Benefits and Risks of Skin Cancer Screening

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Skin Cancer Screening: Pro

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Introduction

In 1968, Wilson and Jungner [1] developed a framework for the implementation of screening programs that has been adopted by the World Health Organization (WHO). The principles of this framework are: i) The detectable disease should be an important health problem, and ii) its natural history should be known; iii) There should be a long pre-clinical stage of the disease (latent stage), and iv) a safe, simple, and inexpensive screening test should be available that is acceptable to the population being screened; v) Additionally, there should be a treatment for earlier-stage disease that is more effective than the treatment for later-stage disease; vi) Finally, facilities for diagnosis and treatment should be available [1].

Since 1971, Germany has a nationwide program for the early detection of cancer, including skin cancer. However, when the program was first implemented, no screening test for skin cancer was conducted; only growth, discoloration, and hemorrhage of malignant melanomas (MM) were documented by urologists and gynecologists. This procedure detected only 200–300 MM per year. In the late 1980s, the executive body of the German healthcare system, the Federal Joint Committee (Gemeinsamer Bundesausschuss), and in particular its Department of Prevention (Unterausschuss Prävention), decided to improve the Na-

tional Program for Early Detection of Cancer by promoting primary preventive activities as well as secondary preventive activities. In this context, the scientific validation of early detection of skin cancer was prepared, and several pilot projects were initiated in subsequent years. The largest of these projects was the SCREEN project (Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany), a systematic population-based intervention which was conducted in the federal state of Schleswig-Holstein between July 2003 and June 2004 [2]. Finally, in 2008, the Federal Joint Committee decided, based on the principles of screening, to implement a nationwide skin cancer screening program in Germany. This article is aimed at describing the development of the unique German Skin Cancer Screening Program including its preceding pilot projects. Further, the impact of skin cancer screening activities on population-based outcomes is discussed.

Background

The burden of skin cancer has increased worldwide over the last decades among light-skinned populations [3–7]. In 2008, the global, age-standardized mortality rate for MM was estimated to be 2.8 per 100,000 inhabitants [8]. In the United States, the lifetime incidence for MM is about 1 in 74 [9]. In Germany, latest reports suggest that skin cancer, including MM and non-melanoma skin cancer (NMSC), has the highest cancer incidence. Thus, skin cancer is the most common cancer in Germany (table 1).

The personal burden of skin cancer can be substantial. While NMSC can lead to considerable morbidity and disfig-

Table 1. Incidence and mortality of skin cancer in Germany 2011 [17]

	Incidence ^a	Mortality ^a
MM		
Women	17.1	1.6
Men	18.2	2.9
NMSC		
Women	81.5	0.3
Men	109.1	0.6

^aAge-standardised rate (European standard) per 100,000 inhabitants.
MM = Malignant melanoma;
NMSC = non-melanoma skin cancer.

urement [10], the prognosis of MM is highly dependent on stage at diagnosis. If detected at an early stage, 5-year survival rates are over 90%. In contrast, if MM is diagnosed at stage IV, only about 15–20% of patients are still alive 5 years after receiving their diagnosis [11]. In addition to the personal impact, the economic burden of skin cancer is considerable. In Germany, for example, annual hospitalization costs for 2003 amounted to 50–60 million Euros for the treatment of MM and 105–130 million Euros for the treatment of NMSC [4]. The total costs caused by skin cancer, which cover more than the costs for inpatient treatment, are hardly assessable; however, in Sweden, for example, annual direct and indirect costs are estimated to be EUR 142.4 million (EUR 15/inhabitant) [12]. In 2000, the loss of disease-adjusted life years worldwide was estimated to be 345,100–621,200 for MM and 88,100–134,800 for squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) [13].

The natural history of skin cancer is known. NMSCs are usually slow-growing tumors with a long preclinical phase. NMSCs therefore predominantly appear in older people. Over 80% of cases occur in people above 60 years [14, 15]. For SCC, actinic keratosis represents the precancerous lesion. Compared with NMSC, MM is a fast growing cancer that often spreads (20–25%) but is also detectable at an early stage.

There is mounting evidence that both MM and NMSC are induced by ultraviolet (UV) radiation. This is supported by the International Agency for Research on Cancer (IARC) that recently defined UV radiation as a carcinogen [16]. The increase in skin cancer incidence may therefore be attributed to an increase in life exposure to UV radiation. While higher life expectancy is one of the reasons for the high incidence of skin cancer in older people, with particularly high incidence rates of MM in men 65 years and above [17], changes in behavior are further reasons for the increase in life exposure to UV radiation and possibly the increase in skin cancer incidence. Examples of such changes in behavior include more time spent outdoors without being sufficiently protected by clothes and/or sunscreen, increased use of solaria, and more frequent travelling to regions closer to the equator [18–20].

To reduce both the burden of skin cancer and the exposure to UV radiation, primary and secondary preventive activities

Fig. 1. The 2-step skin cancer screening process used in the SCREEN project. Residents of Schleswig-Holstein aged 20 + and covered by statutory health insurance were eligible to participate. The first step included an initial visual whole-body examination performed by a non-dermatologist. If a non-dermatologist stated a presumptive clinical diagnosis or if risk factors were prevalent, the patient was referred to a dermatologist for a second whole-body examination (second step). If the dermatologist confirmed the suspicious lesion, a skin biopsy was taken for histopathological confirmation by a dermatopathologist. Diagnosed malignant skin tumors were notified to the state cancer registry. The patient was then given therapy and follow-up care. Alternatively, patients had the possibility to visit a dermatologist for the initial screening examination [2]. This 2-step design was adopted for the nationwide skin cancer screening program launched in July 2008.

are important. Primary preventive activities are predominantly aimed at changing people's behavior [21]. Secondary preventive activities are mainly aimed at early detection of skin cancer [2].

Steps Towards a Standardized and Systematic Skin Cancer Screening Program

In response to the increasing incidence rates of MM and NMSC, the Federal Joint Committee, the highest decision-making body that determines the benefit package of statutory health insurance, commissioned the Association of Dermatological Prevention (ADP) to examine the scientific basis for a systematic skin cancer screening program within the existing setting of primary care in Germany. Starting in 1991, the ADP, supported by German Cancer Aid, carried out studies in order to establish a skin cancer screening program. Until 1998, the 2-step screening process (fig. 1) and the training of healthcare professionals were developed and tested. Additionally, the performance of the screening test and the documentation of the screening examination were standardized. 83 physicians in the federal states of Lower Saxony and Hamburg participated in these studies [22].

Fig. 2. Adjusted malignant melanoma mortality (3-year floating mean, age-standardized rate (World standard)) for screened (Schleswig-Holstein) and non-screened (Germany without Schleswig-Holstein) areas between 1980 and 2008. Grey box = period of SCREEN project, July 2003 to June 2004 (modified according to [2]).

200 physicians in the federal state of Schleswig-Holstein were recruited to participate in the first field study. They completed a newly developed, 8-hour training course. These trained physicians carried out 6,000 screening examinations from 2000 to 2001. The results of the field study were discussed with the Federal Joint Committee and led to the decision to conduct a population-based screening study. A randomized controlled trial (RCT) would have provided the strongest evidence for the feasibility and effectiveness of a population-based skin cancer screening; however, an RCT was not considered necessary by the Committee, since skin cancer had already been part of the statutory early detection program since 1971.

After the training course had been revised and adapted, the SCREEN project was conducted in Schleswig-Holstein with 360,288 screenees from July 2003 to June 2004. Almost 2,000 physicians took part in the screening. To date, this project is the largest skin cancer screening study, and the outcomes and evidence provided by the SCREEN project (level of evidence 1c (SIGN)), assigned by independent review) were sufficient to convince the Federal Joint Committee to implement a nationwide systematic screening program for MM, BCC, and SCC [23]. The national statutory skin cancer screening program was launched in July 2008.

The SCREEN Project

The aim of the SCREEN project was to assess the feasibility of a population-based skin cancer screening program. The screening was organized as a 2-step process (fig. 1). During a 12-month period, residents of Schleswig-Holstein, aged 20+

years and covered by statutory health insurance, were invited to participate in the study. 1.88 million residents met the eligibility criteria, and 360,288 participants were screened with a visual whole-body examination. This corresponds to a population-based participation rate of 19%. All participating physicians received an 8-hour standardized training. A 98% participation rate among dermatologists (116 of 118) and 64% among non-dermatologists (1,673 of 2,614) was achieved. The group of non-dermatologists included general practitioners (GPs) as well as gynecologists, urologists, and surgeons [2].

Evaluation of the SCREEN project revealed that 620 persons had to be screened to find one histopathologically confirmed MM (1.6 MM per 1,000 persons [24]). This number is in line with numbers from screening programs of the Australian and American Academy of Dermatologists [25, 26], but it is lower than findings from European screening programs, such as the Euromelanoma Week, which target high-risk groups [27, 28] in contrast to the mass screening in the SCREEN project. During SCREEN, a total of 15,983 excisions were performed, and the number needed to excise (NNE) to detect one histopathologically confirmed MM in men and women was 28. The NNE was found to be lower (20:1) in men aged 65 years and older [24]. Schmitt et al. [29] showed in their study an excision rate per newly diagnosed MM of 179:1, which indicates a poorer diagnostic accuracy. Physicians in the SCREEN project received additional training in the early detection of skin tumors, which was not the case in the study by Schmitt et al. [29]. This may have resulted in lower NNEs, and it underlines the importance of special training and advanced education for physicians taking part in skin cancer screening.

At the beginning of an effective population-based cancer screening intervention, the total incidence of the target disease should initially increase because prevalent but previously undiagnosed cases are detected [30]. The incidence should decline when screening activities end. Incidence effects of the SCREEN project were analyzed and compared to Saarland, a federal state of Germany where no population-based screening took place. The incidence of MM increased during the SCREEN period and decreased when screening activities stopped in Schleswig-Holstein, while no such changes in incidence were seen in Saarland [31]. A rise in incidence during the SCREEN period has also been observed for BCC and SCC in Schleswig-Holstein, but not in Saarland [32].

Changes in stage-specific incidence were also analyzed. An increase in the incidence of prognostically favorable MM (in situ and T1) took place after implementation of the SCREEN project, whereas at the same time the incidence of advanced MM (T2, T3, only for women T4) substantially declined [2, 33]. This shift towards early tumor stages is consistent with observations from effective breast and cervical cancer screening [34, 35], and indicates that the SCREEN project may be an effective screening initiative to reduce MM mortality. In fact, a reduction in MM mortality by approximately 50% could be

Fig. 3. Incidence of malignant melanoma in Germany (2003–2011, age-standardized rate (European standard)) (modified according to [17]).

Fig. 4. Incidence of non-malignant melanoma skin cancer in Germany (2003–2011, age-standardized rate (European standard)) (modified according to [17]).

observed in Schleswig-Holstein by 2008/2009, while in all adjacent non-screened regions and in the rest of Germany MM mortality remained stable (fig. 2). Before the SCREEN project started, Schleswig-Holstein had one of the highest MM mortality rates in Germany, and 5 years after the completion of SCREEN it showed one of the lowest mortality rates [22]. Even if this result is only based on observational data and thus the level of evidence is rather low, the population-based skin cancer screening was, besides chance, the only reasonable cause for the mortality reduction.

The Nationwide Skin Cancer Screening Program

Based on the results of the SCREEN project and the facts that visual whole-body examination represents a safe, non-invasive, and well accepted screening test and that the risks of skin cancer screening did not outweigh the advantages, the Federal Joint Committee decided to introduce a nationwide skin cancer screening program in July 2008 – very similar to the 2-step procedure tested in SCREEN (fig. 1) [23]. Citizens of Germany who are covered by statutory health insurance have the opportunity to undergo a standardized visual whole-body examination for NMSC and MM by a GP or a dermatologist every 2 years. Screening is linked to a general health check for individuals aged 35 years and above. In contrast to the SCREEN project, the target population in the national skin cancer screening program comprises residents aged 35 and above, the group of non-dermatologists consists of GPs only, and risk factors of individuals screened are not identified and documented [36].

To ensure a high quality of the screening program, it is mandatory for participating physicians to complete an 8-hour standardized training course. To date, 93% of all dermatologists and 77% of GPs have been educated. The curriculum of the training includes the application of the standardized visual

examination of the whole body, communication skills, and topics such as clinical pictures and risk factors of skin cancer [37]. To evaluate the program, participants are asked to complete a questionnaire before and after the training course. The questionnaire measures knowledge on early detection (of cancer), knowledge on skin cancer (screening), and diagnostic accuracy in the assessment of different skin lesions. The analysis of completed questionnaires available until December 2009 shows an increase in knowledge and diagnostic accuracy, with GPs particularly benefiting from the training [38].

Currently, approximately 44.4 million residents in Germany are aged 35+ and are covered by statutory health insurance. Extrapolations made by us show that from 2009 to 2012 approximately 26.5 million residents with statutory health insurance have participated in the screening program. The ‘2-year participation rate’ from January 2009 to December 2010 was 30.8%. Moreover, the participation rates of men and women in Schleswig-Holstein were almost equal (unpublished data), unlike during the SCREEN project where the male to female ratio was 1:3 [2]. These numbers were generated from analyses of 3.8 million billing datasets from January 2009 to December 2012 from Schleswig-Holstein by using the specific billing codes for the skin cancer screening examination (unpublished data). Our projected participation rate is comparable to the ‘2-year participation rate’ (July 2008 to July 2010) of 30% reported by the National Association of Statutory Health Insurance Physicians [39]. However, the billing data we used were from Schleswig-Holstein only, a federal state which has experienced several screening interventions prior to the start of the nationwide skin cancer screening program. This might have influenced the participation rate in Schleswig-Holstein, and thus the extrapolated national participation rate (30.8%) might differ from the actual participation rate. Nevertheless, since the start of the program, a nationwide increase in the incidence for MM and NMSC has been observed (figs. 3 and 4) [17]. This might be a first indicator for an effective skin can-

cer screening program, and it remains to be seen whether a shift towards early-stage tumors will occur and whether this will lead to a reduction in mortality.

Conclusion

To our knowledge, the SCREEN project represents the largest dataset on skin cancer screening, and it provides strong evidence that population-based skin cancer screening with associated professional training and education may likely be effective in reducing morbidity and mortality. The nationwide skin cancer screening program has not yet been evaluated, but given that the design of the German skin cancer screening program is based on the SCREEN project and that the participation rate (30.8%) as well as the acceptance by physicians (93% dermatologists and 77% GPs) is high, similar positive screening outcomes can be expected. Therefore, the current skin cancer program should be continued. A more intensive evaluation of the program is strongly recommended, including physician training, sensitivity and specificity of the screening test, false-positive and false-negative (interval cancers) outcomes, development of stage-specific skin cancer incidence, and skin cancer mortality. The German skin cancer screening provides a worldwide unique opportunity to learn more about the effects of skin cancer screening.

Skin Cancer Screening: Contra

Jürgen Tacke (Cologne)

In July 2008, mass screening for skin cancer was introduced in Germany. 45 million citizens over the age of 35 years are entitled to a skin cancer screening examination every 2 years. The primary aim of the screening is the reduction of MM mortality. Although the incidence of MM in Australia is three times higher than in Germany, the Australian Cancer Network published an MM guideline in October 2008, which states with regard to MM screening: 'In the absence of any substantial evidence as to its effectiveness in reducing mortality population-based screening cannot be recommended' [40]. Why are the recommendations in Australia and in Germany contrasting?

Recommendations for Screening

There is no consensus on the effectiveness of skin cancer screening programs. The U.S. Preventive Services Task Force disapproved of skin cancer screening in 2009, while the American Melanoma Research Foundation recommends annual screenings by dermatologists [41, 42]. A scientific committee in Ontario recommended annual screenings by dermatologists for individuals at high risk for developing skin cancer in 2007 [43]. The renowned Memorial Sloan Kettering Cancer Center

in New York rejects population-based screening and recommends opportunistic screening instead [44]. In Germany, many statutory health insurances even offer extra skin cancer screening programs for citizens under the age of 35 in addition to statutory skin cancer screening. There are now even screening programs without any age restriction [45]. Thus, even young children can participate in the screening for skin cancer. The WHO defines a 'large-scale screening of whole population groups' as 'mass screening' [1]. Since periodic screening is recommended for over 50% of the population, the WHO definition applies to the German statutory skin cancer screening. So far, no other country has followed the German example to introduce mass screening. What are the reasons for this hesitation? The following model calculation addresses the challenges of mass screening for skin cancer.

Melanomas in a German Town

The following model describes a hypothetical German town with a population of 50,000 inhabitants. The inhabitants represent the German population. To simplify the model, an annual mass screening for MM is recommended for all inhabitants over the age of 35 years. It is assumed that all new cases of MM are included in this group. The model is based on the crude rates for incidence and mortality in Germany in 2010 [46]. Overdiagnoses are not considered in the model. Thus, about 12 new cases of MM are expected in this town. In other words, 49,988 inhabitants do not suffer from newly diagnosed MM. To find the 12 MM cases, a screening program is recommended for the 27,000 inhabitants over the age of 35 years. Without screening, 2 of the 12 MM cases will die from MM. The MM screening will only be effective if at least 1 of these 2 MM cases is found among the 27,000 screening participants. For this to happen, two requirements have to be fulfilled: The person must i) participate and ii) test truly positive in the screening examination.

Is Skin Cancer Suitable for Screening?

The statutory skin cancer screening in Germany is not an annual screening as described in the model. The committee that regulates screening programs in Germany, the Federal Joint Committee, arbitrarily chose a 2-year interval for the screening examination. Therefore, the chance to find MM is – compared to the model – even lower in reality. However, it can be argued that the model does not properly describe the German skin cancer screening, since its aim is not only to detect MM but other skin cancers as well. It is therefore prudent to take a closer look at the three major types of skin cancer.

Basal Cell Carcinoma

Every year, 210,000 new cases of skin cancer are counted in Germany [46]. The number of all other types of cancer ex-

Table 2. Epidemiologic indicators for three major skin cancers in Germany in 2010 (numbers rounded) [46]

Indicator	MM	BCC	SCC
New cases, n	19,000	152,000	37,000
Crude incidence ^a	24	185	45 ^c
Crude mortality ^a	3.3	0	0.8 ^c
Proportion of deaths ^b , %	0.3	0	0.1 ^c
Relative 5-year survival rate, %	90	104	95

^aPer 100,000 inhabitants.

^bCompared to all deaths.

^cFigures for non-melanoma skin cancer (NMSC).

MM = Malignant melanoma; BCC = basal cell carcinoma;

SCC = squamous cell carcinoma.

cluding skin cancer amounts to 460,000 new cases. The high number of skin cancer cases is misleading as skin cancer is not a unique entity. The three major types of skin cancer are BCC, SCC, and MM. These three skin cancers comprise 99% of all new cases of skin cancer. The epidemiologic indicators of these cancers are listed in table 2. The figures in table 2 are estimates, since the registration of BCC and SCC is incomplete. The indicators show two peculiarities: Although the number of new cases is high, skin cancer plays a minor role in overall mortality. Approximately 0.4% of all deaths are due to skin cancer in Germany. If only cancer mortality is considered, skin cancer is responsible for 1.2% of all cancer deaths. Some individuals will die from BCC. However, these cases are so extremely rare that they are not considered here. BCC has a most unusual feature for a cancer: A person diagnosed with BCC lives longer, statistically. The relative 5-year survival rate is surprisingly high at 104%. The biology of the tumor partially explains the survival rate: In general, BCC grow very slowly and do not metastasize. The statistical effect can be explained by the population diagnosed with BCC. It is assumed that this elderly population is healthier than the average population in this age group. Of the 210,000 new cases of skin cancer, 150,000 refer to a skin cancer whose diagnosis is associated with a statistical survival advantage. Due to the survival advantage, the importance of this disease is not obvious. There is no evidence that morbidity is significantly reduced by screening.

Squamous Cell Carcinoma

With an estimate of 37,000 new cases per year, SCC are diagnosed twice as often as MM. The prognosis is good with a relative 5-year survival rate of 95%. The exact mortality of SCC is unknown. Most national tumor statistics register skin cancer only as MM or as NMSC. NMSC are all skin cancers without MM. The crude mortality rate of NMSC is approximately 0.8 deaths per 100,000 inhabitants. One characteristic of SCC is the age of the patients. On average, they are over 75 years at onset of the disease, women even 79 years. SCC usually occurs in sun-exposed areas of the skin, i.e. the face or the

back of the hand. Therefore, this skin cancer is generally clearly visible so that the patient can consult a physician before the cancer metastasizes. However, therapy is often complicated by multimorbidity. SCC is not optimal for mass screening. In general, participation in screening examinations drops from the age of 75 years. And even if mass screening for SCC was successful, a benefit would be highly unlikely. It can be assumed that life expectancy in this age group would not change due to screening because deaths caused by other diseases will be frequent. There is no scientific evidence that screening reduces mortality or morbidity from SCC.

Melanoma

It can be summarized that BCC and SCC are not suitable for screening. Hence, early detection of MM is the main focus of skin cancer screening. With 23 new cases per 100,000 inhabitants, MM is a rare disease. However, the incidence is relatively high compared to other cancers. 70% of deaths due to MM are observed in patients over the age of 65 years. In comparison to other cancers, the prognosis is good with a relative 5-year survival rate of 90%. To illustrate the importance of a disease, the German Robert Koch Institute provides a ranking for the mortality of all major cancers. The ranking is based on the absolute number of deaths caused by a cancer. Most deaths in Germany are due to lung cancer in men and breast cancer in women. In 2010, MM was on rank 15 for men and rank 18 for women. Annually, 2,800 deaths due to MM are registered in Germany. All reasonable steps have to be taken to reduce the number of deaths from MM. Undoubtedly, it is an important disease. The success of MM screening depends on the reliability of the 'screening test'.

Visual Whole-Body Examination as a Screening Test

For MM screening, visual whole-body examination is recommended as a screening test. A visual whole-body examination is a naked-eye assessment of the skin by a physician. Intuition leads us to assume that MM are well visible on the skin and are therefore especially suitable for screening. However, this is a popular fallacy! The assumption that MM is well visible is only true in isolated cases. In general, people have many benign lesions that can resemble malignant tumors. This applies especially to older patients. The distinction between benign and malignant tumors by naked eye is often impossible. Dermatologists usually examine suspicious skin lesions by dermoscopy and do not rely on naked-eye examination. However, dermoscopy is explicitly not to be applied in the German mass screening for cost reasons. Data on the reliability of whole-body examination as a screening test are scarce. There is neither a randomized trial examining whether skin cancer can be reduced by whole-body examination nor is there a randomized trial on the question of whether this examination leads to earlier detection of skin cancers.

Table 3. Diagnostic accuracy of visual whole-body examination to detect a lesion suspicious for skin cancer in a mass screening program [23]; total of 36,893 primary and secondary examinations, suspicious lesion detected in the primary examination in 1,280 persons; sensitivity (1,280/4,408) for detection of a suspicious lesion by a non-dermatologist was 29%

Non-dermatologist	Dermatologist		Total
	Yes	No	
Yes	1,280	4,700	5,980
No	3,128	27,785	30,913
Total	4,408	32,485	36,893

There is only one single case-control study that found a statistical relationship between whole-body examination and tumor thickness of MM [47]. This study is, by definition, a retrospective study regarding the time period before MM diagnosis. It was determined by telephone interview how often cases and controls had a medical skin examination in a 3-year period prior to the date of diagnosis or a reference date. The evidence of this study is weak due to the potential biases of case-control studies.

Another study analyzed the accuracy of visual whole-body examination. A period of 2 years after whole-body examination was analyzed [48]. Individual cancer registry data revealed how frequently MM was diagnosed in later studies. The sensitivity for suspicious pigmented skin lesions was 70% regarding a period of 1 year after whole-body examination. For a period of 2 years, a sensitivity of 50% was calculated. A review of the accuracy of MM diagnosis by naked eye displayed a high variation in sensitivity from 40 to 95%, depending on the quality of the investigator and on the population examined [49]. An analysis of skin cancer mass screening was performed to investigate visual whole-body examination comparing dermatologists and non-dermatologists [23]. Data of 36,893 screening participants were evaluable for this analysis. The 36,893 participants were first examined by a non-dermatologist and subsequently by a dermatologist. It was investigated how often non-dermatologists and dermatologists suspected skin cancer. A comparison of the results is presented in table 3. The cross tabulation shows that the sensitivity of non-dermatologists to detect a suspicious skin cancer lesion was only 29%. Information on sensitivity and specificity of screening tests cannot be derived from this analysis, since histological data are missing. The cross tabulation clearly shows: Whole-body examination is unreliable as a screening test for early detection of MM in mass screenings.

Whole-Body Examination in a German Town

Another model calculation for a German town with 50,000 inhabitants will illustrate the diagnostic accuracy of visual whole-body examination. Certain assumptions are again made: Annual MM screening is attended by all 27,000 inhabitants

over 35 years of age. Since there are not enough dermatologists available, primary care physicians also participate in the screening. To simplify matters, it is assumed that dermatologists and primary care physicians detect MM with the same accuracy. The sensitivity for the detection of MM by whole-body examination will be 60% and the specificity 80%. Numbers will be rounded in favor of the screening. The results are as follows: If all 27,000 inhabitants participate in the screening, 8 of 12 MM will be detected by the screening test. To find these 8 MM, 5,406 surgical procedures have to be performed to rule out suspicious lesions. This means that 20% of the screening participants have to undergo invasive surgery. For each histologically confirmed MM, approximately 675 surgical procedures are performed. 4 MM will be missed. If there is a clinical suspicion of MM in 10,000 cases, MM is actually present in only 15 cases.

In reality, however, it can be assumed that not all of the 27,000 inhabitants over 35 years participate in the screening. Data from a major German healthcare fund indicate that about 16% of those eligible for the statutory skin cancer screening actually attended the screening examinations regularly [50]. In favor of the screening, it is assumed that these 16% comprise 50% of all MM cases in town. The following picture emerges: Now, only 4 of the 12 MM cases are found (approximately 35%). Thus, 8 MM in town (approximately 65%) are not detected or overlooked. As a reminder: We are looking for the 2 MM in town that are lethal. To be effective, the screening must detect at least 1 of these 2 MM. However, since only 35% of MM are found within the screening, the probability is not very high – even with favorable assumptions – that the screening will be effective.

With regard to the effectiveness of the screening, another challenge has to be faced: Histological examinations of suspicious moles (melanocytic tumors) are less reliable than generally assumed by the public. A considerable proportion of melanocytic tumors cannot be reliably assessed as benign or malignant by pathologists [51]. The increase in MM incidence in recent decades is partially due to the unreliability of histological examinations, with melanocytic skin tumors often rated false-positive. The National Cancer Institute states that this fact ‘undermines the effectiveness of any screening intervention’ [52].

Evidence for the Effectiveness of Melanoma Screening

There is not one single randomized trial showing a reduction in mortality due to MM screening [10, 53]. Four studies claim a benefit of MM screening [54, 55]. One randomized trial on MM screening was performed in Australia [56]. However, the study was terminated early due to a lack of funding [54]. Relevant endpoints regarding the survival of study participants have never been published. In the U.S., a company with 5,000 employees conducted an MM campaign for over 3 decades [57]. Employees were instructed to examine themselves. If they detected suspicious lesions by self-examination,

they received a medical examination by a physician on the company's premises. Whole-body examination was performed including dermoscopy. Suspicious lesions were subsequently excised. It was found that tumor thickness of MM decreased and that MM mortality was lower than expected. However, the analysis of mortality displays significant methodological weaknesses and is not considered to be valid [54]. In a retrospective study, 566 MM patients were asked whether they had examined their skin themselves and/or had received a skin examination by a physician 12 months prior to their MM diagnosis [58]. A relationship between tumor thickness and self-examination and/or physician examination was found. Mortality was not investigated. However, due to the retrospective study design, the lack of a control group, and the small number of cases, the evidence of this study is weak. In summary, it can be stated that the evidence for the effectiveness of MM screening is weak. The three studies do not provide evidence for a reduction in MM mortality due to screening. In the following, the fourth study will be analyzed in detail.

The Intervention Study in Northern Germany

From 1 July 2003 to 30 June 2004, an intervention study was conducted in Schleswig-Holstein, a federal state in Northern Germany [2]. The intervention consisted of an information campaign and a mass screening. Visual whole-body examination was chosen as the screening test. It was shown that MM mortality in Schleswig-Holstein decreased by 50% 5 years after the screening intervention [22]. There was neither a corresponding reduction in MM mortality in the neighboring federal states nor in Denmark. The U.S. National Cancer Institute (NCI) published a commentary on the intervention study in Northern Germany [52]. According to the NCI, the study has 'numerous methodological weaknesses', and the evidence for a reduction in MM mortality is 'very weak'. What are the methodological weaknesses of the study?

One major weakness is the lack of a randomized control group. It is not clear whether the intervention caused the reduction in mortality. The study initiators consider the intervention to be the cause of the reduction, but this is not certain at all. In addition to natural fluctuations, a variety of other possible reasons for the reduction in mortality must be taken into account. An example: In the U.S., the incidence rate of MM was observed in the State of Washington over time [59]. Washington is located on the Pacific coast and is a preferred place to live for retirees. MM incidence rates showed considerable fluctuations in the years 2000 to 2009. It could be demonstrated that migration from the Southwest was responsible for the variation in MM incidence. It can be concluded that immigration or emigration of a risk population can lead to changes in the incidence of MM.

The NCI considers the use of region-level data for the evaluation of MM mortality a major weakness. Why are region-

level data questionable? In the Schleswig-Holstein study, only cumulative data on the number of deaths per year were used as an outcome. The evidence for a reduction in MM mortality is very weak because a follow-up of the over 1,000 individual MM patients from 2003 to 2009 was not performed. Due to region-level data, it remains unclear whether deaths in the evaluation period (2008/2009) can be attributed to the new cases in the screening period (2003/2004). It is possible that persons who died from MM in the evaluation period were diagnosed before or after the screening period. Another possible explanation is that all deaths in the evaluation period come from the screening population. Accordingly, it is conceivable that of the non-screening population no one died from MM within the evaluation period.

A further major weakness is the inadequate evaluation of negative consequences (= harms) of the screening. Screenings can lead to a variety of harms. It is known that MM screening can lead to false-positive findings and overdiagnosis. Therefore, it would have been interesting to learn how many complications were associated with the 16,000 excisions in the study. The crude incidence of MM in the screening population was 162 per 100,000 inhabitants, while the crude incidence of the non-screening population was 24 per 100,000 inhabitants. It is highly likely that overdiagnoses were made in the screening population. Furthermore, it was not investigated whether inappropriate anxiety was created by the intervention, and what consequences this may have had. In addition, it is unclear whether the use of physician resources for screening examinations may lead to a decline in quality of care.

Finally, it is remarkable that there is no discussion about the diagnostic accuracy of whole-body examinations. The screening test is highly important because low sensitivity may even result in an increase in MM mortality. There are questions about the data validity. The data of in-situ and invasive MM are somewhat conflicting in various publications [23, 24, 60]. It is unclear who exactly was screened. Inclusion and exclusion criteria are not published in detail. MM screening certainly carries a price tag. However, to this day, a cost-benefit analysis is missing.

Conclusion

Reduction in MM mortality is the key criterion for successful skin cancer screening. The evidence for a reduction in MM mortality due to screening is 'very weak'. Risks and harms of the German skin cancer mass screening are unknown. The intervention study in Northern Germany has not increased the evidence. The benefits of MM screening remain unproven. Worldwide, no other country has followed the German example of mass screening. The statutory skin cancer screening in Germany was introduced on the basis of preliminary data from the intervention study in Northern Germany. This study can no longer serve as an argument to continue mass screening in Germany.

Skin Cancer Screening: Comment

Ulrich Keilholz (Berlin)

Prof. Breitbart and colleagues have to be congratulated on their numerous projects to develop, analyze, and promote screening for skin cancer. The advanced programs they conducted include training an increasing number of dermatologists, GPs, gynecologists, and surgeons in skin cancer screening, and inviting people older than 20 years and covered by statutory health insurance to take part in screening. Of all eligible individuals, 19% were actually screened in the SCREEN project [2] carried out in Schleswig-Holstein, 620 persons had to be screened to find one confirmed MM, and the number of suspected lesions excised to find 1 histopathologically confirmed MM was 28. The subsequent nationwide screening program revealed similar results [39].

After conducting these large programs, a few questions have remained. The most important question is, who did actually undergo screening? Was there a bias towards a higher-risk population based on the characteristics known in the population, including high-risk skin type and positive family history? If that was true, the above figures for the number of people needed to screen to find 1 case of MM would be optimistic. The second most important question is, would those individuals complying with screening also be more observant with regard to changes in moles and thus potentially more likely to detect suspicious moles themselves, which again would render the numbers reported optimistic. The questions asked by the authors themselves add to the limitations: the sensitivity of the screening test is unclear as well as the number of interval skin cancers occurring between screening examinations.

The issue is critically reviewed by Dr. Tacke, suggesting that there is currently no indication for general skin cancer screening in Germany, a view in line with the U.S. Preventive Services Task Force recommendations. In a model calculation provided in his article, he concludes that 27,000 people would have to be screened at multiple time points in order to prevent a maximum of 2 MM-related deaths, provided that all 27,000 people would actually comply with screening. In addition, because of the reported sensitivity of only 50% for visual screening [48, 49], approximately 5,400 lesions would need to be excised in order to confirm 8 MM and prevent a maximum of 2 MM-related deaths. In order to arrive at these figures in a nationwide program, a large number of dermatologists and non-dermatologist physicians would have to be educated in skin cancer screening, and also a large number of pathologists would have to be educated to reliably diagnose MM in suspicious lesions with high sensitivity and specificity. In his

article, Tacke also reviews the effect of screening on the other skin tumor types, and again does not come to the conclusion that mass screening for skin cancer should be recommended.

What can we conclude from these two viewpoints? What is the benefit-risk ratio of skin cancer screening? Is reliable skin cancer screening feasible? In the absence of randomized controlled trials, there remains room for speculation, and in the view of the reviewer there is considerable doubt concerning the usefulness of mass screening for skin cancer in Germany. The introduction of regular skin cancer screening by dermatologists and non-dermatologist physicians, including a large number of pathologists, would necessitate huge resources for adequate training, because if screening accuracy was low, the resulting larger numbers of false-positive and false-negative screening results would make all the above calculations shift to the negative side.

What are the potential harms of skin cancer screening? Because of the low specificity of visual screening, a large number of individuals would have to undergo unnecessary surgical interventions and be confronted with the associated anxiety. In addition, if the histopathological reading remains equivocal, more dense follow-up intervals and additional unnecessary interventions would be the result.

What is the way out of this dilemma if randomized studies are not available? Can we educate the population on self-examination, just like in breast cancer screening? There is no robust data on this. Can we change the benefit/risk ratio by applying screening to high-risk populations? Yes, if the incidence of MM is high in a specific identifiable population, the basis of all the above calculations would shift to the beneficial side. However, it remains uncertain how well screening of high-risk populations would work. How would we reliably reach individuals at high risk? Should we restrict screening programs to well defined high-risk individuals, or should we specifically invite high-risk individuals to take part in skin cancer screening? As all questions in this last paragraph cannot be easily answered at this point, the author of this commentary concludes that more specific research is necessary in order to rationally design effective skin cancer screening programs.

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