UDC 681.784.8+616.5-006.6/.81+614.2
DOI: 10.56871/MHCO.2024.44.67.011

MALIGNANT SKIN TUMORS SCREENING

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For citation: Gusarov MV, Barinova AN, Tayts BM, Zaslavsky DV. Malignant skin tumors screening. Medicine and Health Care Organization. 2024;9(2):125–134. DOI: https://doi.org/10.56871/MHCO.2024.44.67.011

Received: 30.04.2024 ***Revised: 27.05.2024*** ***Accepted: 15.07.2024***

ABSTRACT. Screening in medicine represents a major strategy for the early detection of certain diseases and risk factors, thereby facilitating timely intervention and potentially reduce the severity or mortality associated with these conditions. Numerous countries have established screening programs, aiming to provide health screenings and examinations availability for specific groups of the population. The efficacy of these screening initiatives depends on adherence to several key principles, including social significance of a particular disease, the potential treatment, the accessibility of diagnostic and therapeutic services, and the presence of reliable symptoms of a certain disease and diagnostic methods. The primary objective of screening is to diminish morbidity and mortality or to lessen the severity of a disease. Nonetheless, screening necessitates substantial investment and may present false-positive and false-negative results. Cutaneous melanoma, a malignant neoplasm originating from melanocytes (pigment-producing cells) of the skin, has demonstrated a fixed rise in morbidity and mortality rates in recent years. Skin cancer screening has been implemented in various countries being more or less successive. For instance, the SCREEN project conducted in Germany between 2003 and 2004 involved the screening of 360,288 individuals for malignant skin tumors. This initiative led to a notable reduction in melanoma mortality rates five years post-project. However, the introduction of nationwide screening in 2008 did not result in a decrease in melanoma mortality. Conversely, studies conducted at the Livermore Laboratory and in Australia resulted in various findings. The effectiveness of skin cancer screening and its association with melanoma morbidity and mortality continue to be subjects of academic debate. Nevertheless, identification and early treatment of patients with advanced melanoma, as well as targeting of those case that are most likely to progress, are crucial objectives of public healthcare. These efforts aim to reduce the incidence of advanced melanoma cases, thereby contributing to the broader goal of improving patients condition and the overall effectiveness of screening programs.

KEYWORDS: skin cancer screening, melanoma prevention, public health, skin cancer, melanoma diagnosis day, Euromelanoma

СКРИНИНГ ЗЛОКАЧЕСТВЕННЫХ НОВООБРАЗОВАНИЙ КОЖИ

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Для цитирования: Гусаров М.В., Баринова А.Н., Тайц Б.М., Заславский Д.В. Скрининг злокачественных новообразований кожи // Медицина и организация здравоохранения. 2024. Т. 9. № 2. С. 125–134. DOI: https://doi.org/10.56871/MHCO.2024.44.67.011

Поступила: 30.04.2024 ***Одобрена: 27.05.2024*** ***Принята к печати: 15.07.2024***

РЕЗЮМЕ. Скрининг в медицине направлен на раннее выявление заболеваний и факторов риска их развития, что позволяет проводить лечение на начальных стадиях заболевания и снижать смертность. Во многих странах существуют программы скрининга, обеспечивающие доступ к медицинским осмотрам и обследованиям для определенных групп населения. Эффективность скрининга зависит от соответствия определенным принципам, включая социальную значимость заболевания, возможность лечения такого заболевания, доступность диагностики и лечения, существование характерных признаков болезни и методов ее выявления. Целью скрининга является снижение смертности и уменьшение тяжести течения болезни. Однако скрининг требует значительных инвестиций и может приводить к ложноположительным и ложноотрицательным результатам. Меланома кожи — злокачественная опухоль нейроэктодермального происхождения, исходящая из меланоцитов (пигментных клеток) кожи, с растущими на протяжении последних лет заболеваемостью и смертностью. Скрининг рака кожи осуществлялся в разных странах с разной эффективностью. В 2003–2004 гг. в Германии проводился проект SCREEN по диагностике злокачественных новообразований кожи. В скрининге приняло участие 360 288 человек. Снижение смертности от меланомы наблюдалось через 5 лет после проекта. Однако, после введения общенационального скрининга в 2008 г., смертность от меланомы не снизилась. В других исследованиях, таких как в Ливерморской лаборатории и в Австралии, скрининг привел к различным результатам. В целом эффективность скрининга рака кожи и его влияние на заболеваемость и смертность от меланомы остаются предметом дискуссий. Тем не менее сокращение числа пациентов с поздней стадией меланомы, выявление пациентов с наибольшей вероятностью прогрессирования и лечение этих пациентов на самой ранней стадии являются важными задачами общественного здравоохранения.

КЛЮЧЕВЫЕ СЛОВА: скрининг рака кожи, профилактика меланомы, общественное здравоохранение, рак кожи, день диагностики меланомы, Евромеланома

Medical screening is a strategy used to search for diseases or risk markers that have not been recognized yet. In addition, screening interventions are designed to identify conditions that are likely to develop into disease in future, thereby allowing earlier treatment and hopefully reducing mortality and suffering from the disease. In many countries, screening programs are part of public health care [1].

Thus, according to Order No. 404n, issued by the Ministry of Health of Russia on April 27, 2021, "On Approval of the Procedure for Preventive Medical Examination and Regular Medical Screening of Certain Groups of the Adult Population" [2], there is a system of medical screening in Russia. [2]. According to this system, every person aged 18 and over has the right to undergo a medical check-up by specialist and a number of medical examinations to detect chronic non-communicable diseases and risk factors for their development, such as diseases of the circulatory system, cancer, respiratory diseases, and diabetes mellitus.

The UK has an NHS Health Check program that suggests adults aged 40 to 74 years to have a health check every five years to reduce the likelihood of acute coronary syndrome, stroke or developing some forms of dementia [3].

Certain principles must be followed for screening to be effective. Such principles were formulated by James Wilson and Gunnar Jungner.

1. The disease should be an important medical problem.
2. There must be a treatment for the disease.
3. Diagnosis and treatment for the disease should be available.
4. The latent or early symptomatic phase should have characteristic features.
5. There should be a method to detect the disease.
6. The test must be acceptable to the population.
7. An adequate understanding of the natural course of the disease is required, including its progression from latent to overt manifestation of disease.
8. There should be a harmonized policy in the need for treatment.
9. The economic costs of case detection should be balanced against the total costs of the disease.
10. The process of case detection should be continuous [1].

Screening programs exist for a range of conditions. The purpose of each program should be clearly stated and understood. This is necessary to form the structure of the program and to conduct an evaluation of its effectiveness.

The goals of a screening program may include:

- reducing mortality through early detection and early treatment of disease;
- reducing morbidity through detection and treatment of disease precursors;
- reducing the severity of the disease course by identifying people with the disease early and providing effective treatment;
- expanding the choice of treatment tactics by detecting pathologic conditions or risk factors in early life, when choosing the methods of its implementation is available [1].

When mass screening is carried out, a significant number of participants are subject to medical examination. This requires significant investment in equipment, personnel and information technology, which can result in a significant additional burden on the health system. Thus, when deciding to implement screening programs, it is necessary to understand the strength of the evidence base for such screening and the balance of "harms and benefits" in order to count necessary costs and positive outcomes [1].

In addition to the benefits for patients and public health, screening carries some risks, such as false-positive results. For example, some women with false-positive mammograms have increased anxiety compared with women with normal results and are therefore less likely to undergo repeat screening procedures [4].

In addition, false-negative results are also possible, leading to an unwarranted sense of security in patients, ignoring important symptoms and not receiving timely treatment, which worsens the prognosis of the disease [5].

Screening does not always prove to be sufficiently effective. For example, a Cochrane review found that health checks had little or no convincing effect on overall mortality and mortality from cardiovascular disease, including coronary heart disease and acute stroke [6].

Screening for the same disease may be differentially effective in various groups. For example, breast cancer screening every two years is recommended for women aged 50–69 years, once a year for younger women, and longer screening intervals are recommended for women aged 70–74 years [7].

In the Schleswig-Holstein region of northern Germany implemented a SCREEN project for the diagnosis of skin malignancies from 2003 to 2004. Screening took place in two stages; in the first stage, skin examinations were performed by physicians with no specialized training in dermatology. If risk factors or suspicious neoplasms were identified, patients were referred to a dermatologist. Some patients were immediately referred to a dermatologist for evaluation. If a suspicious neoplasm was identified, a biopsy was performed by the dermatologist to confirm the diagnosis and, if necessary, treatment was prescribed. A total of 360,288 people participated in the screening, 15,983 excisional biopsies were performed and 3103 malignant tumors were detected in 2911 people, of which 585 melanomas (1.6 per 1000 screened), 1961 basaliomas (5.4/1000), 392 squamous cell carcinomas (1.1/1000) and 165 other malignant tumors (0.5/1000) were found. An average of about 5 excisions was performed to detect one malignant tumor.

Among 1.88 million eligible citizens, 360,288 participated in the SCREEN program. The overall population participation rate was

19%. Five years after SCREEN, there was a significant decrease in melanoma mortality (men: 0.79/100,000, expected rate of 2.00/100,000; women: 0.66/100,000, expected rate of 1.30/100,000) [8].

A more recent study compared SCREEN screening results with morbidity and mortality rates in the population of the Saarland region, where no screening was performed. Over a 5.5-year period, 1472 SCREEN participants were diagnosed with melanoma and 31 of them died during this period. A comparison showed that in the Saarland region with a population of about one million inhabitants, 1,026 people were diagnosed with melanoma and 111 of them died from it, indicating a lower mortality rate in the SCREEN cohort [9].

At the same time, other authors note that the observed decrease in mortality in Schleswig-Holstein 5 years after the pilot study was accompanied by an increase in the number of deaths from malignant neoplasms of non-specified localizations and secondary malignant neoplasms of non-specified localizations (ICD-10 code C76-C80). Therefore, from their point of view, incorrect assignment of causes of death caused by melanoma as ICD-10 code C76-C80 between 2007 and 2010 may have influenced the temporary decrease in skin melanoma mortality rates observed in Schleswig-Holstein [10].

A pilot project in the Schleswig-Holstein region resulted in nationwide screening organized in Germany in 2008. Every person over the age of 35 was offered a whole-body screening once every two years. By 2013, there was no downward trend in melanoma mortality in Germany since the nationwide screening had been introduced. As for the pilot study area in the Schleswig-Holstein region, melanoma mortality rates returned to pre-screening rates and were equal to average German rates. The authors attribute the lack of the desired result to lower quality of screenings, lower population coverage, and difficulties in data collection in comparison with the pilot study [11].

A training and screening program at the E. Lawrence Livermore National Laboratory took place from 1984 to 1996. Employees were informed about sun protection, signs and risk factors for melanoma. This information was disseminated through direct mailings, news articles at workplaces, meetings and lectures to employees and local physicians, and local media outlets also ran articles about the program. Employees were asked to examine themselves for suspicious lesions. If the self-examination revealed a suspicious neoplasm, a visit to the screening facility for a full body examination, dermatoscopy, and biopsy, was suggested. Alternatively, laboratory workers could be seen by their personal physicians. In this case, employees were asked to report the results to the laboratory medical staff. All employees were also given a form to report the number of their moles at the beginning of the program, and laboratories were subsequently given the same form. Program participants who counted 5 or more moles that were 5 mm or more in diameter or one mole that was 18 mm or more in diameter were offered a screening examination.

After dermatologic screening, employees with melanoma (invasive or *in situ*), dysplastic nevi, 50 or more moles, or a family history of melanoma were offered periodic whole-body screening every 3 to 24 months, often with whole-body photography and dermatoscopy, according to melanoma risk level.

The overall incidence of melanomas thicker than 0.75 mm decreased from 22.1 to 4.62 cases per 100,000 person-years. The overall incidence of melanoma less than 0.75 mm increased and then decreased slightly without a significant linear trend, and the overall incidence of melanoma *in situ* increased significantly. There were no melanoma deaths among employees during the screening period, whereas the expected number of deaths was calculated to be 3.39 deaths. The statistically significant reduction in mortality was maintained for at least 3 years after employees retired or otherwise left the laboratory [12].

Another study reported that intensive public awareness in Central Texas did not reduce the incidence of melanoma or detect the tumor at an earlier stage [13].

A population-based case-control study was conducted among Queenslanders in Australia. Patients aged 20–75 years with histologically confirmed primary invasive melanoma of the skin diagnosed between January 2000 and December 2003 were interviewed. The results of the survey showed that a whole-body clinical skin examination which had been performed three years before the diagnosis provided a 14% reduction in the risk of melanoma thicker

than 0.75 mm (by Breslau), 7% — for 0.76–1.49 mm, 17% — for 1.50–2.99 mm, and a 40% reduction for melanomas ≥3 mm. The possibility of diagnosing melanoma with a thickness ≤0.75 mm by Breslau increased up to 38% [14].

A number of authors have noted that at present there is not enough information to make a decision on population-based screening of the Australian population. Integration of risk-based population stratification and more accurate diagnostic tests is likely to improve the benefit-harm balance of opportunistic screening [15].

An evaluation of a general practitioner training campaign was carried out in the Champagne-Ardenne geographical region of France, which has a population of 1.34 million. In 2008, all GPs were mailed repeatedly and 398 (32.1%) attended training sessions organized by dermatologists. The effectiveness of the campaign was evaluated in comparison with the Du/Belfort area, where a similar campaign was not conducted. As a result, the incidence of melanomas >3 mm by Breslau decreased from 1.07 to 0.71 per 100,000 inhabitants per year, the mean thickness of diagnosed melanomas decreased from 1.95 to 1.68 mm by Breslau, and the proportion of melanomas >3 mm by Breslau decreased from 19.2% to 12.8%. The proportion of melanomas <0.75 mm thick by Breslau and *in situ* melanomas increased from 50.9% to 57.4% and from 20.1% to 28.2%, respectively. No significant changes were observed in the Du/Belfor area. These results confirm the effectiveness of the campaign aimed at raising awareness among general practitioners [16].

A systematic review on skin cancer screening and secondary prevention campaigns conducted a search for studies published in English or German between January 1, 2005 and February 4, 2015. Fifteen articles were included in the study. Overall, the data showed that the incidence of in situ and invasive skin cancer increased with the introduction of skin cancer screening. There was an increase in thin melanoma rates and a decrease in thick melanoma rates. After screening was discontinued, the incidence of invasive melanoma decreased. A German study showed a significant reduction in melanoma mortality; 2 other studies showed fewer deaths than expected. However, the authors note the low level of evidence of the studies [17].

The US Preventive Services Task Force (USPSTF) believes that the available evidence is insufficient to assess the balance of "benefits and harms" of visual inspection of the skin by a physician for skin cancer screening in adults [18].

A Cochrane review on screening aimed to reduce melanoma morbidity and mortality evaluated two studies with a total of 64,391 subjects. The data analysis concluded that screening to reduce melanoma morbidity and mortality did not meet the criteria for making it population-based. However, this review did not examine the effects of screening people with a history of melanoma or people with a genetic predisposition to melanoma [19].

The Cancer Council Australia recommends complete skin screening with dermatoscopy and whole-body photography for patients at very high risk of melanoma to detect new cases of melanoma at an earlier stage, and Australian evidence suggests that such screening is cost-effective [20].

Euromelanoma is a pan-European skin cancer prevention campaign that aims to provide the public with information on the prevention, early diagnosis and treatment of skin cancer. The campaign is mainly dedicated to promote primary and secondary prevention of skin cancer and in particular melanoma in Europe. The ultimate goal is to reduce melanoma morbidity and mortality. Euromelanoma has been conducted by European dermatologists since 1999 and is a free for population. The campaign is promoted through public service announcements and media advertising, as well as educational events on the risk factors for the disease, the warning signs of skin cancer, the dangers of excessive sun exposure and optimal photoprotection methods.

The campaign uses a variety of public relations tools to raise awareness and information about skin cancer, ranging from brochures and posters to media advertisements, and utilizes the online platform http://www.euromelanoma.org with information in different languages [21].

The results of the Euromelanoma campaign were evaluated in Belgium. Researchers did not observe an increase in melanoma incidence after the start of the campaign. However, they

note that primary prevention, focusing on etiologic factors, and informing the population about risk factors are important, but the result should not be expected in the coming years, which is due to the long period between exposure to a risk factor and the development of the disease [22].

Another Belgium research evaluated the effects of an information and screening campaign. The campaign "Be prudent in the sun", aimed at taking appropriate precautions to prevent melanomas. It included the production and distribution of informational material on sun protection and lectures in various municipalities targeting the general population. Similarly to other European countries, the city of Limburg (Belgium) has hosted "Melanoma Monday" since 1999, which is organized every year in the first half of May. The annual number of participating patients is between 4000 and 5000. In ten years, the cancer registry has recorded 735 melanomas, 271 in men and 464 in women, representing 6.8/100,000 patient-years in men and 11.6/100,000 patient-years in women. The authors note that the study was not intended to and could not measure the effect of a sun protection awareness campaign, as this can only be evaluated on a long-term basis. This study found a small effect of the campaign on melanoma incidence in men (there was no effect in women), and there was no effect of the campaign on the distribution of tumor stages. This impact was aimed at the general population. The authors suggested that the effectiveness of skin cancer screening may be higher if it targets only those at high risk of melanoma [23].

The 2013 skin cancer screening program was evaluated in Switzerland. It was concluded that the overall melanoma detection rate was comparable to similar interventions in Europe. The authors believe that the cost of free screening programs compares favorably with the avoided potential therapeutic costs of advanced melanoma [24].

Another study analyzed the results of Euromelanoma 2016 in Switzerland. The participating physicians examined 2795 individuals. A total of 2215 (79.3%) of the examined individuals did not require further treatment. Suspicious neoplasms were found in 580 (20.7%) patients. Among them, 243 (41.9%) patients did not agree to a follow-up survey for quality assessment after 3–6 months and were not included in the study. 337 were willing to participate in the study, 140 (41.5%) of them were unavailable either due to incorrect contact details or non-response. 197 people remained, 40 (20.3%) of the remaining patients stated that they did not fulfill their physician's recommendation to see a dermatologist. The remaining 157 (79.7%) participants had a follow-up examination with a dermatologist. It was reported that a total of 81 out of 157 cases of suspicious neoplasms were biopsied. Among these 157 cases, 6 melanomas, 21 basal cell carcinomas, 2 squamous cell carcinomas, 44 actinic keratoses, and 3 dysplastic/atypical nevi were found. In 74 cases there were no pathologic changes characteristic of malignancy (41 of 74 biopsies), and in 7 cases the diagnosis was not reported. The frequency of detection of melanoma was 1:466 and basal cell carcinoma was 1:133. The detection rate of squamous cell skin cancer was the lowest at 1:1398. The results are mostly in line with other European studies [25].

After a decade of annual campaigns (2000–2010), an attempt was made to evaluate the actual impact of Euromelanoma on skin cancer prevention and education activities in Europe. National Euromelanoma coordinators were asked to participate in a survey to assess the impact of the campaign on public attitudes and medical interventions in relation to the disease, as well as on national skin cancer prevention efforts. This survey received responses from 21 representatives from 27 countries, reporting approximately 260,000 screening examinations since the start of the campaign. The most frequently cited challenges were the difficulty in reaching high-risk groups through screening and maintaining the continued interest of dermatologists to participate in the campaign over the years. Nevertheless, respondents agreed with the success of the Euromelanoma campaign in raising public awareness of skin cancer risk and prevention, in strengthening the role of dermatologists in the detection and treatment of skin cancer, and in stimulating media involvement in education and prevention [26].

Similar studies have been conducted in Russia. A total of 3143 patients over 18 years of age from Samara, Chelyabinsk, Yekaterinburg, and Krasnodar were examined for skin neoplasms. Three patients were found to have skin melanoma, 15 had basal cell carcinoma, and 1 had Bowen's disease [27].

Another study examined the Melanoma Screening Day 2021 questionnaire database which contained 8003 participants. It evaluated the division of patient flow in skin malignancy screening based on risk groups. There were detected 157 melanomas in 140 patients, 98 basalomas in 81 patients, and 6 squamous cell carcinomas in 6 patients. Significant differences in the incidence of malignant skin neoplasms were found in the low- and medium-high-risk groups ($p < 0.05$). When comparing the low and medium-low risk groups and the medium-low and medium-high risk groups of malignant skin neoplasms, reliable differences were also found ($p=0.009$). Statistically significant higher frequency of morphologic confirmation of skin malignancies was revealed during a separate specialist appointment compared to a regular dermatologic appointment: among the identified skin malignancies during a separate appointment by a separate dermatologist, 55.11% were confirmed; among those identified during a regular dermatologic appointment, 4.35% of cases were confirmed ($p < 0.001$).

462 people, including 372 women (80.5%) and 87 men (18.8%) aged 20 to 72 years (three respondents did not indicate their gender (0.7%)) were interviewed to assess the level of professional training of doctors providing specialized dermatovenerological care to patients who need screening for malignant skin neoplasms. Among the respondents, 79 were dermatovenerologists (17.1%), 14 were oncologists (3.0%), and 184 were doctors of other specialties (39.8%). The control group of people without higher medical education (181 people (39.2%)) was selected for comparison, four respondents did not indicate their education (0.9%). The median of correct answers amounted to 16 out of 22 (72.7%). Only 4 people out of 462 (0.9%) answered all questions correctly. Dermatovenerologists and oncologists answered the questions statistically significantly better than doctors of other specialties and respondents of the control group [28].

A set of organizational measures was proposed in order to improve the screening of malignant skin neoplasms: continuity of medical screening; division of patients into risk groups; introduction of a separate specialist for the screening of malignant skin neoplasms in the staff of a skin and venereological dispensary; increasing the knowledge of screening of malignant skin neoplasms among doctors of other specialties in outpatient health care [29, 30].

A review of scientific publications allows us to identify generally recognized approaches to screening for early detection of malignant skin neoplasms and to conduct educational campaigns to train medical personnel and inform the population, despite the diversity of research results obtained in different countries of the world.

The need for screening in medium- and high-risk groups has an evidence base; this work should be carried out on an ongoing basis.

The use of a complete skin examination by means of dermatoscopy and, if necessary, whole-body photography for patients at high risk of melanoma to detect new cases at an earlier stage is cost-effective and efficient.

Involvement of dermatologists to examine patients with suspected skin neoplasms ensures timely qualified therapeutic and diagnostic care with the best results.

In order to raise public awareness, it is necessary: to conduct sanitary and educational work, as well as to involve mass media on skin cancer prevention; to inform the population about the need for screening in outpatient settings.

Since 2007 “Melanoma Diagnostics Day” has been annually held in Russia. Taking into account the morbidity, mortality, financial and social consequences of skin cancer, such all-Russian screening day has an important impact on the public health system, as it raises awareness of participants about risk factors, methods of skin cancer prevention, which, according to the survey conducted, is an urgent problem for doctors of various specialties.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции,

проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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