatment options exist for skin melanoma, including surgical excision, chemotherapy, immunotherapy, and radiotherapy. Surgical excision is widely accepted as the primary treatment for cutaneous melanoma, despite drawbacks such as tissue defects, scarring, prolonged healing, and infection risks. Chemotherapy, though commonly used, is associated with severe side effects and the development of drug resistance over prolonged use, often employed in palliative care. Immunotherapy, a newer therapeutic approach, has shown effectiveness but is limited by high costs, treatment complexity, and the long-term survival of reprogrammed cells.

Radiotherapy's clinical utility is restricted by internal and environmental resistance, typically reserved for specific indications like bone or central nervous system metastases. Phototherapy, a form of radiotherapy that converts light into heat, plays an important role by raising local temperatures to remove tumor cells. (Song et al., 2021; Grozdić Milojević et al., 2023)

Đokanović et al. (2023) conducted a retrospective observational study at the Oncology Clinic of the University Clinical Center of the Republic of Srpska, Bosnia and Herzegovina, spanning from January 2015 to December 2020. The study aimed to assess the efficacy of various treatment approaches for metastatic melanoma, given limited access to newer medications. The primary outcomes evaluated were overall survival and progression-free survival among patients receiving first- or second-line systemic therapy for radiologically or pathohistologically confirmed metastatic melanoma. The study found a statistically significant difference in survival outcomes between the first and second lines in the pembrolizumab group. Specifically, the results indicated lower median overall survival and progression-free survival rates compared to those reported in clinical trials.

In a study examining melanoma mortality trends by gender and age in the Republic of Serbia from 2000 to 2021, Babić et al. (2024) observed a rising mortality trend from skin cancer melanoma, with rates of 2.24 per 100,000 inhabitants for men and 1.34 per 100,000 for women over the period. Mortality rates increased with age in both sexes, with the highest number of deaths occurring in individuals over 80 years old.

The potential applications of artificial intelligence in melanoma recognition, diagnosis, and treatment

are still under-researched but hold significant promise. AI offers advantages such as unbiased decision-making, devoid of fatigue and subjectivity, with vast capabilities for data comparison, memory retention, and reasoning. However, the reliability of AI-driven conclusions depends heavily on the quality and validity of the input data used to develop relevant algorithms. (Kostić et al., 2019)

4. CONCLUSION

Melanoma is becoming an increasing public health issue due to rising incidence and mortality rates, as well as the inadequate response from public health policymakers to these challenges. Particularly concerning is the fact that a small number of melanomas are detected in their early stages, when the disease is most treatable. The paper highlights global regions with the highest incidence and mortality rates of melanoma, indicating significant regional differences in disease burden. Melanoma is among the top 10 most common malignancies in most European countries.

Despite notable progress in prevention, diagnosis, and treatment, broader and more intensive preventive dermatological screening activities are recommended. Focused efforts in public education and raising awareness about the importance of reducing UV exposure, early detection and diagnosis, as well as genetic testing, can contribute to lowering incidence and mortality rates. The use of artificial intelligence in melanoma diagnosis will certainly play a role in the near future, helping to minimize potential errors in measuring clinical parameters.

The focus of researchers and practitioners must be on developing new therapeutic approaches where synergistic effects meet expectations for low doses and minimal side effects.

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