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A Modeling Study of the Cost-Effectiveness of a Risk-Stratified Surveillance Program for Melanoma in the United Kingdom

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ABSTRACT

Background: Population-wide screening for melanoma is unlikely to be cost-effective. Nevertheless, targeted surveillance of high-risk individuals may be. **Objectives:** To estimate the cost-effectiveness of various surveillance strategies in the UK population, stratified by risk using a simple self-assessment tool scoring between 0 and 67. **Methods:** A decision model comparing alternative surveillance policies from the perspective of the UK National Health Service over 30 years was developed. The strategy with the highest expected net benefit for each risk score was identified, resulting in a compound risk-stratified policy describing the most cost-effective population-wide strategy. The overall expected cost and quality-adjusted life-years (QALYs), the incremental cost-effectiveness ratio, and associated uncertainty were reported. **Results:** The most cost-effective strategy is for those with a Williams score of 15 to 21 (relative risk [RR] of 0.79–1.60 vs. a mean score of 17 in the United Kingdom) to be offered a one-off full-body skin examination, and for those with a score of 22 or more (RR 1.79+) to be enrolled into a quinquennial monitoring program, rising to annual recall for those with a risk score greater than 43 (RR 20.95+). Expected incremental cost would be £164 million per annum (~0.1% of the National Health Service budget), gaining 15,947 additional QALYs and yielding an incremental cost-effectiveness ratio of £10,199/QALY gained (51.3% probability <£30,000). **Conclusions:** The risk-stratified policy would be expensive to implement but cost-effective compared with typical UK thresholds (£20,000–£30,000/QALY gained), although decision uncertainty is high. Phased implementation enrolling only higher risk individuals would be substantially less expensive, but with consequent foregone health gain.

Keywords: cost-effectiveness, decision modeling, economic evaluation, melanoma, screening.

Introduction

Approximately 14,500 new cases of malignant melanoma are diagnosed and approximately 2,600 deaths occur in the United Kingdom every year [1]. Early detection is critical: 90% of patients survive for 5 or more years, but this falls to 25% of women and less than 10% of men with metastatic disease at diagnosis [1]. The cost of treating metastatic melanoma far outweighs the cost of treating primary melanoma, and the relative increase has risen sharply with the recent introduction of several high-cost drugs that palliate for the most part. For example, nivolumab costs approximately £70,000 per patient per year for an additional gain of 1.3 quality-adjusted life-years (QALYs) compared with dacarbazine [2]. Screening programs are therefore of increasing relevance. The UK National Screening Committee has not formally reviewed whether a program for melanoma would be an efficient use of public funds [3]. Nevertheless, existing evidence suggests such a program would have difficulty identifying the target population [4], raises concerns about whether a comprehensive program could be cost-effective [5], and cites lack of evidence on the cost-effectiveness of full-body skin examination (FBSE), except in those with a history of melanoma [6].

Two recent systematic reviews [7,8] concluded that although skin cancer prevention initiatives are highly cost-effective [7], there is a lack of evidence on the cost-effectiveness of early detection programs [7], and future research should focus on targeted screening/surveillance in high-risk populations [8]. On the basis of this, the US Preventive Services Task Force (2016) reiterated its previous recommendation [9] that the "current evidence is insufficient to assess the balance of benefits and harms of visual skin examination … to screen for skin cancer in adults" [10].

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Several tools have been developed to enable identification of higher risk individuals [11]. One of the better performing was developed from a case-control study in the United States by Williams et al. [12]. It is a self-assessed clinical risk estimation model not requiring expert FBSE that, in a split-sample validation population, had an area under the receiver operator characteristic curve of 0.70 (95% confidence interval 0.64–0.77) and was able to identify 15% of the population in whom 50% of melanomas would be expected to develop [12]. We have recently shown that it is both feasible and acceptable to collect data on the risk of melanoma in the waiting rooms of UK family practices and that using the Williams model produces a distribution of risk in the attending population, which allows identification of subgroups at different levels of risk [13].

The purpose of this study was to establish whether using the Williams model and resulting score to risk-stratify the population and guide future management is a cost-effective approach to reducing mortality and morbidity from melanoma in a UK setting. Key to this is determining the risk score at which it is most cost-effective to enroll patients into a surveillance program. If the score is set too low, primary care capacity will be absorbed examining patients with an extremely low risk of melanoma at the expense of other patients with a greater capacity to benefit. If set too high, then patients will be falsely reassured and any benefits in terms of reduced melanoma morbidity and mortality will be foregone. Specifically, therefore, this study aimed to identify the optimal cutoff scores from the Williams self-assessment tool [12] at which users are recommended to either 1) visit their primary care practitioner for a one-off FBSE or 2) be entered into a routine primary care–based monitoring program, and if so, 3) the optimal frequency of visits, ranging from 5-yearly to annually.

Methods

We substantially adapted and modified a decision model we previously developed for a novel diagnostic aid for melanoma [14]. The adapted model was a patient-level simulation following a simulated cohort of participants (UK general public) one by one. Uncertainty was propagated through the model via Monte-Carlo simulation (distributions of parameters are specified in Table 1). The code was written in R (R Foundation for Statistical Computing, Vienna, Austria) [15–17] and run on the University of Cambridge High Power Cluster computing facility. The code is available on request from the corresponding author. Ethical approval was not required for this study.

The Williams Self-Assessment Tool

The scenarios we model focus on the Williams self-assessment tool (Appendix 1) [12]. This is a rapid questionnaire comprising eight questions on sex, age, hair color, density of freckles, history of severe sunburn in childhood and adolescence, number of raised moles on the arms, and history of nonmelanoma skin cancer yielding a summary score between 0 (lowest risk) and 67.

Model Definition

The model comprises two modules: natural history and clinical (Fig. 1). The link between the two is determined by the comparator policies, described later. Cohorts of a given age, sex, and Williams score [12] are simulated. In year 0, the distribution of prevalent melanomas and their disease stages in each cohort is estimated on the basis of UK prevalence data and stage at diagnosis [18,19] adjusted for risk score. The natural history module is a Markov-like model and simulates patients' trajectories over a period of 30 years: each year patients are at risk of new melanomas developing according to UK incidence by age and sex [19] adjusted for risk score [12], and undiagnosed (and hence untreated) melanomas progress according to estimated rates of progression [20]. When the model determines that contact is made with the health service, the simulated patient "breaks out" of the natural history module into the clinical module, which has a decision-tree structure. Once reaching a terminal node of the decision tree, the patient is returned to the natural history module.

Natural history module

Cutaneous melanoma is categorized into four main types (superficial spreading, lentigo maligna, acral lentiginous, and nodular) [21], each with nine stages of invasion (stages 1a–4) plus an in situ stage for all except nodular melanoma (which is by definition invasive) [22]. We assumed that invasive disease would progress at the same rate irrespective of primary melanoma subtype, but allowed the rate of progression from in situ disease to vary by subtype, yielding a total of 12 discrete stages describing the disease. The model also included "no melanoma" and "dead" health states. The overall prevalence of undiagnosed melanoma in the community in year 0 was estimated at 0.162%, assumed the same as that observed in a population screening study in Northern Germany [18] (review details are given in Appendix 2). This was distributed according to risk score by combining with UK-relevant epidemiological data [12,19,23,24]. The parameters of the resulting risk function are presented in Table 1. The annual incidence was estimated using an analogous approach. Full details are provided in Appendix 3.

Data on the rate of progression of untreated melanoma do not exist and it would be most unethical to conduct a prospective cohort study to establish this empirically. Therefore, data were elicited from a representative group of experts in melanoma [20] (Table 1; Appendix 4). Age- and sex-specific background and melanoma-specific mortality data were extracted from UK life tables [25] (Appendix 5) adjusted for the odds ratio [22] (Appendix 6).

Clinical module

The clinical module describes the patient pathway after health service contact (Fig. 1). The model allows two ways for patients to present in primary care: of their own initiative with a mole that they are concerned about or because they have been advised to do so after a risk assessment. Any suspicious moles are inspected during an FBSE by a primary care practitioner, and the patient is either referred to secondary care or discharged. Figure 1 (right-hand side) illustrates the pathway; the natural history component of the model will have determined whether a patient is healthy (D–) or has melanoma (D+). For a patient with a melanoma, the probability of the primary care practitioner identifying it and referring a patient to secondary care is the sensitivity of the practitioner, denoted $P(T+|D+)$, and is based on data from the control arm of a recent study of a diagnostic aid in primary care [26]. Likewise, the probability of correctly discharging a patient without melanoma is the specificity (denoted $P(T-|D-)$ in Fig. 1) extracted from the same source. Data are summarized in Table 1.

Patients with melanoma correctly referred (true positives, with probability $P(T+|D+)$) receive appropriate treatment according to disease stage ($D\&T_{stage}$ in Fig. 1; see the "Costs" section later for details). They are then flagged as having a history of melanoma and are at risk of mortality as described in the natural history module (data based on stage-specific prognosis postdiagnosis [22]). Patients with melanoma who are