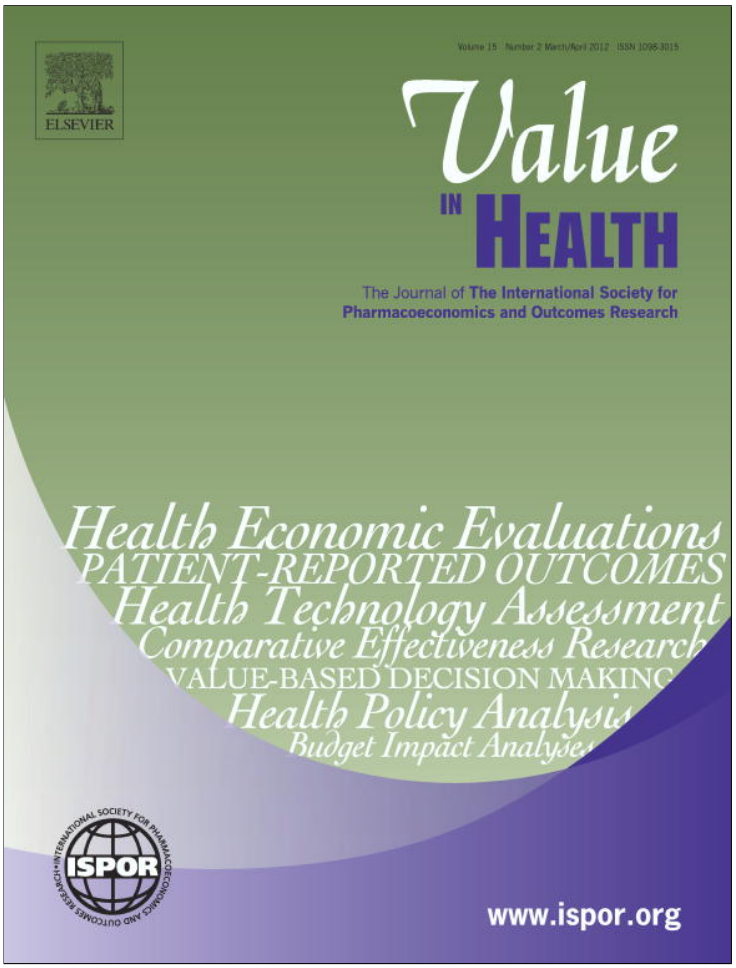
Submission 1:
Attachment A



VALUE IN HEALTH 15 (2012) 261–268

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/jval

Lifetime Cost-Effectiveness of Skin Cancer Prevention through Promotion of Daily Sunscreen Use

Nicholas G. Hirst, MHEcon[1,], Louisa G. Gordon, PhD[1,2], Paul A. Scuffham, PhD[1,2], Adele C. Green, PhD[2,3,4]*

[1]*Centre for Applied Health Economics, Griffith University, Brisbane, Australia;* [2]*Griffith Medical Research College, A Joint Program of Griffith University and Queensland Institute of Medical Research, QIMR, Herston, Australia;* [3]*Queensland Institute of Medical Research, Genetics and Population Health Division, PO Royal Brisbane Hospital, Herston, Australia;* [4]*School of Translational Medicine, University of Manchester, Manchester, UK*

A B S T R A C T

Objectives: Health-care costs for the treatment of skin cancers are disproportionately high in many white populations, yet they can be reduced through the promotion of sun-protective behaviors. We investigated the lifetime health costs and benefits of sunscreen promotion in the primary prevention of skin cancers, including melanoma. **Methods:** A decision-analytic model with Markov chains was used to integrate data from a central community-based randomized controlled trial conducted in Australia and other epidemiological and published sources. Incremental cost per quality-adjusted life-year was the primary outcome. Extensive one-way and probabilistic sensitivity analyses were performed to test the uncertainty in the base findings with plausible variation to the model parameters. **Results:** Using a combined household and government perspective, the discounted incremental cost per quality-adjusted life-year gained from the sunscreen intervention was AU$40,890. Over the projected lifetime of the intervention cohort, this would prevent 33 melanomas, 168 cutaneous squamous-cell carcinomas, and 4 melanoma-deaths at a cost of approximately AU$808,000. The likelihood that the sunscreen intervention was cost-effective was 64% at a willingness-to-pay threshold of AU$50,000 per quality-adjusted life-year gained. **Conclusions:** Subject to the best-available evidence depicted in our model, the active promotion of routine sunscreen use to white populations residing in sunny settings is likely to be a cost-effective investment for governments and consumers over the long term.

Keywords: cost-effectiveness, health-care costs, melanoma, primary prevention, squamous-cell carcinoma, sunscreen.

Introduction

In predominantly fair-skinned populations living in high sunlight environments, the treatment costs for skin cancers exert a significant financial burden on the health-care system. Cutaneous malignant melanoma is the most deadly skin cancer, causing more than 8000 deaths in the United States [1] and more than 1200 deaths in Australia each year [2]. Although seldom fatal, the sheer quantity of basal-cell carcinoma (BCC) and squamous-cell carcinoma (SCC) in these populations causes disproportionately more resources to be expended on these cancers than on any other [3–5]. In the United States, skin cancer treatments cost an estimated $2 billion each year. In addition are costs of other sun-related skin conditions such as actinic keratoses (AKs), which range in prevalence from 6% to 25% in the United Kingdom and United States [6] to 40% to 60% in Australia [6,7], and are one of the strongest predictors of skin cancer [7]. Management of AKs accounts for an additional $1.2 billion in health-care costs in the United States [8].

The evidence that the vast majority of skin cancers are caused by solar ultraviolet radiation (UVR) exposure is accepted [9]. Both acute and chronic overexposure to the sun, including early in life, are important for the development of skin cancers including melanoma [10] and it is thus expected that their prevention is achievable through the engagement of sun-protective behaviors. On this basis, wearing sun-protective clothing, broad-brimmed hat and sunglasses, and seeking shade is recommended by health authorities in many Western countries [11–13]. The topical application of broad-spectrum sunscreens is also recommended as a safe adjunct measure in protecting human skin from UVR damage and cancer development [14,15].

Australia has the highest reported rates of skin cancer in the world, with two in three Australians being diagnosed with skin cancer in their lifetime and more than 1600 deaths attributed to skin cancer each year [5,16]. Not surprisingly, Australia has led the world in the development of sun-protection messages and promotional campaigns such as Slip Slop Slap and SunSmart and these programs appear to have successfully raised public awareness and improved preventive behaviors [17,18], even slowing melanoma and other skin cancer incidence rates in younger cohorts [19].

It is plausible then that health-care costs could be reduced through interventions promoting sun-protection behaviors. Because many skin cancers are treated in relatively low-cost primary care settings, however, some have suggested that it is more economical to treat these conditions as they arise rather than investing in preventive measures that promote sun protection [20]. Re-

Conflicts of interest: The authors have no conflicts of interest to report.

* *Address correspondence to:* Nicholas Hirst, Centre for Applied Health Economics, Griffith University, University Drive, Meadowbrook 4131, Brisbane, Australia.

E-mail: n.hirst@griffith.edu.au.

1098-3015/$36.00 – see front matter

doi:10.1016/j.jval.2011.10.009

futing this with community-based trial data [15], we have shown that a sunscreen intervention provided a practical means of preventing SCCs and produced significant cost-savings for government health providers [21]. The question remained, however, whether these cost-effective benefits could be maintained into the longer term when melanoma, the least prevalent but more often fatal form of skin cancer, was taken into account. Therefore, the purpose of this study was to investigate the potential health costs and benefits of a sunscreen intervention over the longer term (remaining lifetime) with respect to melanoma prevention in addition to the previously demonstrated benefits.

Methods

Description of strategies

The strategies modeled were based on the Nambour Skin Cancer Prevention Trial [22–24] where 1621 residents of Nambour in Queensland, Australia, were randomized to either the sunscreen intervention group or the control group. The intervention group was encouraged to apply a broad-spectrum Sun Protection Factor 15+ sunscreen to their head, neck, arms, and hands every morning ("daily use" group) and received one or more 250-mL bottles of sunscreen free of charge every 3 months at dedicated study clinics. The control group participants were instructed to use sunscreen at their own discretion ("discretionary use" group). All participants received full skin examinations by dermatologists unaware of treatment allocation, at the start (1992), midway (1994), and at the end (1996) of the trial. Any clinically diagnosed skin cancers were confirmed by pathology reports. Participants who withdrew from active trial participation or active follow-up were asked to continue with ongoing "passive" monitoring of skin cancers through their medical records [25]. After the trial ended in 1996, all participants, including those who withdrew from active follow-up, consented to have subsequently diagnosed skin cancers notified to the investigators by regional pathology laboratories in Queensland. Finally, a cross-check for any melanomas diagnosed between 1992 and 2006 in study participants was undertaken through a search of cancer notifications at the Queensland Cancer Registry [26].

Overview of model structure

A decision-analytic model with Markov chains was constructed in TreeAge Pro 2009 software (TreeAge Software, Inc., Williamstown, MA) (Fig. 1). The model tracked multiple hypothetical cohorts separately to examine the health and cost outcomes of individuals with different profiles. Male, female, or mixed-sex cohorts with a mean starting age of 49 years (i.e., the mean age of participants at commencement of the Nambour Skin Cancer Trial) were modeled until age 100 years or death. Key measures in the model included time since diagnosis, costs, number of melanomas, quality-adjusted life-years (QALYs) and life-years lived. Guidelines for best-practice procedures for economic modeling were adhered to during our study [27].

Health states and transition probabilities

The model consists of seven health states—no melanoma; melanoma (in situ); melanoma (stage I); melanoma (stage II); melanoma (stage III); melanoma (stage IV); and dead—with staging defined by the American Joint Committee on Cancer categories [28]. All cohort members begin the model without a melanoma. Individuals will either continue to live without a melanoma or be diagnosed with a melanoma (and treated accordingly based on their American Joint Committee on Cancer stage). Following treatment, individuals diagnosed with melanoma face stage-specific risks of remaining in remission, having a recurrence, a diagnosis of additional tumors, distant metastases, or death. In all health states, individuals also face an age-specific all-cause mortality risk. Time-dependent probabilities have been built into the model to ensure that the risk of cancer progression, recurrence, or death is dependent on the duration since diagnosis.

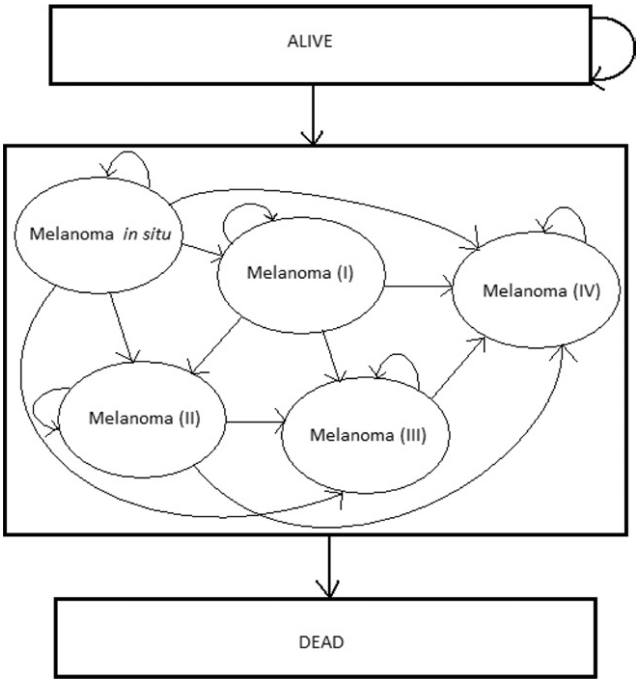


Fig. 1 – Schematic of melanoma-only model. Note: Patients diagnosed with a melanoma of a specific stage may be diagnosed with additional melanomas of the same or later stage. Transition to a higher stage may be disease progression or additional melanoma. Death may be melanoma related or from any cause.

Melanoma stage and incidence rates are the average of the latest three years of Australian melanoma incidence data by age and gender [29] (Table 1). An age-specific risk of melanoma was used in the model, and a constant hazard ratio from sunscreen use applied to this risk. Therefore, the absolute risk reduction (risk difference) is age dependent.

Evidence for the effectiveness of daily sunscreen use in preventing melanoma was sourced from the Nambour study [26] where Cox proportional-hazards regression was performed to estimate the hazard ratio for melanoma development in relation to daily sunscreen use compared with discretionary use. Intention-to-treat analysis was carried out for all reviewed and histologically confirmed melanomas between 1993 and 2006 [26]. The protective effect from sunscreen was statistically significant for invasive melanoma (0.27; 95% confidence interval [CI] 0.08–0.97) [26]. There were no significant differences in sun-protection behaviors (time spent outdoors on the weekend and weekdays, seeking of shade, and hat wearing) other than sunscreen use between the intervention and control groups before and after the intervention.

Estimates of survival rates for melanoma patients were transformed into progression rates to late-stage cancer and subsequent mortality [31]. The annual progression rates to stage IV melanoma from stages I and II were steady at 2% and 7%, respectively. Stage III melanomas had a first-year progression rate of 45%, but it fell by a third each year thereafter. Mortality risk in year 1 of a stage IV diagnosis was 42%, and it fell by approximately one-fifth each year since diagnosis. Additional melanoma diagnoses were assumed to

Table 1 – Parameter estimates used in the model and sources.

Model parameter	Mean*	Low	High	Distribution	Source
Starting age of cohort (y)	49	25	75	Normal	[25]
Discount rate for costs	0.05	0	0.07	–	–
Discount rate for effects	0.05	0	0.07	–	–
Annual hazard ratio of invasive melanoma for sunscreen users	0.27	0.08	0.97	Log normal	[26]
Probability that melanoma is invasive	0.631	0.628	0.636	Beta	[19]
Probability that second melanoma is invasive	0.8	0.76	0.84	Beta	[30]
Invasive melanomas stage I @ diagnosis	0.34	–	–	Dirichlet	[31]
Invasive melanomas stage II @ diagnosis	0.52	–	–	Dirichlet	[31]
Invasive melanomas stage III @ diagnosis	0.07	–	–	Dirichlet	[31]
Invasive melanomas stage IV @ diagnosis	0.07	–	–	Dirichlet	[31]
Annual SCC risk	0.015	0.013	0.018	Beta	[25]
Rate ratio of SCC for sunscreen users	0.59	0.38	0.9	Log normal	[25]
Annual risk of progression from stage I to stage IV	0.02	0.015	0.026	Beta	[31]
Annual risk of progression from stage II to stage IV	0.07	0.051	0.092	Beta	[31]
First-year risk of progression from stage III to stage IV	0.45	0.32	0.58	Beta	[31]
Annual decay in stages III–IV progression risk	0.3	0.15	0.45	–	[31]
First-year mortality risk for stage IV melanoma†	0.42	0.22	0.54	Beta	[31]
Annual decay in stage IV mortality risk	0.2	0.1	0.3	–	[31]
Age- and sex-specific background mortality rate	Life table	–	–	–	[32]
Age- and sex-specific melanoma risk	Table	–	–	Beta	[29]
Time-dependent risk of second melanoma	Table	–	–	Beta	[30]
Utilities					
No melanoma‡	1	0.5	1	Beta	–
Melanoma in situ @ diagnosis§	0.95	0.5	1	Beta	–
Melanoma—stage I @ diagnosis	0.937	0.5	1	Beta	[33]
Melanoma—stage II @ diagnosis	0.753	0.5	1	Beta	[33]
Melanoma—stage III @ diagnosis	0.52	0.5	1	Beta	[33]
Melanoma—stage IV @ diagnosis	0.47	0.3	1	Beta	[34]
Melanoma in situ—stable disease	1	0.5	1	Beta	–
Melanoma—stage I—stable disease	0.96	0.5	1	Beta	[35]
Melanoma—stage II—stable disease	0.93	0.5	1	Beta	[36]
Melanoma—stage III—stable disease	0.93	0.5	1	Beta	[36]
Melanoma—stage IV—stable disease	0.65	0.5	1	Beta	[37]
Dead	0	–	–	–	–
Costs (AU$)					
HH‖: Discounted lifetime melanoma costs	3300	1650	4950	Gamma	[38]
HH: Annual “daily use” sunscreen out-of-pocket costs¶	25.14	13	38	Gamma	[21]
HH: Annual “discretionary use” sunscreen out-of-pocket costs¶	24.92	13	38	Gamma	[21]
Govt: Annual intervention program cost per person#	80.7	40	121	Gamma	[21]
Govt: Cost to diagnose and treat stage I melanoma in first year	2496	1248	3744	Gamma	[37]
Govt: Cost to diagnose and treat stage II melanoma in first year	5544	2772	8316	Gamma	[37]
Govt: Cost to diagnose and treat stage III melanoma in first year	19,644	9822	29,466	Gamma	[37]
Govt: Ongoing annual costs for stages II and III melanoma	2685	1343	4028	Gamma	[37]
Govt: Cost to diagnose and treat stage IV melanoma in first year	30,122	15,061	45,183	Gamma	[37]
Govt: End-of-life/palliative care costs in stage IV melanoma	5472	2736	8208	Gamma	[37]
Govt: Treatment cost for SCC	420	210	630	Gamma	[21]

Govt, government; HH, household; SCC, squamous-cell carcinoma.

* All rates from the data are converted into annual transition probabilities by using the transformation equation 1 −EXP(−RATE).

† Preferences for health states are assumed to be constant across all ages.

‡ Melanoma survival is presumed to be independent of age.

§ Complications during treatment are not explicit in utility estimates but will be accounted for with the beta distribution.

‖ Household costs.

¶ Includes time spent applying sunscreen and visits to skin clinics.

Includes the provision of free sunscreen.

Table 2 – Discounted costs and QALYs per person by intervention group and incremental cost per QALY.

	Discretionary use		Daily use		Incremental		ICER (AU$)
	Costs (AU$)	QALYs	Costs (AU$)	QALYs	Costs (AU$)	QALYs	
Melanoma only	1420	16.12	2451	16.14	1031	0.02	42,614
Melanoma + SCC	1522	16.12	2512	16.14	990	0.02	40,890

ICER, incremental cost-effectiveness ratio; SCC, squamous-cell carcinoma; QALY, quality-adjusted life-year.

be either the same American Joint Committee on Cancer stage or later than the first primary melanoma diagnosis.

A second version of the model was created by incorporating the protective effect of sunscreen on SCC development (0.59 relative risk [RR]; 95% CI 0.38–0.90) [25] in addition to melanoma. The potential for an SCC diagnosis was modeled as a possible occurrence in every cycle except in individuals with stage IV melanoma. Because a significant protective effect of sunscreen in preventing BCCs was not observed in the trial (0.87; 95% CI 0.64–1.2) [25], we did not model this.

Estimates of health outcomes

Health outcomes measured by the model included QALYs, counts of melanomas and SCCs, and melanoma-related deaths. Mortality risk from melanoma but not SCC was included in the model because SCCs rarely metastasize and cause death. Similarly, because there is insufficient evidence of decreases in quality of life for SCCs, these outcomes are also omitted from the model. QALYs are calculated by using preference-based quality-of-life scores, known as utility estimates. The health-related utility estimates used in the model were derived from standard-gamble surveys [34,35], time trade-off surveys [33], and expert opinion [39]. QALYs were discounted by 5% per year.

Estimates of resource use and costs

The study considered a societal (household and government health provider) perspective for measuring resource use. The resources required from households and governments were also presented separately. Health provider resources included staffing, monitoring, and provision of sunscreen during clinics and the subsequent health-care costs of diagnosing, treating, and following up any suspicious skin lesions. Household costs included time and out-of-pocket costs for applying sunscreen and attending clinic visits and a discounted lifetime cost following melanoma diagnosis [35]. Intervention (government and household) and SCC and BCC treatment costs were extracted from a detailed cost-analysis of the Nambour Skin Cancer Trial [21]. Several adjustments were made to take account of cost efficiencies when doctors treated more than one cancer in the same sitting and when benign lesions were treated provisionally as suspected cancers [21]. Melanoma diagnosis and treatment costs were sourced from a previous Australian study of melanoma treatments [37]. All costs (Table 1) were inflated to 2010 prices based on the Australian Bureau of Statistics cost of health inflation (AU$1 ≈ US$0.85) [40]. Costs were discounted at 5% per year.

Analyses

The total lifetime costs and outcomes for each strategy were estimated, and the incremental cost-effectiveness ratio (ICER) was calculated. We assumed a willingness-to-pay threshold of AU$50,000 per QALY gained. In Australia, although there is no fixed threshold, evidence shows that interventions showing ICERs of up to AU$50,000 per QALY are considered cost-effective [41]. A one-way sensitivity analyses was undertaken where each of the model parameters was varied through a range of plausible values (Table 1) and changes to the base results observed. During the sensitivity analysis, the threshold values for key parameters were identified, below (or above) which the sunscreen intervention would be considered cost-effective at AU$50,000 per QALY. A probabilistic sensitivity analysis was also performed by resampling 2000 times at random from assigned probability distributions for each parameter. Log-normal distributions were used for the melanoma hazard ratio and SCC relative risk from daily sunscreen use [42], gamma distributions were used for all cost estimates, and beta distributions were used for probabilities and utility scores. Where data were unavailable, it was assumed that the relative standard deviation of the distribution was 15% of the mean, which was also tested in the sensitivity analysis.

Results

Base case

Based on the mean values of the model parameters over the participants' lifetimes, the discounted incremental cost per QALY gained from daily use of sunscreen was AU$42,600 when considering the protective effect for melanoma only. When the protective effect for SCCs was included in the model, the ICER was AU$40,900 per QALY gained (Table 2; costs and outcomes per person).

Additional outcomes (not discounted) from sunscreen use were also estimated and costs were separated as accruing to government or households based on the same number of participants in the Nambour Skin Cancer Trial (Table 3). We estimated that the program of promotion of daily sunscreen use would prevent 168 SCCs, 33 melanomas, and 4 melanoma-related deaths in the intervention group at an additional cost of AU$808,000 to society. It is estimated that if the cohort had a starting age of 25 years, the intervention would prevent 282 SCCs, 38 melanomas, and 5 melanoma-related deaths at an additional cost of AU$995,600 to society. The cohort with a starting age of 60 years may see the prevention of 119 SCCs, 26 melanomas, and 3 melanoma-related deaths at an additional cost of AU$775,500 to society.

Sensitivity analyses

The most influential model parameters on the results of the combined melanoma and SCC model were the incidence of melanoma, the hazard ratio for invasive melanoma, government and household program costs, and discount rates (Table 4, Fig. 2). Holding other parameters constant, the daily sunscreen use strategy remained cost-effective for individuals aged between 38 and 64 years, when the hazard ratio in relation to sunscreen use was no greater than 0.37 or the annual melanoma risk was at least 0.09%. Figure 3 shows the results from the probabilistic sensitivity analysis as a trade-off between increased costs and increased effectiveness and the percentage of incremental cost and effect pairings that are below a threshold of AU$50,000 per QALY. In the model of melanoma only, the likelihood that the promotion of daily sunscreen use is cost-effective was 64% (Fig. 3).

The very high ICER from the probabilistic sensitivity analysis (Table 5) is an artifact caused by the 95% CI limit of the hazard ratio for melanoma (0.97) being very close to 1, indicating no protective

Table 3 – Projected lifetime costs* and cancers for the control and intervention groups.

	Discretionary use (n = 809)	Daily use (n = 812)	Difference†
Government costs	AU$481,344	AU$1,359,922	AU$878,578
Household costs	AU$749,951	AU$679,444	(AU$70,507)‡
Time to attend skin exam§	AU$69,339	AU$74,370	AU$5031
Time to apply sunscreen‖	AU$538,712	AU$572,074	AU$33,362
Melanoma costs¶	AU$141,900	AU$33,000	(AU$108,900)
Melanomas	43	10	(33)
Melanoma deaths	5	1	(4)
SCCs	413	245	(168)

SCCs, squamous-cell carcinomas.
* Costs are discounted.
† Differences in totals are due to rounding.
‡ Figures in parentheses are cost savings.
§ Based on frequency and duration of skin examinations.
‖ Based on patient-level data of sunscreen use frequency.
¶ Based on a discounted lifetime tariff for melanoma management costs for a household.

effect. In iterations in which the sampled hazard ratio is almost 1, the incremental effect is virtually zero. When a large incremental cost is divided by a miniscule incremental effect, an extremely high ICER is the result (close to AU$100 million per QALY). The handfuls of iterations in which these numbers occur have caused the mean ICER from the probabilistic sensitivity analysis to inflate substantially. The median probabilistic sensitivity analysis ICER is much closer to the base ICER and remains cost-effective at the threshold of AU$50,000 per QALY.

Discussion

Our model suggests that an intervention that promotes frequent sunscreen use is likely to be a cost-effective investment in preventing melanomas and SCCs over a lifetime. We predict that a substantial number of melanomas and SCCs could be prevented and that the intervention is within an acceptable cost-effectiveness range for health interventions. Our results were sensitive to several key model parameters, including the incidence of melanoma, the hazard ratio of melanoma from daily sunscreen use, age of the target cohort, government and household program costs, and discount rates for costs and effects. As expected, the cost-effectiveness is improved if the incidence of melanoma or SCC increases, or the hazard ratio for melanoma or intervention costs decrease. A further finding from the sensitivity analysis was that for a cohort starting age within the range of 38 to 64 years, the strategy was within common bounds of acceptability for cost-effectiveness. Below age 38 years, the effect of discounting health outcomes reduced the current value of perceived benefits. However, when outcomes were discounted at 3.9% per year or less, the cost-effectiveness of daily sunscreen use for a cohort with a starting age of 25 years was again within the acceptable threshold.

Our findings are likely to be conservative for several reasons. Ethically, the discretionary use group could not be given a placebo sunscreen and therefore its members continued applying sunscreen at their usual discretionary frequency. However, this has meant that we have estimated the effectiveness of the intervention by using a pragmatic "real-life" scenario because it is expected that fair-skinned populations will be using sunscreen

Table 4 – One-way sensitivity and threshold values for melanoma and SCC model*.

Variable	Low	Base	High	Threshold for daily use to be cost-effective†	
				Min‡	Max§
Discount rate – effects	0%	5%	7%		5.9%
Discount rate – effects (cohort age = 20 y)	0%	5%	7%		3.9%
Utility for stable melanoma	0.5	–	1		0.986
Hazard ratio for invasive melanoma	0.08	0.27	0.97		0.371
Annual program cost per person (AU$)	30	81	120		92.80
Cohort start age (y)	25	49	75	38	64
Discount rate – costs	0%	5%	7%	3.79%	
Melanoma risk multiplier‖	0.75	1	1.25	0.865	
Risk of distant metastases multiplier‖	0	0.5	1.5	0.576	

SCC, squamous-cell carcinoma; QALY; quality-adjusted life-year.
* For parameters to which results were found to be sensitive.
† At willingness-to-pay threshold of AU$50,000 per QALY.
‡ Parameter values above which the strategy will be cost-effective.
§ Parameter values below which the strategy will be cost-effective
‖ A multiplier was used for time-dependent variables where age and risk changed annually.

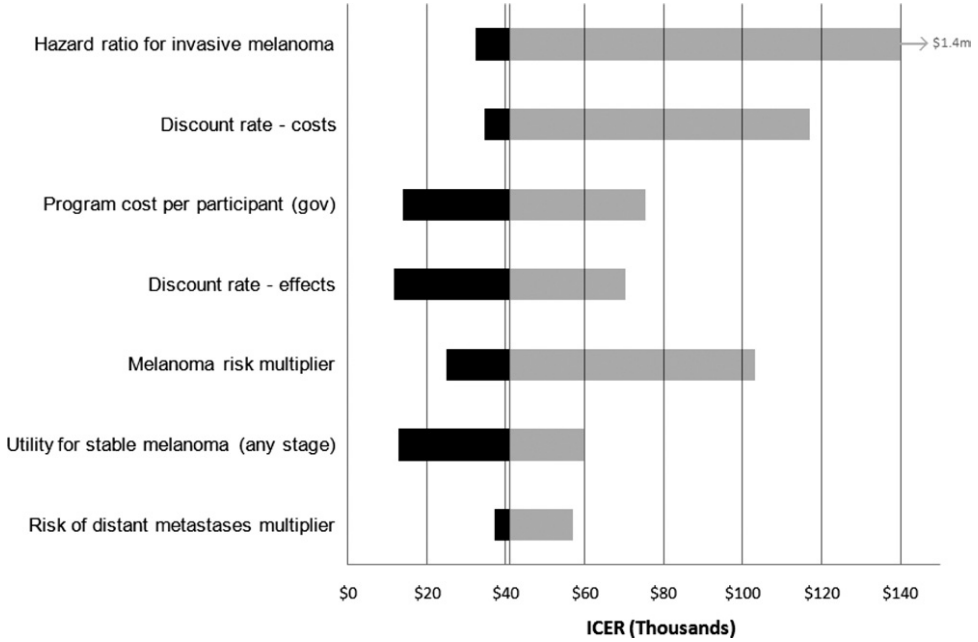


Fig. 2 – Melanoma and squamous-cell carcinoma model—variation from base ICER* with plausible range of influential parameters. gov, government; ICER, incremental cost-effectiveness ratio. *Base ICER is AU$40,890.

in some capacity. While the reduced incidence of SCC in the daily sunscreen use group was included in the model, the quality of life and mortality risk from SCC was not included because of a lack of evidence. Similarly, we took a conservative approach by omitting the potentially protective effect of sunscreen for BCCs and the known protective effect on AKs [7]. While a lower incidence of BCC during the trial was observed in the daily sunscreen use group (2474 per 100,000 person-years at risk) compared with the discretionary use group (2840 per 100,000 person-years at risk), this was not statistically significant and therefore not included in the model. In addition, the appearance of subsequent BCCs was delayed in the daily sunscreen group compared with the discretionary use group [43]. Conversely, a statistically significant protective effect of sunscreen for AKs had been observed [7], but it was omitted from the model because of the complexity of AK epidemiology and because their presence is a marker of skin cancer risk (which has already been modeled). AK distribution in the population is highly skewed, with most individuals having none and a small proportion having many. The natural history of AKs is one of multiplicity and high turnover, which makes it almost impossible to monitor their true incidence [44]. Since AKs in their own right do not represent a substantial disease burden per se, introducing AKs to the model would have had no impact on outcomes, but would have resulted in fewer treatment costs, further improving the cost-effectiveness of sunscreen.

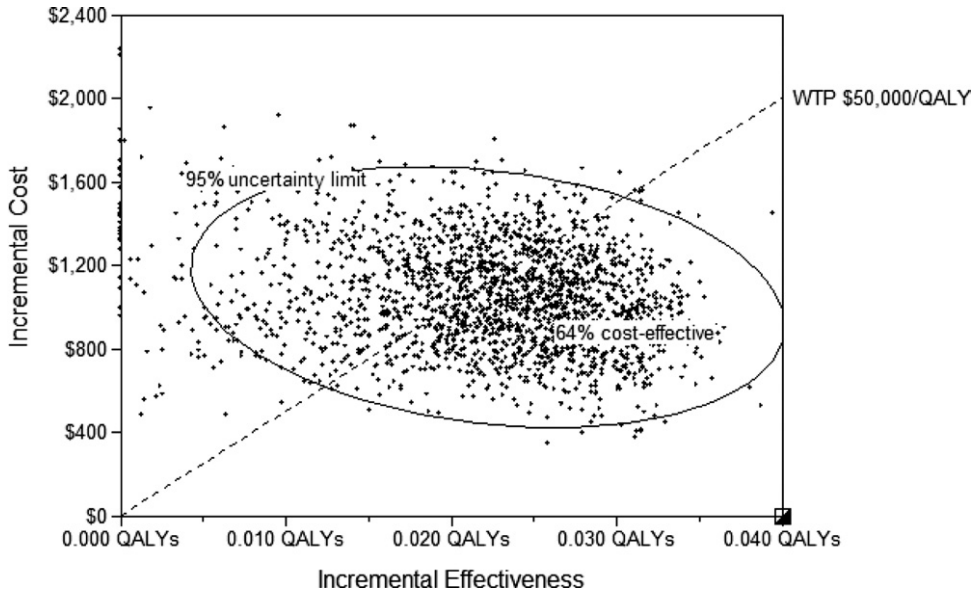


Fig. 3 – Scatter plot of probabilistic sensitivity analyses results for the melanoma and squamous-cell carcinoma model. QALY, quality-adjusted life-year; WTP, willingness to pay.

Table 5 – Incremental cost-effectiveness ratios from probabilistic sensitivity analyses.

	Mean ICER*(AU$)	95% UI (AU$)	Median ICER (AU$)
Melanoma only	724,825	15,559–312,707	43,421
Melanoma + SCC	724,702	15,318–304,839	41,717

ICER, incremental cost-effectiveness ratio; SCC, squamous-cell carcinoma; QALY, quality-adjusted life-year; UI, uncertainty interval.
* Per QALY.

It is important to note that very few QALYs were gained by the daily sunscreen use intervention, primarily because of the presentation of mostly early-stage melanomas and subsequent high survival rates of melanoma, the low incidence of melanoma relative to SCC and BCC, and the effect of discounting future benefits. Despite this marginal gain in QALYs and the conservative approach taken with respect to the above-mentioned factors, the strategy remained cost-effective. This is likely to be heavily influenced by the future costs avoided for treatment of melanomas and SCCs.

The evidence from our study suggests that regular sunscreen use is likely to provide a worthwhile investment for government in preventing skin cancer. The transformation of this single-site intervention to a population-wide policy will have implications for the measurement and attribution of costs. For example, the modeled intervention provided free sunscreen for participants, which is not practicable for a population-wide policy; however, evidence suggests that the cost of purchasing sunscreen is only a minor factor in explaining lower sunscreen use [45]. As such, there would be some cost shifting from the government to households for the purchase of sunscreen, although the cost-effectiveness of the strategy should not be affected significantly. The administration involved with the follow-up for and provision of regular skin examinations for trial participants is another component of the trial that would not be practicable to expand to a state or national level. Therefore, it is likely that a population-wide intervention is likely to cost less per person. At the very least, our findings provide clear support for targeted sunscreen-promotion interventions, such as the Nambour Skin Cancer Trial, at a local level. The results from this study also suggest that state or national interventions that result in moderate increases in sunscreen use may also be cost-effective. In the United Kingdom, a country with a substantially lower skin cancer incidence than Australia, the National Institute for Clinical Excellence has issued public health guidance recommending increased use of sunscreen at school and work to prevent skin cancer [46].

Prior to the publication of Green et al.[26], evidence supporting sunscreen's protective effect from melanoma was inconsistent [47], and some considered the precautionary principle an appropriate rationale for recommending the use of sunscreen [48]. Together with the more recent evidence of sunscreen's effectiveness [26] and safety [49], this study adds an economic aspect and insights by demonstrating that it is also cost-effective. Our study has several drawbacks, however. First, much of UVR exposure is thought to occur early in life [50], and so sun protection in younger cohorts may be more effective in the long term [10], but this is not reflected in our results because of discounting of outcomes. This is a common bias against preventive measures that realize benefits later in life. Including an evidence-based estimate of the lag between UVR exposure and carcinogenesis may offset this bias to some extent. Evidence that sun-protection behaviors in later life have a beneficial effect remains nonetheless [51]. Second, as with all economic decision models, a number of simplifications and assumptions were necessary. Although we have justified and explicitly documented these assumptions, a level of uncertainty remains and reflects the evidence gaps in the etiology of skin cancer development. Further evidence is required to consolidate the long-term protective effects of sunscreen. Finally, our model has not addressed the issue of the adequacy of UV exposure with regular sunscreen use in relation to vitamin D production [52]. There is evidence, however, that vitamin D deficiency is not induced by regular sunscreen use [53] and deficiency primarily occurs in the elderly, or in dark skinned or obese people for reasons unrelated to sunscreen use [54].

To the best of our knowledge, with the exception of our earlier work on BCC and SCC prevention [21], only one research group has investigated the cost-effectiveness of skin cancer prevention through a widespread, multifaceted sun protection campaign [55,56]. The study performed a modeling analysis of investment in the SunSmart program involving a suite of public education strategies (media, school accreditation, structural and environmental changes across workplace and sport settings). Although the overall cost-effectiveness of sun protection was also clearly established by Shih et al. [55], our study is different in that we rely on patient-level data from a pragmatic randomized trial and have undertaken a more micro assessment of costs including the additional costs of managing suspicious benign lesions. Unlike Shih et al's [55] study, we observe a stronger link between the intervention and health outcomes but do not incorporate the widespread health-promoting approaches of SunSmart. The two studies, however, are very complementary in providing sound economic support for sun-protection investments.

Conclusions

The incidence of skin cancer, including melanoma, is a serious public health concern causing substantial losses in quality of life and mortality. Based on estimated costs and benefits of daily sunscreen use with data from a pragmatic randomized controlled trial, our study provides assurance that promoting the use of sunscreen is likely to be a cost-effective investment for governments and households over the long term. Our findings provide support for continued government investment in sun-protection campaigns for populations in high-sunlight conditions to encourage sunscreen use for protection from intense UV exposure.

Acknowledgments

Source of financial support: No financial or other support was provided for the manuscript.

REFERENCES

[1] National Cancer Institute. Melanoma. 2010. Available from: http://www.cancer.gov/cancertopics/types/melanoma. [Accessed October 13, 2010].
[2] Australian Institute of Health and Welfare. Australian Cancer Incidence and Mortality Books. Canberra, Australia: Australian Institute of Health and Welfare, 2010.
[3] Australian Institute of Health and Welfare. Health system expenditures on cancer and other neoplasms in Australia, 2000-01. AIHW Cat. No. HWE 29. In: Health and Welfare Expenditure Series No. 22. Canberra, Australia: Australian Institute of Health and Welfare, 2005.

[4] Housman TS, Feldman SR, Williford PM, Fleischer AB, et al. Skin cancer is among the most costly of all cancers to treat for the Medicare population. J Am Acad Dermatol 2003;48:425–9.
[5] Staples MP, Elwood M, Burton RC, Williams JL, et al. Non-melanoma skin cancer in Australia: the 2002 national survey and trends since 1985. Med J Aust 2006;184:6–10.
[6] Holmes C, Foley P, Freeman M, Chong A. Solar keratosis: epidemiology, pathogenesis, presentation and treatment. Australas J Dermatol 2007;48:67–74.
[7] Darlington S, Williams G, Neale R, Frost C, Green A. A randomized controlled trial to assess sunscreen application and beta carotene supplementation in the prevention of solar keratoses. Arch Dermatol 2003;139:451–5.
[8] Neidecker MV, Davis-Ajami ML, Balkrishnan R, Feldman SR. Pharmacoeconomic considerations in treating actinic keratosis. Pharmacoeconomics 2009;27:451–64.
[9] Young C. Solar ultraviolet radiation and skin cancer. Occup Med (Lond) 2009;59:82–8.
[10] Whiteman DC, Whiteman CA, Green AC. Childhood sun exposure as a risk factor for melanoma: a systematic review of epidemiologic studies. Cancer Causes Control 2001;12:69–82.
[11] US Preventive Services Task Force. Screening for skin cancer, recommendations and rationale. Am J Prev Med 2001;20:44–6.
[12] National Radiological Protection Board UK. Health Effects from Ultraviolet Radiation: Report of an Advisory Group on Non-Ionising Radiation. 2008.
[13] Cancer Council Australia and Australasian College of Dermatologists. Position statement: screening and early detection of skin cancer. 2007. Available from: http://www.cancer.org.au/policy/positionstatements/sunsmart/screeningandearlydetectionofskincancer.htm. [Accessed September 3, 2010].
[14] Thompson SC, Jolley D, Marks R. Reduction of solar keratoses by regular sunscreen use. N Engl J Med 1993;329:1147–51.
[15] Green A, Williams G, Neale R, Hart V, et al. Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. Lancet 1999;354:723–9. Erratum: Lancet 1999;354:1038.
[16] Australian Institute of Health and Welfare (AIHW) and Australasian Associations of Cancer Registries (AACR). Cancer in Australia: an overview 2006. In: Cancer Series No. 37. Canberra, Australia: Australian Institute of Health and Welfare, 2007.
[17] Lucas RM, Repacholi MH, McMichael AJ. Is the current public health message on UV exposure correct? Bull World Health Organ 2006;84:485–91.
[18] Montague M, Borland R, Sinclair C. Slip! Slop! Slap! and SunSmart, 1980–2000: skin cancer control and 20 years of population-based campaigning. Health Educ Behav 2001;28:290–305.
[19] Coory M, Baade P, Aitken J, Smithers M, et al. Trends for in situ and invasive melanoma in Queensland, Australia, 1982–2002. Cancer Causes Control 2006;17:21–7.
[20] Linder JA, Tice JA. Betacarotene and sunscreen use. Lancet 1999;354:2164.
[21] Gordon LG, Scuffham PA, Van der Pols JC, McBride P, et al. Regular sunscreen use is a cost-effective approach to skin cancer prevention in subtropical settings. J Invest Dermatol 2009;129:2766–71.
[22] Neale RE, Green AC. Measuring behavioral interventions by questionnaires and prospective diaries: an example of sunscreen use. Epidemiology 2002;13:224–7.
[23] Neale RE, Williams G, Green AC. Application patterns among participants randomized to daily sunscreen use in a skin cancer prevention trial. Arch Dermatol Res 2002;138:1319–25.
[24] Green AC, Battistutta D, Hart V, Leslie D, et al. The Nambour Skin Cancer and Actinic Eye Disease Prevention Trial: design and baseline characteristics of participants. Contr Clin Trials 1994;15:512–22.
[25] van der Pols JC, Williams GM, Pandeya M, Logan V, Green AC, et al. Prolonged prevention of squamous cell carcinoma of the skin by regular sunscreen use. Cancer Epidemiol Biomarkers Prev 2006;15:2456–8.
[26] Green AC, Williams GM, Logan V, Strutton GM. Reduced melanoma after regular sunscreen use: randomized trial follow-up. J Clin Oncol 2011;29:257–63.
[27] Weinstein MC, O'Brien BJ, Hornberger J, Jackson J, et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR task force on good research practices—modeling studies. Value Health 2003;6:9–17.
[28] American Joint Committee on Cancer. Cancer Staging Manual. NY: Springer Publishing, 2002.
[29] AIHW. Cancer incidence data cubes. Cancer Series 2009. Available from: http://www.aihw.gov.au/cancer/data/datacubes/index.cfm. [Accessed May 23, 2009].
[30] Ferrone CR, Porat LB, et al. Clinicopathological features of and risk factors for multiple primary melanomas. JAMA 2005;294:1647–54.
[31] Balch CM, Soong S-J, Gershenwald JE, Thompson JF, et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. J Clin Oncol 2001;19:3622–34.
[32] Australian Bureau of Statistics. Life Tables, Australia, 2003 to 2005. Canberra, Australia: Australian Bureau of Statistics, 2007.
[33] Bendeck S, Hadley JC, Bonaccorsi P, Brown KM, et al. Can melanoma patients predict the quality of life impact of an alternate melanoma stage?In: CEA: Methods and Applications: Health Services Research. Atlanta: Society for Medical Decision Making, 2004.
[34] Beusterien KM, Ackerman SJ, Plante K, Glaspy J, et al. The health-related quality-of-life impact of histamine dihydrochloride plus interleukin-2 compared with interleukin-2 alone in patients with metastatic melanoma. J Support Oncol 2003;11:304–12.
[35] Kilbridge KL, Weeks JC, Sober AJ, Haluska FG, et al. Patient preferences for adjuvant interferon alfa-2b treatment. J Clin Oncol 2001;19:812–23.
[36] Stratton KR, Durch JS, Lawrence RS. Vaccines for the 21st Century: A Tool for Decision Making. Washington, DC: National Academy Press, 2000.
[37] Morton RL, Howard K, Thompson JF. The cost-effectiveness of sentinel node biopsy in patients with intermediate thickness primary cutaneous melanoma. Ann Surg Oncol 2009;16: 929–40.
[38] Access Economics. Cost of Cancer in NSW. Kings Cross, Australia: The Cancer Council NSW, 2007.
[39] Hillner BE, Kirkwood JM, Atkins MB, Johnson ER, et al. Economic analysis of adjuvant interferon alfa-2b in high-risk melanoma based on projections from Eastern Cooperative Oncology Group 1684. J Clin Oncol 1997;15:2351–8.
[40] Australian Bureau of Statistics. 2010. Available from: http://www.abs.gov.au/. [Accessed March 11, 2010].
[41] Harris AH, Hill SR, Chin G, et al. The role of value for money in public insurance coverage decisions for drugs in Australia: a retrospective analysis 1994–2004. Med Decis Making 2008;28:713–22.
[42] Briggs AH, Claxton K, Sculpher MJ. Decision modelling for health economic evaluation. In: Gray A, Briggs AH, eds., Handbooks in Health Economic Evaluation Series. Oxford: Oxford University Press, 2006.
[43] Pandeya N, Purdie DM, Green AC, Williams G, et al. Repeated occurrence of basal cell carcinoma of the skin and multifailure survival analysis: follow-up data from the Nambour Skin Cancer Prevention Trial. Am J Epidemiol 2005;161:748–54.
[44] Frost C, Williams G, Green A. High incidence and regression rates of solar keratoses in a Queensland community. J Invest Dermatol 2000;115:273–7.
[45] Neale R, Williams G, Green A. Applications patterns among participants randomized to daily sunscreen use in a skin cancer prevention trial. Arch Dermatol 2002;138:1319–25.
[46] Mayor S. NICE recommends greater use of sunscreens at school and work to prevent skin cancer. BMJ 2010;341:c4641.
[47] International Agency for Research on Cancer. Handbooks of Cancer Prevention, Vol. 5: Sunscreens. Lyon, France: International Agency for Research on Cancer, 2001.
[48] Diffey BL. Sunscreens as a preventative measure in melanoma: an evidence-based approach or the precautionary principle? Br J Dermatol 2009;161(Suppl. 3):25–7.
[49] Lautenschlager S, Wulf HC, Pittelkow MR. Photoprotection. Lancet 2007;370:528–37.
[50] Wright CY, Reeder AI. Youth solar ultraviolet radiation exposure, concurrent activities and sun-protective practices: a review. Photochem Photobiol 2005;81:1331–42.
[51] McBride P. Cutaneous squamous cell carcinoma and its determinants, in School of Population Health [thesis]. Brisbane, Australia: University of Queensland, 2009.
[52] Grant WB, Cross HS, Garland CF, Gorham ED, et al. Estimated benefit of increased vitamin D status in reducing the economic burden of disease in western Europe. Prog Biophys Mol Biol 2009;99:104–13.
[53] Norval M, Wulf HC. Does chronic sunscreen use reduce vitamin D production to insufficient levels? Br J Dermatol 2009;161:732–6.
[54] Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266–81.
[55] Shih ST, Carter R, Sinclair C, Mihalopoulos C, Vos T. Economic evaluation of skin cancer prevention in Australia. Prev Med 2009;49:449–53.
[56] Carter R, Marks R, Hill D. Could a national skin cancer primary prevention campaign in Australia be worthwhile? An economic perspective. Health Promot Inter 1999;14:73–81.