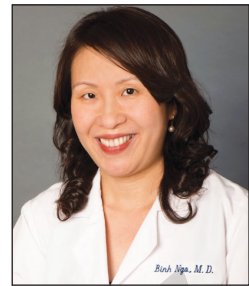


Skin Cancer Screening: The Paradox of Melanoma and Improved All-Cause Mortality



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PRACTICE POINTS

- Screening for skin cancer often is performed at the patient's request.
- Patients who want full-body skin examinations may exhibit other health-promoting behaviors.
- Studies claiming "overdiagnosis" of skin cancer have not previously evaluated all-cause mortality.

In April 2023, the US Preventive Services Task Force (USPSTF) issued a controversial recommendation that the current evidence is insufficient to assess the benefits vs harms of visual skin examination by clinicians for skin cancer screening in adolescents and adults who do not have signs or symptoms of skin cancer.^{1,2} This recommendation by the USPSTF has not changed in a quarter century,³ but a recent study described an interesting paradox that should trigger wide evaluation and debate.

Patel et al⁴ analyzed data from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program from January 2000 to December 2018 to identify adults with a diagnosis of first primary melanoma in situ (MIS). Overall mortality was then determined through the National Vital Statistics System, which provides cause-of-death information for all deaths in the United States. The authors found 137,872 patients who had 1—and only 1—MIS discovered over the observation period. These

patients predominantly were White (96.7%), and the mean (SD) age at diagnosis was 61.9 (16.5) years. During 910,308 total person-years of follow-up (mean [SD], 6.6 [5.1] years), 893 (0.6%) patients died of melanoma and 17,327 (12.6%) died of any cause. The 15-year melanoma-specific standardized mortality rate (SMR) was 1.89 (95% CI, 1.77-2.02), yet the 15-year overall survival relative to matched population controls was 112.4% (95% CI, 112.0%-112.8%), thus all-cause SMR was significantly lower at 0.68 (95% CI, 0.67-0.7). Although MIS was associated with a small increase in cohort melanoma mortality, overall mortality was actually lower than in the general population.⁴

Patel et al⁴ did a further broader search that included an additional 18,379 patients who also experienced a second primary melanoma, of which 6751 (36.7%) were invasive and 11,628 (63.3%) were in situ, with a melanoma-specific survival of 98.2% (95% CI, 97.6%-98.5%). Yet relative all-cause survival was significantly higher at 126.7% (95% CI, 125.5%-128.0%). Even among patients in whom a second primary melanoma was invasive, melanoma-specific survival was reduced to 91.1% (95% CI, 90.0%-92.1%), but relative all-cause survival was 116.7% (95% CI, 115%-118.4%). These data in the overall cohort of 155,251 patients showed a discordance between melanoma mortality, which was 4.27-times higher than in the general population (SMR, 4.27; 95% CI, 4.07-4.48), and a lower risk for death from all causes that was approximately 27% lower than in the general population (SMR, 0.73; 95% CI, 0.72-0.74). The authors showed

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that their findings were not associated with socioeconomic status.⁴

The analysis by Patel et al⁴ is now the second study in the literature to show this discordant melanoma survival pattern. In an earlier Australian study of 2452 melanoma patients, Watts et al⁵ reported that melanoma detection during routine skin checks was associated with a 25% lower all-cause mortality (hazard ratio, 0.75; 95% CI, 0.63-0.90) but not melanoma-specific mortality after multivariable adjustment for a variety of factors including socioeconomic status.

These analyses by 2 different groups of investigators have broad implications. Both groups suggested that the improved life span in melanoma patients may be due to health-seeking behavior, which has been defined as “any action undertaken by individuals who perceive themselves to have a health problem or to be ill for the purpose of finding an appropriate remedy.”⁶

Once treated for melanoma, it is clear that patients are likely to return at regular intervals for thorough full-body skin examinations, but this activity alone could not be responsible for improved all-cause mortality in the face of increased melanoma-specific mortality. It seems the authors are implying a broader concept of good health behavior, originally defined by MacKian⁷ as encompassing “activities undertaken to maintain good health, to prevent ill health, as well as dealing with any departure from a good state of health,” such as overt behavioral patterns, actions, and habits with the goal of maintenance, restoration, and improvement of one’s health. A variety of behaviors fall within such a definition including smoking cessation, decreased alcohol use, good diet, more physical activity, safe sexual behavior, scheduling physician visits, medication adherence, vaccination, and yes—screening examinations for health problems.⁸

The concept that individuals who are diagnosed with melanoma fall into a pattern of good health behavior is an interesting hypothesis that must remain speculative until the multiple aspects of good health behavior are rigorously studied. This concept coexists with the hypothesis of melanoma “overdiagnosis”—the idea that many melanomas are detected that will never lead to death.⁹ Both concepts deserve further analysis. Unquestionably, a randomized controlled trial could never recruit patients willing to undergo long-term untreated observation of their melanomas to test the hypothesis that their melanoma diagnosis would eventually lead to death. Furthermore, Patel et al⁴ do suggest that even MIS carries a small but measurable increased risk for death from the disease, which is not particularly supportive of the overdiagnosis hypothesis; however, analysis of the concept that improved individual health behavior is at least in part responsible for the first discovery of melanomas is certainly approachable. Here is the key question: Did the melanoma diagnosis trigger a sudden change in multiple aspects of health behavior that led to significant all-cause mortality benefits? The average age of the population

studied by Patel et al⁴ was approximately 62 years. One wonders whether the consequences of a lifetime of established health behavior patterns can be rapidly modified—certainly possible but again remains to be proven by further studies.

Conversely, the alternative hypothesis is that discovery of MIS was the result of active pursuit of self-examination and screening procedures as part of individually ingrained good health behavior over a lifetime. Goodwin et al¹⁰ carried out a study in a sample of the Medicare population aged 69 to 90 years looking at men who had prostate cancer screening via prostate-specific antigen measurement and women who had undergone mammography in older age, compared to the contrast population who had not had these screening procedures. They tracked date of death in Medicare enrollment files. They identified 543,970 women and 362,753 men who were aged 69 to 90 years as of January 1, 2003. Patients were stratified by life expectancy based on age and comorbidity. Within each stratum, the patients with cancer screening had higher actual median survival than those who were not screened, with differences ranging from 1.7 to 2.1 years for women and 0.9 to 1.1 years for men.¹⁰ These results were not the result of lower prostate or breast cancer mortality. Rather, one surmises that other health factors yielded lower mortality in the screened cohorts.

A full-body skin examination is a time-consuming process. Patients who come to their physician for a routine annual physical don’t expect a skin examination and very few physicians have the time for a long detailed full-body skin examination. When the patient presents to a dermatologist for an examination, it often is because they have real concerns; for example, they may have had a family member who died of skin cancer, or the patient themselves may have noticed a worrisome lesion. Patients, not physicians, are the drivers of skin cancer screening, a fact that often is dismissed by those who are not necessarily supportive of the practice.

In light of the findings of Patel et al,⁴ it is essential that the USPSTF reviews be reanalyzed to compare skin cancer-specific mortality, all-cause mortality, and lifespan in individuals who pursue skin cancer screening; the reanalysis also should not be exclusively limited to survival. With the advent of the immune checkpoint inhibitors, patients with metastatic melanoma are living much longer.¹¹ The burden of living with metastatic cancer must be characterized and measured to have a complete picture and a valid analysis.

After the release of the USPSTF recommendation, there have been calls for large-scale studies to prove the benefits of skin cancer screening.¹² Such studies may be valuable; however, if the hypothesis that overall healthy behavior as the major outcome determinant is substantiated, it may prove quite challenging to perform tests of association with specific interventions. It has been shown that skin cancer screening does lead to discovery of more

melanomas,¹³ yet in light of the paradox described by Patel et al,⁴ it also is likely that causes of death other than melanoma impact overall mortality. Patients who pursue skin examinations may engage in multiple different health activities that are beneficial in the long term, making it difficult to analyze the specific benefit of skin cancer screening in isolation. It may prove difficult to ask patients to omit selected aspects of healthy behavior to try to prove the point. At this time, there is much more work to be done prior to offering opinions on the importance of skin cancer examination in isolation to improve overall health care. In the meantime, dermatologists owe it to our patients to continue to diligently pursue thorough and detailed skin examinations.

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