Strategizing Screening for Melanoma in an Era of Novel Treatments: A Model-Based Approach

Kemal Caglar Gogebakan[1], Elizabeth G. Berry[2], Alan C. Geller[3], Kemal Sonmez[1], Sancy A. Leachman[2], and Ruth Etzioni[4,5]

ABSTRACT

Background: Benefit–harm tradeoffs of melanoma screening depend on disease risk and treatment efficacy. We developed a model to project outcomes of screening for melanoma in populations with different risks under historic and novel systemic treatments.

Methods: Computer simulation model of a screening program with specified impact on overall and advanced-stage incidence. Inputs included meta-analyses of treatment trials, cancer registry data, and a melanoma risk prediction study

Results: Assuming 50% reduction in advanced stage under screening, the model projected 59 and 38 lives saved per 100,000 men under historic and novel treatments, respectively. With 10% increase in stage I, the model projects 2.9 and 4.7 overdiagnosed cases per life saved and number needed to be screened (NNS) equal to 1695 and 2632 under historical and novel treatments. When screening was performed only for the 20% of individuals with highest predicted risk, 34 and 22 lives per 100,000 were saved under historic and novel treatments. Similar results were obtained for women, but lives saved were lower.

Conclusions: Melanoma early detection programs must shift a substantial fraction of cases from advanced to localized stage to be sustainable. Advances in systemic therapies for melanoma might noticeably reduce benefits of screening, but restricting screening to individuals at highest risk will likely reduce intervention efforts and harms while preserving >50% of the benefit of nontargeted screening.

Impact: Our accessible modeling framework will help to guide population melanoma screening programs in an era of novel treatments for advanced disease.

Introduction

The incidence of melanoma, the most lethal form of skin cancer, continues to increase in the United States. Between 2001 and 2015, the age-adjusted incidence of both localized and advanced melanomas increased by 36% from 20.7 to 28.2 per 100,000 respectively. In 2020, it is estimated that there will be 100,350 new cases of melanoma in the United States (1) and 6,850 additional melanoma-specific deaths, mostly attributable to advanced-stage disease. From 2013 to 2017 the death rates for melanoma declined by 7.0% per year in adults younger than 50 years of age and by 5.7% per year in older adults (2). The falling death rates appear to be in large part due to new immune checkpoint inhibitor (ICI) and targeted therapies. However, these new therapies have substantial adverse effects and huge costs.

The sustained increase in melanoma incidence and adverse effects of new treatments have heightened the urgency for a systematic and evidence-based plan for melanoma control. To date, no randomized controlled trials (RCT) of melanoma screening have been conducted. A few screening programs have reported results but their outcomes are mixed. In Germany, initial results of the Schleswig-Holstein screening initiative showed a 50% reduction in skin cancer–related death but subsequent extension to the German national program yielded inconclusive and potentially contradictory results (3–7). In Australia, the Skin Awareness Trial, aimed to educate men 50 years and older to check their skin regularly and seek care for any suspicious lesions (8). More recently, an observational study of a prospective screening initiative was conducted at the University of Pittsburgh Medical Center (UPMC) among adults seen by a UPMC-employed primary care physician (PCP; ref. 9). The ongoing War on Melanoma in Oregon is an evolving model for population-specific skin cancer screening that promotes skin self-exam and referral to a dermatologist in case of suspicious lesions (10).

Because the available screening programs have not yet provided evidence of a significant mortality benefit, population screening is not currently recommended by the U.S. Preventive Services Task Force (USPSTF; ref. 11). Several studies have suggested that screening of high-risk individuals might be more feasible and less prone to false positive screens, unnecessary procedures, and patient anxiety (12–15). These studies have been supported by modeling studies indicating that targeted screening might be a more cost-effective strategy (16, 17) than broad-based population screening. To define high-risk individuals, several risk prediction models have been developed (18).

As with early detection for other cancers, overdiagnosis of melanoma is likely to be an unavoidable consequence of screening. An overdiagnosed melanoma is one detected by screening that would likely not have manifested clinically meaningful symptoms during the patient's lifetime in the absence of screening. Melanoma is one of the cancer types for which screening has expanded and, along with it, the detection of potentially indolent disease (19). The management of early melanoma involves reexcision of the primary lesion, repeated follow-up appointments and increased anxiety (20). Therefore, any screening program must address the issue of overdiagnosis of melanomas as well as excess diagnosis and treatment of other common

[1]Cancer Early Detection Advanced Research Center, Knight Cancer Institute, Oregon Health & Science University, Portland, Oregon. [2]Department of Dermatology, Oregon Health & Science University, Portland, Oregon. [3]Division of Public Health Practice, Harvard School of Public Health, Boston, Massachusetts. [4]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington. [5]Department of Statistics, University of Washington, Seattle, Washington.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Corresponding Author: Ruth Etzioni, Fred Hutchinson Cancer Research Center, Seattle, WA 98109-1024. Phone: 206-667-6561; E-mail: retzioni@fredhutch.org

Cancer Epidemiol Biomarkers Prev 2020;29:2599–607

doi: 10.1158/1055-9965.EPI-20-0881

lesions. Gordon and colleagues, in an analysis of a skin awareness program in Australia, has concluded that, "overall costs and effects from also detecting more squamous and basal cell carcinomas and benign lesions outweighed the positive health gains from detecting more thin melanomas" (21).

Because of the absence of evidence from randomized trials, several models have been developed to explore benefits and cost-effectiveness of screening for melanoma. Gordon and colleagues modeled the cost effectiveness implications of the Skin Awareness Trial for the broader Australian population (21). Gilmore published a Markov model of melanoma progression and early detection to measure the trade-off between cost of medical resources and reduction in mortality in Australia between 1982 and 2028 (22). Although cost-effective over the period 2013–2028, secondary prevention beyond 2013 was projected to produce only modest improvement in advanced stage melanoma survival. Gordon and Rowell reviewed 11 modeling studies of skin cancer prevention and early detection. They concluded that melanoma early detection programs aimed at high-risk individuals may be cost-effective, but noted that updated analyses were needed (23).

The treatment landscape for advanced melanoma has changed dramatically after the FDA-approved ipilimumab, an anti–CTLA-4 antibody, in March 2011 and vemurafenib, a BRAF inhibitor in August, 2011. Treatment opportunities further increased following the approval of other oncogene-targeted BRAF and MEK inhibitors and anti–PD-1 receptor antibodies. Randomized controlled trials have demonstrated improvements in progression-free (PFS) and overall survival (OS; refs. 24–31) but with notable toxicity in some cases.

The change in the therapeutic landscape will likely impact the potential benefits of early detection. The improvement in advanced-stage survival could attenuate any benefits of early detection; this would increase motivation to focus these efforts within the highest-risk individuals. Factors that increase risk of melanoma are well known and have been included in algorithms to predict individual risk and interactive risk assessment tools (13, 18, 32–34).

Empirical investigation of the tradeoffs between early detection, increased use of novel treatments, and risk-targeted screening is not possible, thus, modeling is of value for this purpose. In prior work (35), we developed an evidence-based microsimulation model for breast cancer that decouples the effects of early detection and treatment on stage-specific survival. The model projected incidence and mortality under a specified stage shift due to early detection and treatment efficacy based on clinical trials. This study adapted the breast cancer model to melanoma, incorporating the use of novel systemic therapies and risk stratification. We focused on cutaneous melanoma as it is more common and amenable to screening than mucosal or ocular melanoma. We used the adapted model to project the number and years of lives saved corresponding to screening programs yielding a specified reduction in advanced stage disease. The model also included overdiagnosis which generates a specified excess incidence under screening and permits project of overdiagnoses per life saved. While we are presenting the results for specified set of model input parameters, the model is accessible via a user-friendly interface that permits users to enter their own values for the key model inputs.

Methods

We used a microsimulation modeling framework to generate a virtual population of melanoma diagnoses with stage distribution replicating that in the SEER registry between 2011 and 2015, and stage-specific survival based on SEER data for cases diagnosed from 2006 to 2010, just prior to the advent of novel systemic therapies. We considered this population to be the baseline (no screening, no novel systemic therapies). We then simulated screening by altering the baseline incidence and stage distribution, and implementation treatment by improving the stage-specific survival. The modeling framework allowed us to project age at diagnosis and individual-level survival times with and without early detection or novel treatments. Because melanoma screening efforts could result in overdiagnosis, we incorporated the number of over-diagnosed cancers into the model by inflating the cancer incidence by a specified rate of overdiagnosis.

Model structure

The model is a state-transition model as described by Birnbaum and colleagues (35). The individual-level state transitions were modeled from healthy to clinically detected or screen-detected melanoma and death (**Fig. 1**). All patients received surgical excision as standard treatment. Systemic treatments for advanced stage extended the corresponding disease-specific survival beyond historical (prior to novel treatments) estimates. The screening leaded to a stage shift, moving some cases which would have been diagnosed at advanced stage to an earlier stage.

We included overdiagnosed cases of melanoma under screening to our model via a simple excess-incidence scheme. Following Gilmore (22), the overdiagnosis rate in our model was defined as the increase in stage I incidence compared with the incidence under no early detection over and above any increase associated with the shift in stage from advanced to localized disease due to screening. Overdiagnosed cases were not entered into the mortality calculations because they were excess cases who would not have been detected in their lifetimes in the absence of screening.

We simulated two distinct populations of 200,000 non-Hispanic white men and women with a specified common age distribution at entry (35–75 years) in historical and novel treatments eras. The simulated populations were partitioned into control and screening settings, and outcomes were generated under historical and novel treatments (immune checkpoint inhibitor (ICI) and oncogene-targeted therapies). In total, there are four simulation scenarios (M0–M3) for each gender. M0 and M1 are the labels for no screening with historical and novel treatments, respectively. M2 and M3 are the labels for screening with historical and novel treatments, respectively.

Stage distribution and disease incidence in the absence of screening

Invasive disease incidence and stage in the absence of screening was characterized by age-specific rates of diagnosis (within 5-year age categories), based on the SEER-18 database for 2011 to 2015. We defined advanced disease as corresponding to SEER stages III and IV and nonadvanced disease as SEER stages I and II using the AJCC 7 staging system. We partitioned invasive cases according to their BRAF status; based on published studies (36–38), and assumed that approximately 45% of cases with advanced stage are BRAF-positive.

Disease incidence and stage distribution in the presence of screening

While the potential for overdiagnosis in melanoma early detection is a concern, the expected frequency of overdiagnosis is not known. Gilmore (22) varied the overdiagnosis frequency, expressed as an increase in stage I diagnoses, between 0% and 10%. For our main analysis, we assumed an inflation factor of 10% over 25 years, and varied this in sensitivity analysis. The additional cases were not included in the mortality model, as overdiagnosed cases were by

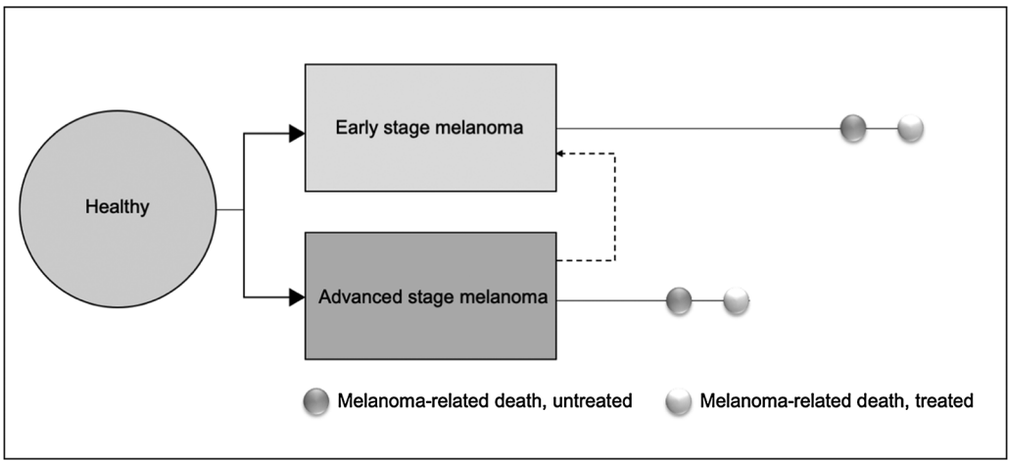

Figure 1.
Schematic of melanoma state transition microsimulation model.

definition not at risk of death from melanoma. Inputs for incidence and their sources are detailed in **Table 1**.

The stage shift with screening was modeled only among non-overdiagnosed cases. For these cases, we reclassified a fraction of patients who were diagnosed at advanced stage in the absence of screening to be localized at diagnosis. The extent to which melanoma early detection reduces advanced-stage disease is not known, in practice, this will depend on the natural history of the disease, the screening protocol, compliance with screening and biopsy recommendations. Our main analysis assumed a reduction in advanced-stage melanoma under screening of 50%; we vary this in sensitivity analysis.

Disease-specific mortality

Disease-specific survival was determined by stage at diagnosis and the treatments received for patients at each stage. For historical survival, we used disease-specific survival from patients in SEER diagnosed between 2006 and 2010, the period before the advent of novel systemic therapies (**Table 1**). We used SEER 5-year survival estimates to fit an exponential distribution for stage-specific survival, and then generated survival times from this distribution. For each individual, the date of death was determined as the earlier of time of disease-specific death and the time of other-cause death, generated on the basis of the Human Mortality Database (**Table 1**).

As noted above, screening changes stage at diagnosis for a fraction of patients whose stage without screening is advanced. For these cases, we regenerated survival from their original date of diagnosis to avoid lead-time bias. Novel systemic therapies inflated disease-specific survival by applying HRs obtained from published clinical trial results as detailed below. In this way, these therapies extended time from clinical diagnosis to melanoma-specific death.

Melanoma treatment distributions and efficacies

Prior to the advent of novel systemic treatments, available, FDA-approved treatments consisted of chemotherapy, high-dose IL2, and IFN. However, based on a review of the literature, we determined that these treatments did not demonstrate significant survival

Table 1. Inputs to the microsimulation model.

Measures	Men	Women
1. Clinical melanoma incidence, by age	Male 5-year age-specific rates of diagnosis, SEER database (2011–2015)	Female 5-year age-specific rates of diagnosis, SEER database (2011–2015)
2. Proportion of cases that are advanced stage[a]	13.1%	9.2%
3. Proportion of cases that are stage I[a]	73.1%	79.3%
4. Proportion of BRAF-positive cases (%)	45% (36–38)	Same as for men
5. Five-year baseline disease-specific survival	Early 95.6%, advanced 44.8% (2006–2010 diagnoses)	Early 96.8%, advanced 53.4% (2006–2010 diagnoses)
6. Other cause mortality rates, by age	Male age-specific rates, Human Mortality Database (2015)	Female age-specific rates, Human Mortality Database (2015)
7. Overdiagnosis rate[b]	10%	Same as for men
8. Treatment distributions and efficacies for advanced-stage patients	See **Table 2**	Same as for men
9. RR of high- and low-risk population[c]	See **Table 3**	Same as for men

[a]Stage classification was made according to AJCC 7 Staging System. Stage I/II were assigned to early stage, and Stage III/IV were assigned to advanced stage, and stage distribution was taken from SEER database for melanomas diagnosed from 2011 to 2015.
[b]Determined on the basis of the assumption of authors and ref. 22.
[c]Authors' calculation based on Williams and colleagues' 2011 Washington State melanoma case–control study conducted by collecting self-assessed risk factors (34).

Table 2. Treatment distributions and efficacies for advanced melanoma before and after treatment advances conditional on BRAF status.[a]

	Treatment distributions (%)[a]		Treatment efficacies[b]	
	Historical treatments	Novel treatments	Historical treatments	Novel treatments
BRAF-positive				
Chemotherapy-high-dose IL2	100	—	1	—
Anti–PD-1 monotherapy	—	30	—	0.50 (0.29–0.87)
Anti–CTLA-4 monotherapy	—	6	—	0.69 (0.53–0.89)
Anti–PD-1 combination therapy	—	25	—	0.33 (0.24–0.47)
BRAF Inhibitor monotherapy	—	5	—	0.81 (0.68–0.96)
BRAF Inhibitor combination therapy	—	31	—	0.55 (0.41–0.76)
Other[c]	—	3	—	1
BRAF-negative				
Chemotherapy-high-dose IL2	100	—	1	—
Anti–PD-1 monotherapy	—	58	—	0.50 (0.29–0.87)
Anti–CTLA-4 monotherapy	—	11	—	0.69 (0.53–0.89)
Anti–PD-1 combination therapy	—	27	—	0.33 (0.24–0.47)
BRAF inhibitor monotherapy	—	4	—	1
BRAF inhibitor combination therapy	—	—	—	1
Other[c]	—	—	—	1

[a]Treatment distribution for novel treatments era was taken from Whitman and colleagues' 2018 analysis of treatment dissemination of novel therapies using Flatiron Health Database from the first quarter of 2014 (Q1) through the second quarter of 2016 (Q2). We calculated the average of first and second quarter of 2016 (2016 Q1–2016 Q2) to represent the most recent treatment distribution (47).
[b]Treatment efficacies were incorporated into the model by using HRs with the ranges of 95% CI taken from published results of randomized clinical trials (26, 28, 49–52). The efficacies other than chemotherapy were calculated with direct comparison to chemotherapy.
[c]Other treatments are temozolomide, interferon, carboplatin, and paclitaxel.

benefit (39–46). Thus, in our historical treatment models, we combined all treatments into one category and assume that all advanced-stage patients received at least one of these treatments.

The impact of novel, systemic treatments on survival depends on their uptake and efficacy. Treatment uptake distributions were determined based on a retrospective study of medical records from Flatiron Health (47). This study provided the frequencies of treatments for BRAF-mutant (BRAF-positive) and BRAF wild-type (BRAF-negative) advanced melanoma. In order to reflect the dissemination of these novel treatments, we used the treatment distributions in 2016 (**Table 2**).

Although the treatment of advanced melanoma has evolved rapidly over the past few years, early melanoma management has not changed. Early-stage melanoma patients are still treated by surgical excision with margins based on the presence and depth of invasion (48). Therefore, in all models, we assumed that early-stage patients received surgical therapy alone and focused on the additional benefits of systemic treatments for advanced-stage patients.

For novel treatment efficacies, we used published RRs (HRs) on overall survival as proxies for the effect on disease-specific survival. Because there was no significant survival benefit of older systemic therapies for advanced stage patients, we assigned HRs of 1 to these therapies. The treatment efficacies for novel immune checkpoint inhibitors and targeted therapies for patients with BRAF-positive and BRAF-negative advanced melanoma were taken from published results of clinical trials (26, 28, 49–52). The HRs of these treatments were recalculated compared with cytotoxic chemotherapy (**Table 2**).

Targeted screening

To define a high-risk subpopulation, we used published RRs from a Washington State melanoma case–control study with self-assessed risk factors (34). This study analyzed data from an age range that was the

Table 3. RR for various risk score cutoffs and populations.

Risk level	Risk score cutoff[a]	RR (high-risk to low-risk population)[a]	RR (high-risk to average-risk population)[b]	RR (low-risk to average-risk population)[b]
Top 20%	25	5.41	2.87	0.53
Top 15%	28	5.42	3.26	0.60
Top 10%	30	6.20	4.08	0.66
Top 5%	34	7.35	5.57	0.76

[a]Values were taken from Williams and colleagues' 2011 Washington State melanoma case-control study where self-assessed risk factors were collected (34). RRs of melanoma are those considered high risk (those with a score at or above the cutoff value) to those considered as low risk (those with a score below the cutoff value).
[b]Authors' own calculation. Approximate calculation of RR of high- and low-risk population compared to average risk population can be described as follows: Consider 20% of population at high risk, and 80% of population at low risk for melanoma diagnosis. Thus, RR of average risk = 5.41 (RR of high risk) *0.2 + 1 (RR of low risk) *0.8 = 1.882. Then, we inflated the incidence of high risk with respect to average risk by 5.41/1.882 = 2.87 and deflated the incidence of low risk with respect to average risk: 1/1.882 = 0.5325 to make sure that overall incidence was approximately the same as in the original analysis. Calculations for other risk levels are similar.

same as in our analysis and computed the sensitivity and specificity values for different risk percentiles which are used as inputs in our model. Therefore, the values presented in this study are valuable inputs for our model to perform risk stratified screening analysis for various high-risk groups. In this study, the most predictive risk factors were considered as male sex, older age, higher number of severe sunburns between ages 2–18, lighter natural hair color at age 15, higher density of freckles on the arms before age 20, higher number of raised moles on both arms, and prior nonmelanoma skin cancer.

We defined the subgroup with the top 20% of risk level as high risk. On the basis of the published RRs for thus defined high- versus low-risk cases, we calculated the RR of melanoma for high- versus average-risk and low- versus average-risk to be 2.87 and 0.5325, respectively. We then simulated two distinct populations of 100,000 non-Hispanic white men and women, inflating melanoma incidence rates for 20% using a factor of 2.87, and reducing melanoma incidence rates for the remaining individuals using a factor of 0.5325. We then modeled screening only for individuals in the high-risk group, applying both historic and novel treatments following the schema used for the nontargeted setting.

We took RRs of melanoma diagnosis for high-risk versus low-risk cases from Washington State melanoma case–control study. For our modeling purposes, we calculated RRs for high-risk versus average-risk cases, and for low-risk versus average-risk cases by using the values taken from this case–control study. All RRs values including calculation procedure were reported in **Table 3**.

Model outcomes

While reporting model outcomes, we set M0 as standard-of-care (S) and M1–M3 as intervention (I) scenarios. For all of these scenarios, the model projected cumulative melanoma incidence (C), mortality (D), and average years of life (Y) among the cohort over the specified follow-up interval. Mortality benefits of interventions were measured by comparison of intervention settings to standard-of-care setting by three statistics: mortality rate ratio (MRR: D_I/D_S), number of lives saved (NLS: D_I-D_S), and years of lives saved (YLS: Y_I-Y_S). The number of overdiagnosed cancers (ODC) was estimated by inflating stage I cumulative incidence by a specified overdiagnosis rate (od%; ODC: C × od%). Number needed to be screened (NNS) was calculated by dividing number of people screened by lives saved under screening (53). Uncertainty intervals were calculated by running repeated simulation models with different random number seeds.

Sensitivity analyses

To investigate the sensitivity of our outcomes under different settings, we explored alternatives for the key assumptions of our model. First, we assumed a smaller stage shift from advanced stage to earlier stage by decreasing decline in advanced stage to 15%. This increase can capture the effect of older technology or less frequent screening on stage shift. Second, we decreased the overdiagnosis inflation factor to 5%. Third, we varied the risk level for stratified screening and screened the top 15%, 10%, and 5% patients to evaluate the NNS under screening different risk groups. Finally, to investigate how the screening results are influenced by the range of treatment efficacies, we used 95% confidence interval (CI) values of the HRs of the novel treatments.

Reproducible research statement

All data are from publicly available sources. The Code Ocean page is available for reproducibility of the results at https://codeocean.com/capsule/0387150. The user interface for the model is available at https://kemalgogebakan.shinyapps.io/melanomaadvanced/.

Results

Main analyses

Results were projected over 25 years for four screening/treatment scenarios (M0-M3) for men and women aged 35–75 years.

Table 4 presents the outcomes with and without nonstratified early detection. With a 50% decrease in advanced stage incidence (from 312 to 156 cases), 59 lives per 100,000 individuals were saved by early detection under historic treatments, and 39 per 100,000 were saved under novel treatments. Thus, as expected, early detection saved fewer lives under improved systemic treatments for advanced disease. The model projected 2.9 and 4.7 over-diagnosed cases per life saved under

Table 4. 25-year melanoma outcomes, by change in treatment landscape of advanced melanoma with and without screening.[a]

		No early detection		Early detection	
Treatment program		**Policy M0 Historical**	**Policy M1 Novel**	**Policy M2 Historical**	**Policy M3 Novel**
Cumulative incidence	Men	2,382 (2,294–2,473)	2,382 (2,294–2,473)	2,556 (2,462–2,653)	2,556 (2,462–2,653)
	Women	1,144 (1,080–1,206)	1,144 (1,080–1,206)	1,235 (1,166–1,301)	1,235 (1,166–1,301)
Overdiagnosed cases	Men	0	0	174 (168–181)	174 (168–181)
	Women	0	0	91 (86–96)	91 (86–96)
Number of advanced-stage cases	Men	312 (301–324)	312 (301–324)	156 (150–162)	156 (150–162)
	Women	105 (99–111)	105 (99–111)	53 (50–56)	53 (50–56)
Cumulative mortality	Men	235 (205–266)	193 (170–217)	176 (146–201)	155 (133–175)
	Women	105 (86–127)	88 (73–108)	81 (64–101)	74 (59–92)
Mortality rate ratio	Men	1	0.82 (0.72–0.92)	0.75 (0.7–0.8)	0.66 (0.58–0.74)
	Women	1	0.85 (0.68–0.99)	0.77 (0.69–0.86)	0.71 (0.55–0.89)
Number of lives saved	Men	0	43 (17–69)	59 (45–73)	80 (52–108)
	Women	0	16 (1–37)	24 (15–33)	31 (10–52)
Years of life saved	Men	0	327 (72–577)	443 (331–572)	597 (351–906)
	Women	0	162 (2–345)	204 (132–306)	284 (106–486)

[a]Results reflect mean values of 25-year follow-up in a cohort of 100,000 men and women aged 35–75 years, with 95% uncertainty intervals across 100 simulations by screening entire population without risk stratification. Effects of Policies M1–M3 are compared with the historical M0. Historical and novel treatment programs reflect systemic treatments for advanced melanoma before and after 2011, respectively.

Table 5. 25-year melanoma outcomes under the change in treatment landscape of advanced melanoma, with and without stratified screening.[a]

Treatment program		Nonstratified screening		Stratified screening	
		Historical	Novel	Historical	Novel
Overdiagnosed cases	Men	174 (168–181)	174 (168–181)	98 (94–103)	98 (94–103)
	Women	91 (86–96)	91 (86–96)	52 (48–56)	52 (48–56)
Number of advanced stage cases	Men	156 (150–162)	156 (150–162)	235 (216–242)	235 (216–242)
	Women	59 (56–62)	59 (56–62)	88 (80–93)	88 (80–93)
Number of lives saved	Men	59 (45–73)	38 (28–50)	34 (25–44)	22 (12–32)
	Women	24 (15–33)	15 (8–23)	13 (7–20)	8 (3–13)
Years of lives saved	Men	443 (331–572)	270 (185–378)	248 (158–344)	158 (99–240)
	Women	204 (132–306)	122 (59–194)	113 (62–182)	68 (25–122)
Overdiagnoses to lives saved	Men	2.98 (2.38–3.8)	4.72 (3.48–6.17)	2.97 (2.24–3.98)	4.63 (3.07–7.8)
	Women	4.02 (2.79–6.16)	6.71 (3.9–10.88)	4.3 (2.56–7.45)	7.08 (4.01–15)
Number needed to be screened	Men	1,695 (1,370–2,222)	2,632 (2,000–3,571)	588 (455–800)	909 (625–1,666)
	Women	4,166 (3,030–6,667)	6,667 (4,347–12,500)	1,538 (1,000–2,857)	2,500 (1,538–6,667)

[a]Results reflect 25-year follow-up in a cohort of 100,000 men and women aged 35–75 years, where under stratified screening, 20,000 people who are at the top 20% high-risk group are screened. 95% uncertainty intervals are derived around mean across 100 simulations.

historic and novel treatments. Qualitatively similar results were obtained for women, but reflect their lower risk of the disease. Among women, 24 and 15 per 100,000 lives were saved under historic and novel treatments. Still, the ratio of overdiagnoses relative to lives saved was at least as high for women; screening generated 4 and 6.7 overdiagnoses per lives saved under historical and novel systemic therapies, respectively.

Table 5 presents the comparison of stratified and nonstratified screening. By screening only 20,000 men who were at the top 20% risk level, 34 lives were saved under historic treatments and 22 lives saved under novel treatments. As expected, these benefits were lower than the 61 and 39 lives saved when the whole population was screened. Under risk-stratified screening, 98 cases were overdiagnosed, compare with 174 cases under nonstratified screening. For women, 13 lives were saved by screening under historic treatments and 8 lives under novel treatments. The number of overdiagnosed cases was 52, which was much lower than under nonstratified screening. Finally, for men, NNS over 25 years to avert one death were 588 and 909 under historic and novel treatments, compared with 1,695 and 1,632 in the nonstratified setting. NNS was higher for women but similarly reduced under risk-stratified screening.

In summary, the results projected markedly lower absolute screening benefit under novel systemic therapies for advanced disease than under historic therapies. In contrast, relative screening benefit was similar and only modestly attenuated under novel treatments. Life years saved tracked lives saved, with fewer life years saved due to screening under novel therapies. Risk stratified screening, reduced both lives saved and overdiagnoses considerably, but preserved roughly 60% of the benefit of whole-population screening.

Sensitivity analyses

When we assumed a smaller reduction in advanced-stage incidence (15% decrease under screening), the projected mortality reductions decreased accordingly. (Supplementary Table S1). Smaller reduction in advanced stage cases resulted in increase in overdiagnoses to lives saved. Across sensitivity analyses, we observed similar reductions due to early detection under novel treatments compared with historical treatments. Under stratified screening, we projected qualitatively similar results as in the base case analysis. (Supplementary Table S2).

Decreasing the frequency of overdiagnosis to 5%, over 25 years, decreased the projected ratio of overdiagnosis to lives saved for both stratified and non-stratified screening. (Supplementary Tables S3 and S4).

When varying the risk threshold for stratified screening, (Supplementary Table S5), we found that as the threshold for screening increased, the NNS decreased along with the overall lives saved. For men, the NNS was estimated to be 2631, 833 and 500 for average, top 15% and top 5% risk populations, respectively.

Last, instead of using point estimates, we analyzed the effect of incorporating a range of novel treatment efficacies based on 95% CI's around point estimates (Supplementary Table S6). For men, the range for number of lives saved under screening varied between 27 and 49. Years of lives ranged between 192 and 363. The range of the projected ratio of overdiagnoses to lives saved was 5.03 to 9.8 and NNS 2,041 to 3,703. As expected, a decrease (increase) in treatment efficacy leads to an increase (decrease) in the value of screening.

Discussion

This study provides a quantitative modeling framework for exploring the potential impacts of population-wide and risk-targeted detection polices for melanoma and how they might change under novel and evolving treatments. Unlike more common cancers like breast and prostate cancer, for which screening trials are available, there are no randomized studies of early detection for melanoma. Modeling is a way of filling in the gaps in the evidence about screening benefit and how it might change under different settings. Our results indicate that novel therapies could attenuate any mortality benefit expected from early detection, but focusing screening among individuals predicted to be at highest risk of disease could cut screening and its adverse consequences dramatically while preserving 60% of the benefit.

The mechanism for representing screening benefit in our model is through a stage shift. Screening reduces the incidence of advanced, incurable disease, and those cases detected earlier by screening receive survival that is similar to the survival documented for early-stage cases. Thus, key drivers of screening benefit are the incidence of disease and of advanced stage disease without screening, and the change in the incidence of advanced stage disease under screening. Besides the benefit of saving lives, decrease in late-stage melanoma due to a potential early detection could reduce cost and morbidity. The key drivers of treatment benefit are the stage-specific survival in the

absence of screening and novel treatments, and the uptake and efficacies of novel treatments.

The stage-shift assumption represents an intuitive mechanism for the impact of early detection on disease-specific mortality. It is also the driver of model results that are subject to the greatest degree of uncertainty. The realized stage shift under screening depends on the disease natural history (extent to which early and *in situ* disease progresses, and time to progression), the intensity and accuracy of screening, and the frequency of biopsy. Gilmore developed a detailed natural history model of melanoma prevention, detection and treatment in Australia that included disease onset and progression through four clinicopathologic stages (22). An important limitation is that there is no good model for the natural history of melanoma and it has been pointed out by many researchers that aggressive melanomas, which lead to death, may not be caught by screening, in the same fashion that aggressive breast cancer lesions are often discovered outside of routine screening.

The stage shift assumption, although unverified, underlies much of the intuition that motivates early detection. To the extent that aggressive cancers that would be at late stage without screening are not diagnosable early, there will be lesser reduction in late stage incidence under screening. Because of the difficulty identifying progression parameters, we instead parametrized the model of screening benefit via the reduction in advanced-stage disease. In addition to being a more succinct and transparent summary of the impact of screening on disease, this is an observable quantity in any screening program. For example, it has already been identified as one of the key outcomes in the ongoing War on Melanoma in Oregon. A corollary of this choice is that we did not capture benefits of stage shifts due to within-stage shifts due to early detection, thus our results regarding screening benefit may be modestly conservative.

Overdiagnosis has been mentioned as a concern in several commentaries about melanoma early detection and is one of the adverse effects cited in USPSTF's review of factors driving their recommendation (insufficient evidence) for melanoma screening (11, 54–56). The potential frequency of overdiagnosis is not known and in other cancers (e.g., breast and prostate cancer), attempts to estimate it have generated a range of results varying according to population, metric, and method. We specified a very modest frequency of overdiagnosis simply to demonstrate how overdiagnosed cases might compare with lives saved in melanoma screening programs. This specification is prominent, because the majority of patients with melanoma do not die of their disease.

Our modeling framework does not yet extend to the calculation of other adverse impacts. These include unnecessary biopsies and their consequences (pain, infection), as well as the monetary costs of screening, excision of localized lesions, and systemic treatment of metastatic cases. In nonscreening settings, estimates of the frequency of unnecessary biopsies (based on estimated positive predictive values) are quite high (57, 58); one study estimated that 10 biopsies were necessary to detect one cancer, and another study estimated this number to be 28 (59, 60). Thus, by presenting only the ratio of projected overdiagnoses to lives saved, we might be underestimating the harms of screening. Moreover, immunotherapy and targeted molecular therapy have high toxicity and may leave patients with morbidities far more significant than their scars (i.e., life-long adrenal failure, life-threating pneumonitis, pancreatitis and innumerable other autoimmune sequelae). In our model, we did not take these adverse effects into the account. In addition, we assumed independence between BRAF status and risk in our model. However, ambient UV exposure has been associated with BRAF-mutated melanoma (61, 62). Because our model did not accommodate this type of correlation, it might have overestimated screening benefit in the high-risk subgroup. Finally, some stage IIC patients have poorer survival than some patients who belong to stage III subcategories. These exceptions might have skewed our results. Work to extend the modeling framework to accommodate more comprehensive cost-benefit tradeoffs is ongoing.

Despite the uncertainty in our modeling assumptions about drivers of benefit and harm, we were able to leverage the framework to produce a fairly robust set of conclusions. Our findings indicate that novel treatments, used at the same frequencies as in 2016, would reduce the potential lives saved by a melanoma early detection program by about one half, with a corresponding increase in the ratio of overdiagnoses to lives saved. Our risk-targeted models suggest that targeting early detection efforts toward the stratum of the population deemed to be at highest risk could dramatically reduce costs and harms while preserving a significant proportion of the benefit.

In any practical setting, the impact of early detection will depend on the penetrance of screening, the corresponding changes in incidence overall and for advanced stage disease, and the intensity of treatment. Therefore, in practice, the outcomes of a melanoma early detection program could differ from the figures presented in this study. Our user interface permits input of key outcome-driving parameters specific to any program and should facilitate projection of harms and benefits in practice.

Disclosure of Potential Conflicts of Interest

E.G. Berry reports personal fees from Bristol-Myers Squibb (served on an advisory board in April 2019 for which consulting fees and travel reimbursement were received) outside the submitted work and served as a consultant for Barco Inc in the spring of 2020 on a dermoscopy project for which consulting fees were received. K. Sonmez reports grants from Knight Cancer Institute during the conduct of the study. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

K.C. Gogebakan: Conceptualization, data curation, software, formal analysis, investigation, methodology, writing–original draft. **E.G. Berry:** Investigation, writing–original draft. **A.C. Geller:** Writing–review and editing. **K. Sonmez:** Writing–review and editing. **S.A. Leachman:** Writing–review and editing. **R. Etzioni:** Conceptualization, supervision, investigation, methodology, writing–original draft, writing–review and editing.

Acknowledgments

This work was supported by the Cancer Early Detection Advanced Research Center at Oregon Health & Science University.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received June 9, 2020; revised August 5, 2020; accepted September 17, 2020; published first September 21, 2020.

References

1. Thrift AP, Gudenkauf FJ. Melanoma incidence among non-Hispanic whites in all 50 United States from 2001 through 2015. J Natl Cancer Inst 2020;112:533–9.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7–30.

3. Waldmann A, Nolte S, Weinstock MA, Breitbart EW, Eisemann N, Geller AC, et al. Skin cancer screening participation and impact on melanoma incidence in Germany–an observational study on incidence trends in regions with and without population-based screening. Br J Cancer 2012;106:970–4.
4. Stang A, Jockel KH. Does skin cancer screening save lives? A detailed analysis of mortality time trends in Schleswig-Holstein and Germany. Cancer 2016;122: 432–7.
5. Anders MP, Fengler S, Volkmer B, Greinert R, Breitbart EW. Nationwide skin cancer screening in Germany: evaluation of the training program. Int J Dermatol 2017;56:1046–51.
6. Kaiser M, Schiller J, Schreckenberger C. The effectiveness of a population-based skin cancer screening program: evidence from Germany. Eur J Health Econ 2018; 19:355–67.
7. Stang A, Jockel KH, Heidinger O. Skin cancer rates in North Rhine-Westphalia, Germany before and after the introduction of the nationwide skin cancer screening program (2000–2015). Eur J Epidemiol 2018;33:303–12.
8. Janda M, Baade PD, Youl PH, Aitken JF, Whiteman DC, Gordon L, et al. The skin awareness study: promoting thorough skin self-examination for skin cancer among men 50 years or older. Contemp Clin Trials 2010;31:119–30.
9. Ferris LK, Saul MI, Lin Y, Ding F, Weinstock MA, Geller AC, et al. A large skin cancer screening quality initiative: description and first-year outcomes. JAMA Oncol 2017;3:1112–5.
10. Petrie T, Samatham R, Witkowski AM, Esteva A, Leachman SA. Melanoma early detection: big data, bigger picture. J Invest Dermatol 2019;139:25–30.
11. Force USPST, Grossman DC, Curry SJ, Davidson KW, Ebell M, Epling JW Jr, et al. Screening for skin cancer: US Preventive Services Task Force Recommendation Statement. JAMA 2016;316:429–35.
12. Quéreux G, Nguyen J-M, Volteau C, Lequeux Y, Dréno B. Creation and test of a questionnaire for self-assessment of melanoma risk factors. Eur J Cancer Prev 2010;19:48–54.
13. Cho E, Rosner BA, Feskanich D, Colditz GA. Risk factors and individual probabilities of melanoma for whites. J Clin Oncol 2005;23:2669–75.
14. Koh HK, Lew RA, Prout MN. Screening for melanoma/skin cancer: theoretic and practical considerations. J Am Acad Dermatol 1989;20:159–72.
15. Harbauer A, Binder M, Pehamberger H, Wolff K, Kittler H. Validity of an unsupervised self-administered questionnaire for self-assessment of melanoma risk. Melanoma Res 2003;13:537–42.
16. Freedberg KA, Geller AC, Miller DR, Lew RA, Koh HK. Screening for malignant melanoma: a cost-effectiveness analysis. J Am Acad Dermatol 1999;41:738–45.
17. Losina E, Walensky RP, Geller A, Beddingfield FC, Wolf LL, Gilchrest BA, et al. Visual screening for malignant melanoma: a cost-effectiveness analysis. Arch Dermatol 2007;143:21–8.
18. Usher-Smith JA, Emery J, Kassianos AP, Walter FM. Risk prediction models for melanoma: a systematic review. Cancer Epidemiol Biomarkers Prev 2014;23: 1450–63.
19. Esserman LJ, Thompson IM Jr, Reid B. Overdiagnosis and overtreatment in cancer: an opportunity for improvement. JAMA 2013;310:797–8.
20. Moynihan R, Henry D, Moons KG. Using evidence to combat overdiagnosis and overtreatment: evaluating treatments, tests, and disease definitions in the time of too much. PLoS Med 2014;11:e1001655.
21. Gordon LG, Brynes J, Baade PD, Neale RE, Whiteman DC, Youl PH, et al. Cost-effectiveness analysis of a skin awareness intervention for early detection of skin cancer targeting men older than 50 years. Value Health 2017;20:593–601.
22. Gilmore S. Melanoma screening: informing public health policy with quantitative modelling. PLoS One 2017;12:e0182349.
23. Gordon LG, Rowell D. Health system costs of skin cancer and cost-effectiveness of skin cancer prevention and screening: a systematic review. Eur J Cancer Prev 2015;24:141–9.
24. McArthur GA, Ribas A. Targeting oncogenic drivers and the immune system in melanoma. J Clin Oncol 2013;31:499–506.
25. Robert C, Thomas L, Bondarenko I, O'Day S, Weber J, Garbe C, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011;364:2517–26.
26. Robert C, Ribas A, Schachter J, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. Lancet Oncol 2019;20:1239–51.
27. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015; 372:320–30.
28. Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med 2015;372:30–9.
29. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–23.
30. Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012;380:358–65.
31. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011;364:2507–16.
32. Whiteman D. Predicting melanoma risk: theory, practice and future challenges. Melanoma Manag 2014;1:105–14.
33. Taylor NJ, Mitra N, Qian Lu, Avril MF, Bishop DT, Bressac-de Paillerets B, et al. Estimating CDKN2A mutation carrier probability among global familial melanoma cases using GenoMELPREDICT. J Am Acad Dermatol 2019;81:386–94.
34. Williams LH, Shors AR, Barlow WE, Solomon C, White E. Identifying persons at highest risk of melanoma using self-assessed risk factors. J Clin Exp Dermatol Res 2011;2:1000129.
35. Birnbaum J, Gadi VK, Markowitz E, Etzioni R. The effect of treatment advances on the mortality results of breast cancer screening trials: a microsimulation model. Ann Intern Med 2016;164:236–43.
36. Eggermont AM, Spatz A, Robert C. Cutaneous melanoma. Lancet 2014;383: 816–27.
37. Menzies AM, Haydu LE, Visintin L, Carlino MS, Howle JR, Thompson JF, et al. Distinguishing clinicopathologic features of patients with V600E and V600K BRAF-mutant metastatic melanoma. Clin Cancer Res 2012;18:3242–9.
38. Colombino M, Lissia A, Capone M, De Giorgi V, Massi D, Stanganelli I, et al. Heterogeneous distribution of BRAF/NRAS mutations among Italian patients with advanced melanoma. J Transl Med 2013;11:202.
39. Hill GJ 2nd, Krementz ET, Hill HZ. Dimethyl triazeno imidazole carboxamide and combination therapy for melanoma IV. Late results after complete response to chemotherapy (Central Oncology Group protocols 7130, 7131, and 7131A). Cancer 1984;53:1299–305.
40. Serrone L, Zeuli M, Sega FM, Cognetti F. Dacarbazine-based chemotherapy for metastatic melanoma: thirty-year experience overview. J Exp Clin Cancer Res 2000;19:21–34.
41. Hauschild A, Garbe C, Stolz W, Ellwanger U, Seiter S, Dummer R, et al. Dacarbazine and interferon alpha with or without interleukin 2 in metastatic melanoma: a randomized phase III multicentre trial of the Dermatologic Cooperative Oncology Group (DeCOG). Br J Cancer 2001;84:1036–42.
42. Keilholz U, Punt CJA, Gore M, Kruit W, Patel P, Lienard D, et al. Dacarbazine, cisplatin, and interferon-alfa-2b with or without interleukin-2 in metastatic melanoma: a randomized phase III trial (18951) of the European Organisation for Research and Treatment of Cancer Melanoma Group. J Clin Oncol 2005;23: 6747–55.
43. Garbe C, Eigentler TK, Keilholz U, Hauschild A, Kirkwood JM. Systematic review of medical treatment in melanoma: current status and future prospects. Oncologist 2011;16:5–24.
44. Lebbe C, Lorigan P, Ascierto P, Testori A, Bédane C, Middleton M, et al. Treatment patterns and outcomes among patients diagnosed with unresectable stage III or IV melanoma in Europe: a retrospective, longitudinal survey (MELODY study). Eur J Cancer 2012;48:3205–14.
45. Lorigan P, Marples M, Harries M, Wagstaff J, Dalgleish AG, Osborne R, et al. Treatment patterns, outcomes, and resource utilization of patients with metastatic melanoma in the U.K.: the MELODY study. Br J Dermatol 2014;170:87–95.
46. Atkins MB, Lotze MT, Dutcher JP, Fisher RI, Weiss G, Margolin K, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. J Clin Oncol 1999;17: 2105–16.
47. Whitman ED, Liu FX, Cao X, Diede SJ, Haiderali A, Abernethy AP. Treatment patterns and outcomes for patients with advanced melanoma in US oncology clinical practices. Future Oncol 2019;15:459–71.
48. Rosko AJ, Vankoevering KK, McLean SA, Johnson TM, Moyer JS. Contemporary management of early-stage melanoma: a systematic review. JAMA Facial Plast Surg 2017;19:232–8.
49. Robert C, Grob JJ, Stroyakovskiy D, Karaszewska B, Hauschild A, Levchenko E, et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. N Engl J Med 2019;381:626–36.

50. Chapman PB, Robert C, Larkin J, Haanen JB, Ribas A, Hogg D, et al. Vemurafenib in patients with BRAFV600 mutation-positive metastatic melanoma: final overall survival results of the randomized BRIM-3 study. Ann Oncol 2017;28: 2581–7.
51. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 2019;381:1535–46.
52. Maio M, Grob JJ, Aamdal S, Bondarenko I, Robert C, Thomas L, et al. Five-year survival rates for treatment-naive patients with advanced melanoma who received ipilimumab plus dacarbazine in a phase III trial. J Clin Oncol 2015; 33:1191–6.
53. Rembold CM. Number needed to screen: development of a statistic for disease screening. BMJ 1998;317:307–12.
54. Rubin R. Melanoma diagnoses rise while mortality stays fairly flat, raising concerns about overdiagnosis. JAMA 2020;323:1429–30.
55. Weyers W. The 'epidemic' of melanoma between under- and overdiagnosis. J Cutan Pathol 2012;39:9–16.
56. Nufer KL, Raphael AP, Soyer HP. Dermoscopy and overdiagnosis of melanoma in situ. JAMA Dermatol 2018;154:398–9.
57. Morton DL, Thompson JF, Cochran AJ, Mozzillo N, Nieweg OE, Roses DF, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. N Engl J Med 2014;370:599–609.
58. Wong SL, Faries MB, Kennedy EB, Agarwala SS, Akhurst TJ, Ariyan C, et al. Sentinel lymph node biopsy and management of regional lymph nodes in melanoma: American Society of Clinical Oncology and Society of Surgical Oncology Clinical Practice Guideline Update. Ann Surg Oncol 2018;25:356–77.
59. Welch HG, Woloshin S, Schwartz LM. Skin biopsy rates and incidence of melanoma: population based ecological study. BMJ 2005;331:481.
60. Weinstock MA, Lott JP, Wang Q, Titus LJ, Onega T, Nelson HD, et al. Skin biopsy utilization and melanoma incidence among Medicare beneficiaries. Br J Dermatol 2017;176:949–54.
61. Thomas NE, Edmiston SN, Alexander A, Millikan RC, Groben PA, Hao H, et al. Number of nevi and early-life ambient UV exposure are associated with BRAF-mutant melanoma. Cancer Epidemiol Biomarkers Prev 2007; 16:991–7.
62. Maddodi N, Setaluri V. Role of UV in cutaneous melanoma. Photochem Photobiol 2008;84:528–36.