Melanoma Screening: The Ethics of Over- and Underdiagnosis

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ABSTRACT

Cutaneous melanoma is the fifth most diagnosed cancer in the United States and the incidence is increasing yearly. At present, population screening for melanoma is not recommended by national guidelines on account of insufficient evidence to assess the balance of benefits and harms. Indeed, there remains significant controversy over whether screening for melanoma via increasing the frequency of routine skin checks leads to tangible long-term health benefits for patients. In this paper, we highlight how skin cancer screening can impose harms such as overdiagnosis and suggest that the principle of non-maleficence should play a greater role in the formulation of screening policies. We also explore the pressing issue of the underdiagnosis of melanoma in particular populations. In so doing, this paper underscores how the ethical duties of non-maleficence and justice must be balanced in current dermatological practice.

KEYWORDS: cancer screening, public health ethics, non-maleficence, justice

INTRODUCTION

Cutaneous melanoma is the fifth most commonly diagnosed cancer in the United States and the incidence is increasing yearly. In 2021 alone, it is estimated that there will be 106,110 new melanoma cases with an associated 7,180 deaths.[1] In Rhode Island, there are approximately 230 new cases of malignant melanoma each year with an associated 30 deaths.[2] In addition, the healthcare costs associated with melanoma in Rhode Island is estimated to be $10 million annually.[2] More generally, the United States spends $3.3 billion annually on conditions related to the morbidity and mortality from melanoma.[3] Consequently, the accurate diagnosis and treatment of melanoma poses a notable health and financial burden for patients in our state.

Recent literature has underscored melanoma screening as a potentially important strategy to reduce melanoma-related morbidity and mortality.[4] The past several decades have seen several campaigns to increase public awareness of skin cancers, to incorporate novel diagnostic technologies, and to educate the public and health care professionals in efforts to promote the early detection of melanoma. Apart and distinct from the increased emphasis on early detection, therapies for melanomas have become ever more effective over the years. Contemporary treatments can now include wide local excision, Mohs, slow Mohs, immunotherapies, and topical treatments with imiquimod depending on the subtype of the tumor and discussion between the provider and patient.[5]

Nonetheless, there remains significant controversy over whether screening for melanoma via increasing the frequency of routine skin checks leads to tangible long-term health benefits for patients. At present, population screening for melanoma is not recommended by the United States Preventive Services Task Force (USPSTF) on account of insufficient evidence to assess the balance of benefits and harms.[6] In an ideal world, the impact of screening would be evaluated through a randomized controlled trial. This is because non-randomized studies examining the effect of screening on mortality are plagued by sources of bias including the healthy screenee effect, lead-time bias, and length-time bias.[7] However, not only has there never been a randomized controlled trial evaluating the impact of melanoma screening, but there is also no trial currently underway or planned.[8] Given the absence of randomized controlled trial data or planned future trials, decisions about whether to recommend melanoma screening must rely on indirect evidence, disease epidemiology, and the current understanding of pathophysiological mechanisms including the natural course of melanomas detected via screening.

In recent years, several non-randomized studies have deepened our understanding of the appropriateness of melanoma screening. For example, a recent cohort study of 2,452 patients diagnosed with melanoma from 2006–2007 in New South Wales reported a reduction in all-cause mortality, but not melanoma-specific mortality, for melanomas diagnosed through routine skin checks.[9] This may indicate that an individual's interaction with the healthcare system led to the detection of other issues that were impeding their healthcare status. In another study specific to Rhode Island, free public skin cancer screening events were held at beaches between 2015–2019, and data collected provided broad insights into the local epidemiology of disease amongst "presumptively-at-high-risk" individuals: of 2,354 people screened, 7 malignant melanomas were ultimately diagnosed.[2] Equally, however,

recent studies have also underscored the harms of increased diagnostic scrutiny for melanoma. Although cutaneous melanoma was once a rare neoplasm, the incidence has rapidly increased over the past 40 years, rising six-fold in that time frame.[10] A key question underlying these epidemiological trends is whether the significant rise in incidence constitutes a genuine increase in the occurrence of melanomas or, rather, an "epidemic of diagnosis" for some patient populations.

In this paper, we explore the question of what it means for melanoma screening to be ethically justifiable. Our focus is on population-wide screening for melanoma as formulated by guidelines issued from national institutions such as the USPSTF. Although it is tempting to assume that the controversy around population screening is solely an empirical matter, it is worth underscoring that conceptual and ethical clarity are prerequisites, too. After all, unless we can agree on what it means for melanoma screening to be ethically justifiable, the question of whether screening should be recommended has little prospect of empirical resolution, no matter how much data is collected.

CLARIFYING THE SCREENING DEBATE

Screening aims to reduce disease-related morbidity and mortality via the earlier detection of cancer. The premise is that early-stage cancer has better outcomes than later-stage disease. Therefore, it is theorized that the early detection of cancer should improve health outcomes. Though attractive in theory, the story has been very complicated in practice. For example, in several types of cancer including prostate, thyroid, lung, and breast cancers, there is evidence that screening increases the early detection of cancer *without* decreasing later-stage disease or improving health outcomes.[11] In other words, screening often leads to overdiagnosis, defined as cases in which individuals meet the diagnostic criteria for a particular disease but, in the absence of detection, the individual would not have suffered any reduction in length or quality of life.

Controversies around screening require distinguishing two different types of questions:

1) Does screening constitute a favorable benefit-harm ratio for a particular population?

2) Given the evidence, what are we licensed to conclude about the benefits and harms of screening?

The source of disagreement in screening debates is often ambiguous. We can see this by holding one issue fixed and varying the other.[12] To illustrate, consider the case of breast cancer screening. Although projections vary across studies, the USPSTF estimates that biennial mammography screening for women aged 50 to 74 years old saves one life from breast cancer for every 143 women screened over their lifetime. However, for every life saved, biennial mammography in this population leads to approximately 136 false-positive tests, 21 unnecessary breast biopsies, and 3 overdiagnosed breast tumors that may have been unnecessarily treated.[13]

Suppose we are absolutely certain that breast cancer screening saves one life for every 143 women screened but leads to all of the aforementioned harms. One way to disagree is if you think this is a favorable benefit-harm ratio, and if I do not. In this scenario, disagreement arises around how to aggregate the benefits and harms for those affected. Contrast this with the following. Suppose we both believe that screening should be recommended once we are 80% certain that an agreed upon benefit-harm ratio would be achieved for those affected. However, we disagree about whether the available evidence translates into 80% certainty that, were guidelines published to that effect, such a favorable benefit-harm ratio would be attained. This might occur if the population studied in trials is different in relevant ways from the intended population to be screened, or as in the case of melanoma screening, if there is an absence of randomized controlled trial data to rigorously assess the effectiveness of screening. In this scenario, disagreement arises not around what constitutes a favorable balance of benefits and harms, but rather, when the evidence is sufficient to act on recommending screening for a particular population.

THREE ETHICAL CONSIDERATIONS IN MELANOMA SCREENING

While there is a growing literature on the ethics of cancer screening in general,[14] the ethics of skin cancer screening in particular is less developed. One framework advanced by Stoff and Grant-Kels (2021) highlights the principles of utilitarianism, justice, and caring to guide our ethical thinking around skin cancer screening.[15] In their framework, they address three concerns: "Do skin cancer screening events reduce mortality from skin cancer?" (Utilitarianism), "Do skin cancer screening events provide access to care for underserved populations?" (Justice), and "Do skin cancer screening events cultivate relationships between the public and dermatologists?" (Caring). This section aims to further develop this ethical framework for skin cancer screening by highlighting three key ethical considerations.

DOES MELANOMA SCREENING IMPOSE HARM ON HEALTHY PEOPLE?

Discussions of the benefit-harm ratio for melanoma screening must acknowledge that screening may impose harm on otherwise asymptomatic people. As noted above, approximately 230 malignant melanomas are diagnosed annually in Rhode Island, which has a population of roughly 800,000 adults above the age of eighteen.[2] It is a truism of population screening that the lower the baseline incidence of disease, the higher the likelihood of false-positive results.[7] While it

may be tempting to dismiss false-positive results as trivial, this would be a mistake. In the context of mammography screening, false-positive results can lead to psychosocial consequences such as increased anxiety and sleep disturbance that persist even three years after the initial false-positive finding.[16]

A potentially more serious harm of melanoma screening is the overdiagnosis of pigmented lesions. Welch *et al.* (2021) recently argued that the six-fold increase in the incidence of melanoma over the past 40 years is largely the result of increased diagnostic scrutiny.[10] Several factors underpin this increased scrutiny: an increasing number of screening exams of the skin, decreasing thresholds for biopsy of pigmented lesions, decreasing pathological thresholds to diagnose morphological abnormalities as neoplasms, and an increasing amount of medical malpractice litigation. In further service of their argument, Welch and colleagues point to epidemiological signatures of cancer. While the incidence of melanoma has sharply risen in previous decades, there has been little reduction in melanoma mortality in that same timeframe. These population trends are highly suggestive of melanoma overdiagnosis. That is, increased diagnostic scrutiny may lead to more melanomas detected without much concomitant benefit.[17] Although it is true that melanoma mortality has declined slightly in recent years, Welch *et al.* (2021) point out that the timing of such mortality reductions coincides with advances in melanoma treatment such as checkpoint-blockade immunotherapies and targeted therapies for metastatic disease. It would thus appear that the better explanation for the decline in mortality is improved treatment for melanoma, rather than early detection.

Apart from the unnecessary treatment associated with the overdiagnosis of melanoma, we agree with Welch *et al.* (2021) that there are several additional screening-related harms to be considered. In the United States healthcare system, a cancer diagnosis can impose a crushing financial burden.[18] Of the total $8.1 billion for all direct skin cancer annual costs in the United States, melanoma comprises $3.3 billion of the costs.[3] Biopsies or excisions pose risks of harm as well. It is estimated that for every melanoma diagnosis, over 10 pigmented lesions are biopsied.[19] Excisions for overdiagnosed or benign pigmented lesions confer no benefit to the recipient, yet there remain the risks of scarring, bleeding, infection, and out-of-pocket costs.[10] Lastly, as Welch *et al.* (2021) point out, frequent, full skin exam surveillance is common in dermatology. Persons diagnosed with suspicious lesions are faced with potentially increased appointments, co-pays, and possible anxiety related to more frequent scrutiny of their skin moving forward. In light of there also being a paucity of dermatologic providers, an indirect harm can arise, namely, patients with more pressing dermatological issues may be impeded from receiving timely care because appointment slots are reserved for routine surveillance.[10]

NON-MALEFICENCE AND MELANOMA SCREENING

As discussed above, the ethical framework advanced by Stoff and Grant-Kels (2021) highlights the principles of utilitarianism, justice, and caring to guide our thinking around skin cancer screening. In their framework, a utilitarian perspective on skin cancer screening aims to "promote the most good for the most people using a relatively simple metric… reduction of death from skin cancer, specifically melanoma."[15] However, in light of the harms underscored in the previous section, the relationship between screening and the principle of non-maleficence should also be underscored.[20] Bracketing the issue of whether the "most good" should be understood solely in terms of melanoma-specific mortality, there is an additional ethical complexity here: improving aggregate population outcomes is consistent with violating the principle of non-maleficence.[21] By analogy, it is ethically impermissible to harvest one living patient's organs without consent for the sake of saving three others in need of organ transplantation, even if doing so would lead to better population outcomes.

Ethically speaking, there is an asymmetry between intrapersonal justification (justifying harms with benefits to the same person) and interpersonal justification (justifying harms to some people with benefits to different people). It has been argued that this ethical asymmetry is what the principle of non-maleficence is intended to capture.[21] Moreover, this asymmetry is one explanation for why it is ethically impermissible to harvest patients' organs for the sake of benefiting other people. From a population perspective, screening policies are ethically complex because screening-related harms such as false-positive results and overdiagnosis are inevitably imposed on some individuals in order to help others. To be ethically justifiable and avoid violating non-maleficence, we believe that population-screening should be recommended only when the expected benefits and harms of screening are favorable for *each individual* affected by the guidelines.[21]

Two implications of the preceding discussion are worth emphasizing. First, guidelines for screening typically include a criterion about the "balance of benefits and harms" for the intended population.[6] However, it is important not to conflate the interests of the "average individual" within a population with the interests of *each* individual.[21] Ignoring this distinction would be to assume that policies that lead to better aggregate outcomes are always in the interests of each individual. As the organ harvesting example illustrates, this can be problematic. Second, when debates around screening are only framed in terms of "cost-effectiveness" or "promoting the most good for the most people," we run the risk of obscuring the role of non-maleficence in population health policies. It is important to recognize that screening policies are not just a matter of deciding whom to help. Rather, screening can involve imposing real harm

on some as a means of helping others. These are precisely the circumstances that the principle of non-maleficence is intended to deem ethically objectionable.

JUSTICE AND MELANOMA SCREENING

While screening-related harms such as overdiagnosis are a pressing concern, the underdiagnosis of melanoma in particular populations must also be explored. With respect to the epidemiology of melanoma, it is reported that geriatric patients with lighter skin are at the highest risk.[22] Additionally, several studies have linked indoor tanning to a significant increase in the risk of melanoma. In particular, individuals who began tanning younger than 35 are at a high risk for melanoma.[23] However, studies suggest that individuals who reported engaging in indoor tanning were more likely to *avoid* skin cancer screening.[23] How might skin cancer screening be optimized by focusing on the subpopulations that would benefit the most from routine skin examinations?

Although skin cancer is more prevalent in White patients, studies have identified that when skin cancer does occur in patients of color, it presents at a more advanced stage with worse prognosis.[24] The morbidity and mortality is often higher for patients of color despite that in current data only about 2% of non-Hispanic Black and 5% of Hispanic patients are diagnosed with either a malignant melanoma or keratinocyte skin cancer.[25] For melanomas, there is a lower 5-year survival rate for both Hispanic and non-Hispanic Black populations as compared to White populations.[26] Previous studies have discovered that at the time of presentation, melanomas are likely to be greater in Breslow thickness and are more advanced in Hispanic and non-Hispanic Black patients.[27] One retrospective study examined demographics and trends for diagnoses of late-stage melanomas.[28] They found that advanced or late-stage melanomas were diagnosed in about 16% of White patients. However, late-stage melanomas were disproportionately diagnosed in 52% of non-Hispanic Black patients and 26% of Hispanic patients. From a justice-based perspective, it is imperative that if melanoma screening is to be recommended, then guidelines should be formulated to address the underdiagnosis of melanomas in underserved populations.

CONCLUSION

Population screening for melanoma and other skin conditions is an ethically complex intervention that rests at the intersection of clinical medicine and public health. To be ethically justifiable, melanoma screening must balance ethical duties including non-maleficence and justice. Focusing screening on high-risk individuals or limiting screening to solely an initial exam for patients who have had benign exams may reduce the risks of overdiagnosis while also reducing melanoma-related health inequities. However, high-quality studies are direly needed to provide evidence of an acceptable benefit-harm ratio prior to recommending population-wide melanoma screening. In Rhode Island, several community-wide interventions other than skin cancer screening have been implemented to increase sun protection behaviors, such as educational programming and behavioral counseling.[29] Such evidence-based interventions reflect the undeniable importance of reducing the burden of skin cancer in Rhode Island. Nonetheless, in the face of insufficient evidence to justify recommending population-wide skin cancer screening, thinking through the ethical dimensions of screening offers a different avenue to assessing a key question facing dermatology: when is melanoma screening ethically justifiable to both patients and populations?

References

1. National Cancer Institute. Cancer Stat Facts: Melanoma of the Skin. https://seer.cancer.gov/statfacts/html/melan.html
2. Lee KC, Fulton JP, Kazemi L, et al. Clinical Outcomes of Free, Public Skin Cancer Screening Events, Rhode Island, 2015-2019. *RIMJ.* 2021 Aug 2;104(6):22-27.
3. Guy Jr GP, Machlin SR, Ekwueme DU, et al. Prevalence and costs of skin cancer treatment in the U.S., 2002-2006 and 2007-2011. *Am J Prev Med.* 2015 Feb; 48(2):183-187.
4. Halpern AC, Marchetti MA. Melanoma Screening: Time for a Reset? *JAMA Dermatol.* 2021;157(12):1409-1411.
5. Davis LE, Shalin SC, Tackett AJ. Current state of melanoma diagnosis and treatment. *Cancer Biol Ther.* 2019;20(11): 1366-1379.
6. US Preventive Services Task Force. Screening for skin cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2016;316(4):429-435.
7. Raffle A, Gray M. 2007. *Screening: Evidence and Practice*. Oxford: Oxford University Press.
8. Halvorsen JA, Løberg PG, Roscher I, et al. Why a randomized melanoma screening trial is not a good idea. *Br J Dermatol.* 2018 Aug;179(2):532-533.
9. Watts CG, McLoughlin K, Goumas C, et al. Association Between Melanoma Detected During Routine Skin Checks and Mortality. *JAMA Dermatol.* 2021;157(12):1425-1436.
10. Welch HG, Mazer BL, Adamson AS. The Rapid Rise in Cutaneous Melanoma Diagnoses. *NEJM.* 2021;384:72-79.
11. Welch HG, Black WC. Overdiagnosis in Cancer. *JNCI.* 2010; 102(9):605-613.
12. Wu JH. The Limits of Screening. https://doi.org/10.17863/CAM.53085
13. Siu AL; U.S. Preventive Services Task Force. Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med*. 2016;164(4):279-96.
14. Plutynski A. Ethical issues in cancer screening and prevention. *J Med Philos.* 2012; 37(3):310-323.
15. Stoff BK, Grant-Kels JM. The Ethics of Skin Cancer Screening. In: Bercovitch L, Perlis CS, Stoff BK, Grant-Kels JM. (eds) Dermatoethics. 2021. Springer, Cham.
16. Brodersen J, Siersma VD. Long-Term Psychosocial Consequences of False-Positive Screening Mammography. *Ann Fam Med*. 2013;11(2):106-115.
17. Welch HG, Kramer BS, Black WC. Epidemiologic Signatures in Cancer. *NEJM*. 2019;381:1378-1386.

18. Gilligan AM, Alberts DS, Roe DJ, et al. Death or Debt? National Estimates of Financial Toxicity in Persons with Newly-Diagnosed Cancer. *Am J Med.* 2018;131(10):1187-1199.
19. Lott JP, Boudreau DM, Barnhill RL, et al. Population-Based Analysis of Histologically Confirmed Melanocytic Proliferations Using Natural Language Processing. *JAMA Dermatol.* 2018;154(1):24-29.
20. Beauchamp TL, Childress JF. *Principles of Biomedical Ethics, 5th edn.* Oxford University Press, 2001.
21. John SD, Wu JH. "First, Do No Harm"? Non-Maleficence, Population health and the Ethics of Risk. *Soc Theory Pract.* Published online Feb 23, 2022. Available at: https://www.pdcnet.org/soctheorpract/content/soctheorpract_2022_0999_2_18_152.
22. Matthews NH, Li WQ, Qureshi AA, et al. Epidemiology of melanoma. *Exon Publications*. 2017;30:3-22.
23. Fischer AH, Wang TS, Yenokyan G, et al. Association of Indoor Tanning Frequency With Risky Sun Protection Practices and Skin Cancer Screening. *JAMA Dermatol.* 2017;153(2):168–174.
24. Gloster Jr. HM, Neal K. Skin cancer in skin of color. *J Am Acad Dermatol*. 2006;55:741-760.
25. Halder RM, Bridgeman-Shah S. Skin cancer in African Americans. *Cancer*. 1995;75:667-673
26. Byrd KM, Wilson DC, Hoyler SS, et al. Advanced presentation of melanoma in African Americans. *J Am Acad Dermatol*. 2004;50:21-24.
27. Cockburn MG, Zadnick J, Deapen D. Developing epidemic of melanoma in the Hispanic population of California. *Cancer*. 2006;106:1162-1168.
28. Hu S, Soza-Vento RM, Parker DF. Comparison of stage at diagnosis of melanoma among Hispanic, black, and white patients in Miami-Dade County, Florida. *Arch Dermatol*. 2006;142: 704- 708.
29. Tran MM, Smith CK, Andoscia G, et al. The Value of Partnerships in Multi-Component Skin Cancer Prevention Interventions. *RIMJ. 2022* Feb 1;105(1):42-45.

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Financial disclosures

Drs. Negbenebor and Wu declare no conflict of interest.

Funding/Support

None.

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