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A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Screening for Skin Cancer

L. From, L. Marrett, C. Rosen, C. Zwaal, M. Johnston, K. Bak, G. Sibbald, J. Fong, and V. Mai

Report Date: June 19, 2007

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Section 1: Clinical Practice Guideline
Section 2: Systematic Review
Section 3: Guideline Development and External Review - Methods and Results

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Evidence-based Series #15-1: Section 1

Screening for Skin Cancer: A Clinical Practice Guideline

L. From, L. Marrett, C. Rosen, C. Zwaal, M. Johnston, K. Bak, G. Sibbald, J. Fong, and V. Mai

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Questions

1. Should primary care providers routinely perform total-body skin examination on members of the general population to screen for melanoma, basal cell carcinoma, and squamous cell carcinoma of the skin?
2. Should primary care providers routinely counsel members of the general population to perform skin self-examination for early detection of melanoma, basal cell carcinoma, and squamous cell carcinoma of the skin?
3. Should individuals at high risk for melanoma, basal cell carcinoma, and squamous cell carcinoma of the skin be offered surveillance by a physician, including total-body skin examination and counselling to perform skin self-examination?
4. What characteristics should clinicians assess in order to determine risk for melanoma, basal cell carcinoma, and squamous cell carcinoma of the skin?

Recommendations

Very limited evidence was available to inform the following recommendations on screening. No prospective studies have evaluated the impact of screening on survival, quality of life, or morbidity from treatment for skin cancer nor are there data on the adverse effects of screening for skin cancer. As experts in the treatment and epidemiology of skin cancer, the guideline panel members were aware that some individuals are at increased risk for skin cancer because of personal characteristics or history. They reviewed key papers on risk and identified groups of patients who might be expected to benefit from increased surveillance for skin cancer. Separate recommendations are offered for two groups at increased risk (very high risk and high risk) and the general population.

Very high risk of skin cancer

- Individuals with <u>any</u> of the following risk factors have a <u>very high risk</u> of skin cancer (approximately 10 or more times the risk of the general population):
  - on immunosuppressive therapy after organ transplantation,
  - a personal history of skin cancer,
  - two or more first-degree relatives with melanoma,

- more than 100 nevi in total or 5+ atypical nevi,
- have received more than 250 treatments with psoralen-ultraviolet A radiation (PUVA) for psoriasis
- received radiation therapy for cancer as a child

Individuals at very high risk should be identified by their primary health care provider and offered total body skin examination by a dermatologist or a trained health care provider on a yearly basis. They should also be counselled about skin self-examination and skin cancer prevention by a health care provider (e.g., physician, nurse practitioner, or public health nurse). In the case of childhood cancer survivors, the site of radiation therapy should be monitored.

High risk of skin cancer

- Individuals with two or more of the main identified susceptibility factors are at a high risk for skin cancer (roughly 5 times the risk of the general population):
  - a first-degree relative with melanoma,
  - many (50-100) nevi,
  - one or more atypical (dysplastic) nevi,
  - naturally red or blond hair,
  - a tendency to freckle,
  - skin that burns easily and tans poorly or not at all

  Other factors that may influence the risk of skin cancers that are environmental include an outdoor occupation, a childhood spent at less than latitude 35^0, the use of tanning beds during teens and twenties, and radiation therapy as an adult.

  Individuals at high risk should be identified by their primary health care provider and counselled about skin self-examination (specifically focused on the site of radiation for those having had therapeutic radiation) and skin cancer prevention by a health care provider (e.g., physician, nurse practitioner, or public health nurse). High-risk individuals should be seen once a year by a health care provider trained in screening for skin cancers.

The general population not at increased risk of skin cancer

- There is at this time no evidence for or against skin cancer screening of the general population at average risk of developing skin cancer.
- Based on the limited evidence available at present, routine total body skin examination by primary care providers is not recommended for individuals at average or low risk for skin cancer (i.e., those not included in the increased risk groups described above).
- Based on the limited evidence available at present, routine counselling on skin self-examination by primary care providers is not recommended for individuals at average or low risk for skin cancer.

Key Evidence

(Please see Section 2 for the complete systematic review of the evidence conducted by the Skin Cancer Screening Guideline Panel)

- The guideline panel reviewed three evidence-based guidelines on screening for skin cancer (1-3), results from a pilot randomized controlled trial of a community-based screening program, a comparative cohort study of work-place screening and a case-control study of skin self-examination.

- The pilot phase of a randomized trial demonstrated the feasibility of implementing a screening program consisting of community education, general practitioner education and screening clinics to promote self-screening and whole-body screening by general practitioners. Early results detected an increase in the percentage of subjects reporting whole-body skin examination by a physician (4).
- The randomized trial and the work-place screening study both found that people were more likely to perform skin self-examination if they had undergone a whole-body skin examination by a physician (4,5).
- A case-control study detected the reduced risk of melanoma and reduced mortality from melanoma associated with skin self-examination (6).
- Epidemiologic studies have found that people who have any of the following characteristics have a very high risk of developing skin cancer: on immunosuppressive therapy after organ transplantation, a personal history of skin cancer, two or more first-degree relatives with melanoma, more than 100 nevi in total or 5+ atypical nevi, have received more than 250 treatments with PUVA for psoriasis, or received radiation therapy for cancer in childhood. The risk of skin cancer is more than 10 times higher in these individuals than in the general population.
- There are other factors associated with significant but lower relative risks (roughly 5 times the risk of the general population for multiple susceptibility factors), such as a first-degree relative with melanoma, many (50-100) nevi, one or more atypical (dysplastic) nevi, naturally red or blond hair, a tendency to freckle, or skin that burns easily and tans poorly or not at all**.** Because risk is assumed to be multiplicative, overall risk can be estimated from the products of the relative risk associated with each factor present in an individual. Those who have two or more of the high-risk traits have a higher than average risk of developing skin cancer.

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Evidence-based Series #15-1: Section 2

Screening for Skin Cancer: A Systematic Review

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INTRODUCTION

The skin is the most common site of cancer in humans. With an estimated 72,500 new cases to be diagnosed in Canada in 2006, skin cancer of all types makes up about one third of all cancers (1). The three most common types usually referred to by the term “skin cancer” are basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma. Of the total estimated cases, the vast majority will be BCC and SCC (approximately 68,000) and 4,500 will be melanomas (1). Among cancer sites, skin cancer ranks fifth in health care costs among the Medicare population in the United States (2). In Ontario, data are available from the Ontario Cancer Registry on melanoma cases and deaths but not on BCC or SCC (1). In the year 2006, an estimated 1,910 new cases of melanoma will be diagnosed, and 430 people will die from melanoma in Ontario. By extension of the national estimates, about 28,000 Ontarians will be diagnosed with basal or squamous cell carcinoma in 2006 (1).

Melanoma is a cancer that affects younger people. A higher proportion of individuals with melanoma are diagnosed under the age of 50 compared to the most common cancers. The incidence of melanoma has increased by an average of 2.4% in men and 1.8% in women each year between 1992 and 2001. This increase has been postulated to be primarily related to increased ultraviolet radiation exposure but may also be due to improved detection in recent years. Mortality rates in men have also increased by an average of 1.3% annually during this

time period but have declined in women (-0.5%) (1). Data on the incidence and mortality for other types of skin cancer are not available for Ontario, but increases in rates would likely be consistent with those for melanoma. While BCC and SCC cause limited mortality, they can result in substantial morbidity.

The thickness of a melanoma at diagnosis is a key prognostic indicator, as it is a determinate of the stage of cancer and clinical outcome (3). By detecting disease early, screening aims to decrease the number of deaths from skin cancer—in particular, melanoma—and the morbidity associated with the treatment of more advanced basal or squamous cell carcinoma. Early detection manoeuvres include skin self-examination and total body skin examination by health care professionals. The relative ease of carrying out visual skin examinations makes screening for skin cancer a candidate for secondary skin cancer prevention.

Advice on early detection is often incorporated into skin cancer prevention campaigns and events for the public, but current practice in Ontario is variable across campaigns and physicians. Although several guidelines have been developed by other groups, recommendations and the populations addressed are not consistent among the guidelines. Some guidelines address screening for the general population and others only those at high risk for skin cancer. The Screening Guidelines Steering Committee of Cancer Care Ontario's Program in Evidence-based Care (PEBC) identified the need for a review of the existing guidelines and primary evidence on skin cancer screening so that evidence-based recommendations could be developed to guide clinicians and health educators in Ontario.

METHODS

This draft report was developed by the PEBC, using the methods adapted from the Practice Guidelines Development Cycle (4). Published practice guidelines from other guideline-development groups and supplementary evidence were selected and reviewed by four members (LM, LF, VM, CR) of the PEBC Skin Cancer Screening Guideline Panel. The panel included dermatologists, a family physician, an epidemiologist, and Cancer Care Ontario's Acting Vice-President, Preventive Oncology.

This guideline report is an up-to-date source of the best available evidence on screening for skin cancer, developed through the systematic review and synthesis of the evidence. The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

Literature searching was conducted in three stages.

Stage 1: Clinical Practice Guidelines

For the first stage, the following Web sites were searched in February 2003 and August 2006 to locate existing practice guidelines published in English: Guideline Advisory Committee (http://gacguidelines.ca/), Canadian Medical Association Infobase of Clinical Practice Guidelines (http://mdm.ca/cpgsnew/cpgs/), National Guideline Clearinghouse (http://www.guideline.gov/), MEDLINE (Ovid, 1996-August 2006), National Comprehensive Cancer Network (http://www.nccn.org/), National Institute for Clinical Excellence (http://www.nice.org.uk/), American Society of Clinical Oncology (http://www.asco.org/), Scottish Intercollegiate Guidelines Network (http://www.sign.ac.uk/), Canadian Dermatology Association (http://www.dermatology.ca/), and the American Academy of Dermatology (http://www.aad.org/). The text of each guideline report was scanned for references to other guidelines.

Stage 2: Primary Evidence on Screening for Skin Cancer

The second stage was a search for systematic reviews and studies of skin cancer screening published between 1999 and August 2006. The search was conducted to find evidence published after the completion of the most recent evidence-based screening guideline found by the search above (5,6). Sources searched included MEDLINE (Ovid), EMBASE (Ovid), and the Cochrane Library (2006, Issue 3). Separate searches were conducted for systematic reviews and primary studies (clinical trials, prospective cohort studies, or case-control studies). Individual search strategies were devised for each database, using text words and subject headings such as "skin neoplasms", "skin", "cancer", "carcinoma", "squamous", "basal", "melanoma", "mass screening", "physical examination", "self examination", and 'skin examination".

Stage 3: Risk Factors for Skin Cancer

MEDLINE, EMBASE, and personal files were searched for recent reviews and key studies on risk factors for skin cancer.

Study Selection Criteria

Inclusion Criteria

Clinical Practice Guidelines

To be considered for inclusion as evidence-based clinical practice guidelines, guideline reports were required to:

- contain explicit recommendations about screening for skin cancer with total body skin examination or skin self-examination;
- document a systematic review of the literature;
- list references for the evidence considered.

Primary Evidence on Screening for Skin Cancer

Studies were eligible for the evidence review if they:

- were clinical trials with an intervention and control group (randomized or non-randomized), comparative cohort studies, or case-control studies,
- evaluated screening using total body skin examination or skin self-examination,
- included members of the general population or individuals at increased risk of skin cancer,
- screened for melanoma, basal cell carcinoma, or squamous cell carcinoma of the skin.

Ideally, guideline recommendations would be based on evidence from randomized controlled trials. In the absence of randomized trials, other types of comparative studies were included. For screening manoeuvres without evidence from comparative studies, prospective single-cohort studies were considered.

Risk Factors for Skin Cancer

A comprehensive systematic review of the evidence on risk factors for skin cancer was beyond the scope of this guideline report. Instead, the panel summarized quantitative evidence available from published reviews and key primary studies.

Exclusion Criteria

- Abstracts, letters and editorials were not eligible for inclusion in the systematic review of the evidence.

- Literature searches for primary studies on screening were not restricted by language, but searches for guidelines and information about risk factors were restricted to papers published in English.

Synthesizing the Evidence

Data from screening studies were not pooled quantitatively. Only three comparative studies were found, and they had different designs, interventions, and primary outcome variables (7-9).

RESULTS

Literature Search Results

Three evidence-based practice guidelines summarized the literature on screening up to the end of 1999 (5,10,11). At that time, there were no published randomized trials and only one comparative study of screening—a case-control study of the association between skin-self examination and mortality (9). It is possible that papers indexed exclusively in databases other than MEDLINE, such as EMBASE, may have been missed, but the panel is not aware of any additional studies published before 1999. Update searches found two additional comparative studies (7,8).

Outcomes

Published Practice Guidelines

In February 2003, practice guidelines on skin cancer screening were available from 15 organizations. Only three of these were eligible for further review by the guideline panel (5,10,11). Of the remaining guidelines, ten were not explicitly based on systematic reviews of the evidence, and one, although listed on the Guidelines Advisory Committee (GAC) Web site as a skin cancer screening guideline, was judged by the panel to be a systematic review of diagnostic aids for differentiating between a mole and a melanoma and did not contain recommendations (12). The GAC is sponsored by the Ontario Ministry of Health and Long-Term Care and the Ontario Medical Association to promote evidence-based health care in Ontario by reviewing and endorsing practice guidelines. Based on an evaluation using the AGREE (Appraisal of Guidelines for Research & Evaluation) instrument (13), GAC recommended the U.S. Task Force Guideline for use in Ontario (5).

Screening guidelines from Canada (10), the United States (5), and Australia (11) were based on evidence located by searching MEDLINE and reviewing reference lists. The Canadian and Australian guidelines did not report eligibility criteria for selecting studies to include in their evidence reviews (10,11). The U.S. guideline included studies that reported data on "yield of screening, screening tests, risk factors, risk assessment, effectiveness of early detection, or cost-effectiveness" and excluded studies in patients with familial atypical mole and melanoma syndrome (5,6). Please see Appendix A where the recommendations made in the three guidelines summarized below are compared.

Canadian Guideline (1994)

A guideline from the Canadian Task Force on Preventive Health Care (10) made the following recommendations:

- Routine screening for skin cancer by primary care providers is not recommended for the general population.
- For individuals with significantly increased risk (familial melanoma syndrome and first-degree relative with melanoma), monitoring them regularly by physical examination would seem prudent, and dermatologists may be the most appropriate assessors.

- Currently, there is insufficient evidence to recommend either for or against counselling patients to perform periodic skin self-examinations.

Evidence for those recommendations came from a total of seven before/after studies.

The Ontario panel noted that the Canadian Task Force guideline had not been updated since its completion in 1994 and covered the literature only up to March 1993. At that time, there was very limited evidence available to the guideline developers, especially related to the high-risk population and self-examination.

U.S. Guidelines (2001)

The U.S. Preventive Services Task Force concluded that "the evidence is insufficient to recommend for or against routine screening for skin cancer using a total-body skin examination for the early detection of cutaneous melanoma, basal cell cancer, or squamous cell skin cancer" (5). The guideline report also noted, under the heading "Clinical Considerations," that the "benefits from screening are unproven, even in high-risk patients." However, the U.S. Task Force added that "Clinicians should be aware that fair-skinned men and women aged older than 65 years, patients with atypical moles, and those with more than 50 moles constitute known groups at substantially increased risk for melanoma." The U.S. guideline was based on a systematic review of the evidence published up to June 1999 (6) that included 13 studies of risk factors for melanoma, five prospective studies of the accuracy of total-body skin examination, 26 studies that reported the yield of various screening approaches in terms of suspected melanomas, and one case-control study of the relationship between skin self-examination and death from melanoma (9). The guideline did not make recommendations on surveillance of patients with familial syndromes.

The U.S. Task Force also published a guideline on preventing skin cancer in October 2003, which included skin self-examination among a list of preventative behaviours that could be included in patient counselling (14,15). The literature search for that guideline was more extensive than that for the screening guideline, with searches of MEDLINE, PsycInfo, and CINAHL. The Task Force stated that the single case-control study completed to date, which was also included in their screening guideline, provided insufficient evidence to make a recommendation for or against self-examination in reducing the incidence of melanoma (9).

Australian Guideline (1999)

The Australian Cancer Network completed a comprehensive guideline on the management of cutaneous melanoma in 1999 (11). Based on a review of the literature up to 1994, the guideline recommended that "People at very high risk of melanoma, (e.g., those with multiple banal or dysplastic naevi or who have a history of melanoma in first-degree relatives) should be advised on the specific changes which suggest melanoma, encouraged to perform self-examination and offered a surveillance program." The guideline report cited six non-randomized studies that supported a relationship between surveillance and detection of melanoma among the high-risk group. (16-21)

Primary Evidence on Screening for Skin Cancer

The total body of evidence from comparative studies on screening included:

- the feasibility stage of a randomized controlled trial of a community-based screening program results following the three year intervention period (7,22,23,24,25);
- a comparative cohort study of work-place screening plus health education (8);
- a case-control study of skin self-examination (9).

These are summarized below, along with a prospective uncontrolled study of screening in the primary care setting (26). All the evidence related to the potential benefits of screening rather

than to the potential harms (e.g., misdiagnosis of melanoma or increased rates of biopsy or other procedures for benign skin conditions).

Community-based Screening Programs

Aitken et al initiated a large randomized trial to determine the effectiveness of community-based screening in reducing mortality from melanoma in Australia (7). In 2002, results from the first phase of the trial demonstrated the feasibility of implementing the program, which consisted of community education, general practitioner education, and screening clinics to promote self-screening and whole-body screening by general practitioners. Early results detected an increase in the percentage of subjects reporting whole-body skin examination by a physician 12 months after randomization compared to control communities (27% versus [vs] 12%; 11% in both groups reported receiving an exam in the year before the study). The impact of screening on mortality will require follow-up of those communities over 15 years, although the lack of adequate funding has jeopardized the completion of the trial as planned.

At the end of the three-year intervention period (1998-2001), a telephone survey of a sample of people in the study communities indicated that people could accurately recall whether they had had a clinical whole-body skin exam in the previous three years. Concordance of self- and medical record reports was 94%, with sensitivity 92% and specificity 96% (22).

Results from cross-sectional surveys (telephone and postal) that were conducted in intervention and control communities at baseline, during the 3 year intervention and 2 years after the intervention showed an increased 12 month prevalence of whole body skin exams 2 years into the intervention period (from 11.2 percent to 34.8) in the intervention arm. However this declined in the third year to 29.2 (when clinics were discontinued) and dropped a further 10 percent 2 years after the program ended. In comparison, control communities had stable screening rates over the same time periods. The authors note that without the provision of dedicated skin screening clinics it would not be possible to maintain high screening levels (24).

The trial completed a total of 16,383 screens over three years and 2302 referrals were made for suspicious lesions (14 percent). A total of 33 melanomas, 259 BCCs, and 97 SCCs were confirmed from the 16383 screens for an overall probability of detecting skin cancer of 2.4 percent (25).

Screening by Primary Care Providers

There were no comparative studies of screening by primary care providers, but a non-comparative prospective study evaluated screening for skin cancer in the primary care setting (26). The generalizability of results from that Italian study is limited by low participation rates.

Veronesi et al invited 1,038 general practitioners in Italy to participate in a skin cancer-screening program (26). They were asked to screen all adults presenting to their offices for any reason over a two-year period. A regional program provided education for practitioners and procedures for referral to specialists. Among 74 participating practices, 11,040 patients had a skin examination and 820 were referred to dermatologists. The study report did not provide details about the patient population. The yield from screening was 38 melanomas (0.3% of patients screened) and 94 non-melanoma skin carcinomas (0.9%). The purpose of the screening program was the early diagnosis of cutaneous melanoma, and little information is reported about the non-melanoma skin cancers detected.

Skin Self-Examination

Data from three studies are summarized below. A case-control study examined the impact of skin self-examination (SSE) on melanoma detection and mortality (9). The other two studies provided information about the impact of skin examination by a physician on subsequent SSE (8,23).

Berwick et al used a case-control study of melanoma to investigate whether SSE was beneficial (9). The study assessed the potential of SSE for primary prevention of melanoma (i.e., reduction of melanoma risk) and secondary prevention (early detection) separately, as well as the joint impact on melanoma mortality reduction. Interviews were conducted with 650 individuals with melanomas diagnosed in 1987-1989, identified from the Connecticut Tumor Registry, and 549 population controls, selected from the Connecticut population by random-digit dialling. All subjects were Caucasian. Participants were asked about their history of doing "careful, deliberate and purposeful skin self examination" prior to diagnosis/interview; 17% of controls (n=96) and 13% (n=86) of cases replied affirmatively. Melanoma cases were followed through 1994 for development of "lethal melanoma"; 30 developed distant metastases but were still alive, and 80 died from melanoma.

The comparison of the use of SSE in cases and controls indicated a reduced risk of melanoma associated with SSE for primary prevention, with an odds ratio (OR) of 0.66 (95% confidence interval [CI], 0.44 to 0.99) after an adjustment for age, sex, and a number of phenotypic risk factors and estimated sun exposure. In terms of secondary prevention, SSE was associated with a reduced risk of developing "lethal melanoma" (OR, 0.56). The combined primary and secondary prevention effects of SSE represent an estimate of the potential for SSE to reduce melanoma mortality, the usual desirable end point for evaluating screening effectiveness. The adjusted OR representing this reduction is 0.37 (95% CI, 0.16 to 0.84), which is also the product of primary and secondary prevention ORs (i.e., 0.66 x 0.56 = 0. 37).

There are some methodological problems with this approach to the assessment of screening effectiveness. The most serious challenge to the validity of the estimate relating to secondary prevention, and therefore to the combined effect, is the possibility of lead-time bias (i.e., that those doing SSE find their lesions earlier and so survive longer from the time of diagnosis to death but do not necessarily live to an older age than they would have in the absence of SSE). The study authors argued that lead-time bias is unlikely to be a major issue because, by the end of follow-up, the number of new "lethal melanomas" had reached a plateau in both the SSE and non-SSE groups.

Azizi et al conducted a non-randomized prospective trial of interventions to improve skin cancer awareness and prevention among outdoor workers in Israel (8). The control and intervention subjects came from different work sites but worked for the same company. A baseline evaluation found that 44% of workers reported performing SSE at least once a year. Eight months after the introduction of an education and screening program, three quarters of the intervention subjects reported performing SSE, compared to half of the control group.

In the Australian randomized trial of community-based screening noted above, Aitken et al found that one of the most important determinants of conducting SSE was having had a skin examination by a physician within the past three years (23). Almost as important was having had a physician suggest doing SSE or giving instruction on how to perform SSE.

Risk Factors for Skin Cancer

It is well accepted that some individuals are at an increased risk for skin cancer because of personal characteristics or history. Although the evidence on the benefits of screening is very sparse, the guideline panel proposed that any benefit expected from increased surveillance for skin cancer would have the biggest impact in high-risk groups.

There are five categories of defined risk factors for skin cancer:

1. phenotypic characteristics,
2. exposure to ultraviolet radiation from either the sun or artificial tanning devices,
3. gene mutations, family or personal history of skin cancer, and inherited conditions such as atypical nevi or dysplastic nevus syndrome,
4. medical conditions or treatments,
5. dysplastic nevi without a family history.

Personal risk of skin cancer depends on both the relative risk (RR) associated with each factor and the number of risk factors. Risk is assumed to be multiplicative, so that overall risk can be estimated from the products of the relative risk associated with each factor present in an individual (27).

Phenotype

People with naturally blond or red hair, with a tendency to freckle, and whose skin burns easily and tans poorly or not at all (skin type I) have an increased susceptibility for all forms of skin cancer (28). Those with light skin colour also have a higher than average risk. Skin colour is correlated with hair colour, and either one or the other captures the trait of "fairness," but hair colour is easier to assess. Additionally, those with many nevi are at increased risk for all melanoma variants (29). The tables below further summarize these risk factors. Table 1 provides data on the associations of skin colour, tanning ability, freckling, and nevi with the three types of skin cancer in an Australian population (30), while Table 2 includes a similar set of characteristics from a case-control study of melanoma conducted in southern Ontario in the 1980s (27). These comprise the set of phenotypic factors that were jointly significantly associated with increased risk of melanoma.

Multiple nevi represent an indicator of both exposure and susceptibility. Nevi arise in childhood and adolescence in response to sun exposure. Some people get many nevi and others none or few for the same amount of sun exposure. A recent meta-analysis found that the relative risk of melanoma was 1.019 for each additional nevus when whole-body counts were used (31). Thus, people with 101-120 nevi would have a relative risk of 6.89 (95% CI: 4.63-10.25) compared to those with 15 or fewer. The vast majority of nevi are common acquired moles.

Immediately apparent from Tables 1 and 2 is the fact that, apart from high nevus density, the relative risks are not large. However, those who have two or more of the highest risk traits have a fairly substantial increase in melanoma risk (e.g., RR = 3.9 x 1.9 = 7.4 for someone with red hair and many freckles, compared to someone with black hair and few or no freckles) (Table 2).

Table 1. Estimates of the relative risk for skin cancer by phenotypic characteristics in an Australian population (adapted from Armstrong and Kricker [30]).

	Basal cell carcinoma	**Squamous cell carcinoma**	**Melanoma**
Colour of unexposed skin			
Darkest	1.0	1.0	1.0
Lightest	1.5	2.3	3.1
Ability to tan			
Deep tan	1.0	1.0	1.0
No tan	3.7	6.9	3.5
Freckling as a child			
Yes vs. no	1.8	1.6	1.5
Melanocytic nevi			
Some vs. none	1.0	0.8	2.7

Notes: vs., versus.

Table 2. Estimates of the relative risk of cutaneous malignant melanoma by phenotypic characteristic in Southern Ontario (Marrett et al [27]).

Characteristic	Prevalence in controls	Relative Risk
Hair colour		
Black	11%	1.0
Brown	43%	1.6
Light brown	27%	2.2
Blond or fair	14%	2.7
Red	5%	3.9
Skin reaction to repeated sun exposure		
No burn	74%	1.0
Burn, then tan	18%	1.8
Burn, no tan	7%	1.4
Freckle density, forearm		
None or few	69%	1.0
Moderate	17%	1.5
Many	14%	1.9
Nevus density, whole body		
None	26%	1.0
Few	63%	3.5
Moderate/many	11%	10.7

Exposure to Ultraviolet Radiation

Ultraviolet radiation (UVR) has been identified as a carcinogen by the International Agency for Research on Cancer (IARC) (32). Although most UVR exposure comes from the sun, it is also emitted from tanning equipment and UV emitting sources used in the treatment of psoriasis. UVR dose is a function of both duration of exposure and the intensity of the UVR. Intensity is largely dependent on latitude, season and time of day for solar UVR and on lamp output for tanning equipment. The amount of UVR emitted by tanning equipment can exceed that from the midday summer sun in southern Europe (33).

Although UVR causes BBC, SCC and melanoma, epidemiologic studies suggest that the mode of action of UVR differs for these three types of skin cancer. SCC is related to high cumulative lifetime exposure, such as that obtained by outdoor workers. Melanoma, on the other hand, is more associated with “intermittent” exposure of the type that normally occurs during recreation or on sunny vacations. BCC is in between, with both types of exposure being somewhat important. Sunburn at any time of life is, therefore, a stronger risk factor for melanoma than for BCC, and also for BCC compared to SCC—probably because sunburn is an indicator of the intermittent form of exposure. Exposure to tanning equipment is generally most like intermittent exposure and has been shown to increase the risk of melanoma, particularly at high doses or early in life (34). Table 3 below summarizes the current state of evidence from epidemiologic studies of sun exposure.

Table 3. Estimates of the relative risk for skin cancer by personal sun exposure (from Armstrong and Kricker [30] and Elwood and Jopson [35]).

	Basal cell carcinoma	Squamous cell carcinoma	Melanoma
Total exposure	1.0	1.5	1.2
Occupational exposure	1.2	1.6	0.9
Intermittent exposure	1.4	0.9	1.7
Sunburn at any age	1.4	1.2	1.9

People living in a country with a sunny climate in childhood carry the risk of that country. In an Australian study, children born in non-sunny countries carry the risk of the country of origin if they migrate after age 15 but acquire the risk of their adoptive country if they migrate before age 15 (36). Those who spend their childhood years living at latitudes where the UVR is more intense have a higher risk of developing a second primary melanoma and, by extension, a first melanoma, than those living at higher latitudes (30). The highest risk is found in those who spent their childhood at latitudes less than 35^0 (30). As children have higher exposure rates than every other group of the population other than outdoor workers, attention to protective practices are especially relevant for them (37). High numbers of nevi are associated with a markedly increased risk of melanoma. High nevus counts in childhood are associated with sun exposure and freckling. Good sun-protective measures are associated with decreased numbers of nevi and, presumably, decreased risk of melanoma (38).

Genetic factors, including history of skin cancer and related conditions

Individuals with two or more relatives with melanoma are at an increased risk of developing melanoma themselves and may do so at an earlier age than others (39). Melanoma in multiple members of a family could be related to genetic susceptibility or common exposures (27). Ford et al conducted a pooled analysis of a number of case-control studies and estimated a relative risk of 2.2 (95% CI, 1.8 to 2.9) for a history of melanoma in one or more first-degree relatives (40). More recently, Begg et al estimated the relative risk of melanoma in first-degree relatives of melanoma cases who provided detailed family history data (e.g., dates of birth and death of every first degree relative, along with date of diagnosis of melanoma, if any) (41). They found that relatives of male and female melanoma cases in North Americans had 3.7- and 3.9-fold increased risks of melanoma, respectively, compared to the general population. Cumulative risks of a melanoma diagnosis by age 80 were 6.4% and 4.4%, respectively; the cumulative risk was even higher among relatives of cases diagnosed at a young age. Germ line mutations in the CDKN2A gene have been shown to occur at increased frequency in melanoma-prone families (42,43). Although the risk of non-melanoma skin cancer increases with increased susceptibility to the effects of ultraviolet radiation, such as in xeroderma pigmentosum (where there is an inability to repair UV–induced DNA damage), there is no evidence of a genetic component for non-melanoma skin cancer.

A personal history of skin cancer is an important predictor of risk for a subsequent skin cancer. For example, using data from the U.S. Surveillance Epidemiology and End Results (SEER) program, a person who already has melanoma is 7.5 times more likely to develop melanoma (i.e., a second primary) than someone in the general population (i.e., their first melanoma) (43). Giles has estimated that about 5% of those with melanoma will develop a second melanoma within five years in Australia (44). Recently, Ferrone found that in a cohort of 4484 patients the estimated five-year cumulative risk of a second primary melanoma was 11.4%. In addition, patients with a positive family history or dysplastic nevi had a significantly

greater risk (19.1% and 23.7%, respectively) of developing a second primary tumour at five years from the initial diagnosis (45). From their systematic review of studies that examined the risk of developing a subsequent non-melanoma skin cancer in patients with a history of non-melanoma skin cancer, Marcil and Stern estimated that patients with SCC of the skin were 10 times more likely to develop a subsequent SCC (46). Similarly, those with BCC or SCC were 10 times more likely to develop a subsequent BCC. Cumulative three-year risks are summarized in Table 4.

Gandini et al's meta-analysis estimates that the presence of five or more atypical (or dysplastic) nevi increases the risk of melanoma six-fold (31). Atypical moles are moles whose appearance is different from that of common moles. They are generally larger than ordinary moles and have irregular and indistinct borders. Their colour frequently is not uniform and ranges from pink to dark brown; they usually are flat, but parts may be raised above the skin surface.

Table 4. Three-year cumulative risk of subsequent non-melanoma skin cancer in patients with a history of non-melanoma skin cancer (46).

	Three-year Cumulative Risk of Subsequent Skin Cancer	
Index Skin Cancer	Squamous cell carcinoma	Basal cell carcinoma
Squamous cell carcinoma	18%	43%
Basal cell carcinoma	6%	44%

Medical Conditions/Treatments

Organ transplant recipients are at greatly increased risk for skin cancer, particularly SCC. The relative risks of SCC have been reported to be up to 109 times compared to the general population, with a cumulative risk at 15-20 years post-transplant of 20-30% (47-49). There seems to be some variation according to age at transplant, type of transplant, and immunosuppressive treatment used. There is also a documented increased risk of melanoma, but it is much more modest. In large cohorts of transplant patients, Jensen estimated the relative risk of melanoma to be 3.4 (47) and Adami, 1.8 (48), compared to the general population. Multiple cancers are also common in this population. Because SCC can metastasize and cause death, SCC is a significant cause of morbidity and mortality after organ transplantation.

Patients with psoriasis who have been treated with psoralen-UVA (PUVA), especially those who have had greater than 200 treatments, have a markedly increased risk of nonmelanoma skin cancer, both squamous cell carcinoma and basal cell carcinoma (50-51). This risk persists after the discontinuation of PUVA therapy (52). Stern et al (53) reported that patients who had received more that 250 PUVA treatments were much more likely to develop melanoma (relative risk, 5.5; 95% CI 2.0 to 12.0) than the general population.

Therapeutic doses of ionizing radiation appear to increase the risk of non-melanoma skin cancer at the site of radiation. One case-control study estimated odds ratios for both squamous cell and basal cell at about 3 (54). The risk associated with radiotherapy for childhood cancer may be particularly high: the sole study estimated a 6.3 fold increase in risk (55).

DISCUSSION

While the panel agreed in principle with the recommendations made in the U.S., Canadian, and Australian guidelines, they decided that it was worthwhile to develop their own guideline report. The Ontario guideline integrates and updates the work done by the U.S., Canadian, and Australian groups and presents recommendations in a format consistent with other guidelines from the PEBC. The panel felt that, to be most useful to its target audience (primary care providers and dermatologists), the guideline should deal separately with the surveillance of individuals at increased risk for skin cancer and screening of the general population. The recommendations in this Ontario guideline are consistent with those from the Canadian Task Force, U.S., and Australian guidelines in that none of the guidelines recommend routine screening for skin cancer in the general population. While the other guidelines make recommendations for high-risk populations, the Ontario document has gone further in describing the high-risk population and making specific recommendations for identifying and screening this group.

There is very little evidence about the effects of screening for skin cancer on clinical outcomes. The pilot phase of a randomized trial demonstrated the feasibility of implementing a screening program consisting of community education, general practitioner education, and screening clinics to promote self-screening and whole-body screening by general practitioners (7). Early results detected an increase in the percentage of subjects reporting whole-body skin examination by a physician. The randomized trial and a work-place screening study both found that people were more likely to perform skin self-examination if they had undergone a whole-body skin examination by a physician (8,23). A case-control study detected a reduced risk of melanoma and reduced mortality from melanoma associated with skin self-examination, but there are no survival data from randomized controlled trials (RCTs) (9). Mounting an RCT with sufficient power to detect survival benefits from screening requires the commitment of significant resources over many years of follow-up. The challenges are illustrated by the aborted attempt to conduct such a trial in Australia, a country with high rates of skin cancer. There are no ongoing randomized trials and little likelihood of RCTs being initiated in the future. Given that there is limited evidence for or against the case of screening for skin cancer in the general population and the relatively low rates of skin cancer among those without known risk factors, the panel does not recommend that members of the general public undergo routine screening for skin cancer.

In addition to considering the impact of screening on melanoma mortality reduction, the guideline panel considered other potential benefits from detecting skin cancer early through screening. They noted that non-melanoma skin cancer, which is not usually lethal except in transplant patients, if diagnosed early, results in less extensive surgery and/or radiation therapy on highly visible sites such as the head and neck.

Because of personal characteristics or history, some individuals are at increased risk for skin cancer. The panel examined the evidence for a range of well-known risk factors related to phenotype, exposure to ultraviolet radiation, family or personal history of skin cancer, and medical conditions or treatments. They looked at the relative risk and assessment issues for each risk factor. The risks associated with ultraviolet radiation exposure from the sun or artificial sources vary with the frequency and intensity of exposure. Past UVR exposure is difficult to quantify and, therefore, may not be useful to easily identify high-risk people for screening. A history of frequent sunburns or a tendency to burn rather than tan is a more useful indicator of risk. Some risk factors (e.g., hair colour) are more easily ascertained in the clinical setting. High risk for skin cancer associated with melanoma in a first-degree relative (especially if diagnosed at a young age), a personal history of skin cancer or organ transplantation, or long-term treatment with PUVA for psoriasis suggest that screening may be beneficial in these people.

Even without evidence of mortality reduction, the guideline panel thought that surveillance by dermatologists of individuals at very high risk has the potential to reduce

morbidity and mortality. Earlier detection of smaller lesions should lead to less extensive surgical procedures and/or radiation therapy. In malignant melanoma, the panel assumes that surveillance will result in the detection of thinner lesions, therefore leading to a better prognosis. The very high-risk group includes those with a cumulative cancer risk of 5% or more over a five-year period or very high odds or risk ratios compared to the general population. Since those who have undergone organ transplantation and are on chronic immunosuppressant therapy will have extensive and ongoing interaction with a health care team, the panel recommends that a member of this team with dermatological expertise or an external dermatologist undertake skin surveillance of these patients. It is important to note that a group of people with a higher than average risk of developing skin cancer may not warrant total-body skin examination. The panel recommends that health care providers teach these high-risk individuals to examine their own skin for signs of cancer and counsel them about skin cancer prevention.

Due to the lack of strong evidence for or against screening, the panel has recommended that screening not be offered to the general population. Based on the risk factors described in the literature and the combined clinical expertise of the panel, the group identified populations at sufficient risk for melanoma, SCC, or BCC of the skin for whom screening by a health care provider or self-screening by the patient is warranted.

IMPLICATIONS FOR PRACTICE

To implement the recommendations made in this practice guideline, clinicians will need to be able to identify people at high and very high risk for skin cancer, and to counsel these individuals about skin self-examination and skin cancer prevention. Education should be available to health care workers and individuals at high risk who want to update their knowledge or increase their confidence in performing these tasks (56).

The guideline panel recommends that very high-risk patients should be seen once a year for a total-skin exam by a dermatologist or other health care provider with expertise in skin examination. High-risk patients should be seen once a year by a health care provider trained in screening for skin cancers. All patients at risk should be taught how to examine their own skin and should do so once a month. Depending on clinical circumstances, a physician may elect to examine the patient more or less frequently (for example, in the case of a recent diagnosis of skin cancer, a patient unable to do a skin self-examination, or a patient demonstrating excellent mastery of a skin self-examination).

Assessing Risk

The first challenge is to identify the level of risk for an individual person. Although some work has been done to develop questionnaires for self-assessment of risk, these have only moderate validity and reliability (57,58). The recommendations in this guideline are based on the assessment of risk factors that can be ascertained from a clinical history and physical exam conducted during routine patient care. History taking should include questions about completed or pending organ transplantation, personal history of skin cancer, family history of skin cancer, and history of psoriasis and of skin that burns and does not tan. Family physicians, and other primary health care providers, are encouraged to observe the skin when examining patients during office visits and to note if the patient has many nevi, dysplastic nevi, red or blond hair, freckles, or obvious sunburn.

Full-Body Skin Examination

Some family physicians may need additional education to become proficient and confident in performing full-body skin exams. de Gannes et al recruited 43 family physicians in Vancouver for a randomized trial of an educational video (59). At baseline, the average score on a multiple-choice questionnaire about skin cancer, prevention strategies, and the initial management of suspicious skin lesions was 57%. Six percent of lesions submitted to the

Department of Pathology by these physicians were malignant or premalignant. Six months after randomization, 13% of excised lesions in the intervention group were malignant compared to 7% in the control group (p>0.05). Only 27 of 43 physicians completed a follow-up questionnaire. There was no significant change in knowledge score in either group.

As with SSE, full-body skin examination techniques can be improved by using photographs. A randomized trial involving 973 men over age 50 from the general population, found that baseline photographs helped primary care practitioners to correctly identify skin lesions over a two-year period (60). To assure photographs of optimum quality, it is advisable to use the services of a medical photographer, if available. The whole skin should be photodocumented (61). If no medical photographer is available, a family member can take the photographs but should receive instruction on views to take. Using digital cameras with a minimum of five megapixels, enlarged prints can be made or the photograph can be stored on disk. Photographs are kept by the patient for regular monthly use. If a change is noted, the patient and the photos should be evaluated by a health care provider and a decision made as to whether treatment is required.

A random survey of 632 primary care physicians across the U.S. found a positive association between the use of multiple information sources to learn about skin cancer screening and performing screening on patients (62).

Teaching Skin Self-Examination

Patients must receive proper instruction to successfully perform SSE. Simply increasing the patient's knowledge—even those at increased risk—will not necessarily translate into an ability to recognize and count pigmented lesions or to recognize changes in lesions (63). Currently, there are a number of tools available that may assist patients in SSE. The Canadian Dermatology Association has recently developed a Guide to Skin Cancer Self-Examination outlining a comprehensive ten-step process. The guide explains what constitutes an abnormality and provides instructions on how to perform total-body SSE with the assistance of a partner and a wall mirror. (A printable format of this guide can be obtained in both English and French at http://www.dermatology.ca). A recent survey of 2,126 primary practice patients found that having a partner assisting and a wall mirror available increased the likelihood that the patients performed SSE (64). Two studies in which moles were drawn or altered on the skin of patients attending a pigmented lesion clinic, found that SSE was moderately accurate (specificity 63% for new moles and 55%-62% for altered moles; sensitivity, 58% for a 2mm change and 75% for a 4mm change) (65,66).

There is evidence that providing photographs of the skin to the patient improves their ability to detect changes. In one study, performance improved when patients were provided with baseline photographs of their chest, abdomen and, back for comparison during a self-exam (sensitivity 72%) (65). Furthermore, a randomized trial (66) involving the same patients evaluated the impact of photographs added to instruction on SSE by a physician or nurse. The study concluded that self-reported rates of SSE increased by 50% in patients provided with photographs compared to those who received only the educational component (18%). In another survey, knowledge and confidence in the ability to carry out SSE were predictors of SSE performance among individuals at risk for skin cancer (67).

Counselling about Skin Cancer Prevention

While it is important that all individuals (other than those with very dark or black skin) know about the role of sun protection in reducing the risk of skin cancer, those identified as being at very high or high risk as defined earlier in this document should be explicitly counselled about the need to practice sun protection. Such counselling should also be directed at two other groups, outdoor workers because of their high levels of exposure and children because of the evidence that excessive sun exposure early in life is particularly important in determining skin

cancer risk. Results of a survey of farmers and soccer players in the U.S. showed a positive association between having ever been counselled by a health care provider about "how to prevent skin cancer" and sun protective behaviours including sunscreen use, getting clinical skin examinations, wearing protective head gear and performing skin self exams (68,69).

Public health experts and dermatologists recommend the following sun safety strategies:

- Try to avoid the summer sun when it is highest in the sky (between 11 a.m. and 4 p.m. in Ontario)
- Seek shade when you are outside—or create your own
- Wear a wide-brimmed hat that shades the back of your neck, your ears, and your face.
- Wear clothing that covers your arms, back, and legs.
- Liberally apply broad-spectrum sunscreen with a sun protection factor (SPF) of at least 15 to exposed skin.
- Never use tanning equipment.
- Wear UV-protective sunglasses (70,71).

ONGOING TRIALS

The panel was not aware of any randomized trials of screening for skin cancer that were open to recruitment or in active follow-up.

CONFLICT OF INTEREST

Members of the panel disclosed information on potential conflicts of interest. None of the principal authors of this report identified any conflicts. One panel member has acted as a consultant to pharmaceutical companies, but that was not considered to be in conflict with this screening guideline.

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Appendix A. Evidence-based guidelines from other groups.

Developer	Recommendations & Qualifying Statements	
	General Population	**High Risk Population**
Canadian Task Force on Preventive Health Care, 1994 (10)	Routine screening for skin cancer by primary care providers is not recommended for the general population. Currently there is insufficient evidence to recommend either for or against counselling patients to perform periodic skin self-examinations.	For individuals with significantly increased risk (family melanoma syndrome, first-degree relative with malignant melanoma) it would seem prudent to monitor regularly by physical examination and dermatologists may be the most appropriate assessors.
U.S. Preventive Services Task Force (USPSTF), 2001 & 2003 (5, 15)	The evidence is insufficient to recommend for or against routine screening for skin cancer using a total-body skin examination for the early detection of cutaneous melanoma, basal cell cancer, or squamous cell skin cancer. The USPSTF finds insufficient evidence to recommend for or against routine counseling by primary care clinicians to prevent skin cancer. Although counseling parents may increase children's use of sunscreen, the USPSTF found little evidence to determine the effects of counseling on the sun protection behaviours of adults. These behaviours include wearing protective clothing, reducing excessive sun exposure, avoiding sun lamps and tanning beds, or practicing skin self-examination.	Clinicians should be aware that fair-skinned men and women aged older than 65 years, patients with atypical moles, and those with more than 50 moles constitute known groups at substantially increased risk for melanoma. The USPSTF did not examine the outcomes related to surveillance of patients with familial syndromes, such as familial atypical mole and melanoma (FAM-M) syndrome.
Australian Cancer Network/National Health and Medical Research Council, 1999 (11)		People at very high risk of melanoma (e.g. those with multiple banal or dysplastic naevi or who have a history of melanoma in first-degree relatives) should be advised of the specific changes which suggest melanoma, encouraged to perform self-examination, and offered a surveillance program. Consider referral of these high-risk individuals to a melanoma centre for inclusion in genetic studies.

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Evidence-based Series #15-1: Section 3

Screening for Skin Cancer: Guideline Development and External Review - Methods and Results

L. From, L. Marrett, C. Rosen, C. Zwaal, M. Johnston, K. Bak, G. Sibbald, J. Fong, and V. Mai

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: June 19, 2007

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

The Evidence-based Series: A New Look to the PEBC Practice Guidelines

Each Evidence-based Series is comprised of three sections.

- *Section 1: Clinical Practice Guideline*. This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.

- *Section 2: Systematic Review.* This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.
- *Section 3: Guideline Development and External Review: Methods and Results.* This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This Evidence-Based Series was developed by the Skin Screening Guidelines Panel of CCO's PEBC. The series is a convenient and up-to-date source of the best available evidence on skin screening, developed through systematic review, evidence synthesis, and input from practitioners in Ontario. The panel included dermatologists, a family physician, an epidemiologist, and Cancer Care Ontario's Acting Vice-President, Preventive Oncology.

External Review by Ontario Clinicians

Following the review and discussion of Sections 1 and 2 of this Evidence-Based Series, the Skin Cancer Screening Guidelines Panel circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Box 1 summarizes the draft clinical recommendations and supporting evidence developed by the panel.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review April 28, 2005)

Recommendations

High or very high risk of skin cancer

- Individuals with <u>any</u> of the following risk factors:
  - on immunosuppressive therapy after organ transplantation,
  - a personal history of skin cancer,
  - two or more first-degree relatives with melanoma,
  - more than 100 nevi in total or 5+ atypical (dysplastic) nevi,
  - have received more than 250 treatments with PUVA for psoriasis
  - received radiation therapy for cancer as a child

  have a <u>very high risk</u> of skin cancer (approximately 10 or more times the risk of the general population).

  Individuals at very high risk should be identified by their primary health care provider and offered total body skin examination (site of radiation therapy in the case of childhood cancer survivors) by a dermatologist or a trained health care provider. They should also be counselled about skin self-examination and skin cancer prevention by a health care provider (e.g., physician, nurse practitioner, public health nurse).

- Individuals with <u>two or more</u> of the main susceptibility factors:
  - a first-degree relative with melanoma,
  - many (50-100) nevi,
  - one or more atypical (dysplastic) nevi,
  - naturally red or blond hair,
  - a tendency to freckle,
  - skin that burns easily and tans poorly or not at all

- received radiation therapy as an adult

are at high risk for skin cancer (roughly 5 times the risk of the general population).

Individuals at high risk should be identified by their primary health care provider and counselled about skin self-examination (specifically focused on the site of radiation for those having had therapeutic radiation) and skin cancer prevention by a health care provider (e.g., physician, nurse practitioner, public health nurse).

The General population not at increased risk of skin cancer

- Based on the limited evidence available at present, routine total body skin examination by primary care providers is not recommended for individuals at average or low risk for skin cancer (i.e., those not included in the increased risk groups described above).
- Based on the limited evidence available at present, routine counselling on SSE by primary care providers is not recommended for individuals at average or low risk for skin cancer (i.e., those not included in the increased risk groups described above).

Key Evidence

- The guideline panel reviewed three evidence-based guidelines on screening for skin cancer (1-3), preliminary results from a randomized controlled trial of a community-based screening program, a comparative cohort study of work-place screening and a case-control study of skin self-examination.
- The pilot phase of a randomized trial demonstrated the feasibility of implementing a screening program consisting of community education, general practitioner education and screening clinics to promote self-screening and whole-body screening by general practitioners. Early results detected an increase in the percentage of subjects reporting whole-body skin examination by a physician (4).
- The randomized trial and a work-place screening study both found that people were more likely to perform skin self-examination if they had undergone a whole-body skin examination by a physician (4,5).
- A case-control study detected a reduced risk of melanoma and reduced mortality from melanoma associated with skin self-examination (6).
- Epidemiologic studies have found that people who have any of the following characteristics have a very high risk of developing skin cancer: on immunosuppressive therapy after organ transplantation, a personal history of skin cancer, two or more first-degree relatives with melanoma, more than 100 nevi in total or 5+ atypical nevi, or have received more than 250 treatments with PUVA for psoriasis. The risk of skin cancer is more than 10 times higher in those individuals than in the general population.
- There are other factors associated with significant but lower relative risks (roughly 5 times the risk of the general population for multiple susceptibility factors): a first-degree relative with melanoma, many (50-100) nevi, one or more atypical (dysplastic) nevi, naturally red or blond hair, a tendency to freckle, skin that burns easily and tans poorly or not at all**.** Risk is assumed to be multiplicative, so that overall risk can be estimated from the products of the relative risk associated with each factor present in an individual. Those who have two or more of the high-risk traits have a higher than average risk of developing skin cancer (roughly 5 times the risk of the general population).

Methods

Practitioner feedback was obtained through a mailed survey of 114 practitioners in Ontario (47 dermatologists, 53 family physicians, and 14 members of the Melanoma Disease Site Group). The survey consisted of 23 questions about the quality of the evidence-based recommendations and whether the draft report should be approved as a practice guideline. Written comments were invited. The practice guideline report and questionnaire were mailed on April 28, 2005. Follow-up reminders were sent at two weeks by postcard and four weeks (complete package mailed again). The results were then reviewed by the Skin Cancer Screening Guideline Panel.

Results

Forty-nine responses were received out of the 114 sent (40% response rate). Of the practitioners who responded, 41 indicated that the report was relevant to their clinical practice, and they completed the questionnaire. Key results of the practitioner feedback survey are summarized in Table 5.

Table 5. Practitioner responses to eight items on the practitioner feedback survey.

Item	**Number (%)**		
	Rated "strongly agree" or "agree"	**Rated "neither agree nor disagree"**	**Rated "disagree" or "disagree strongly"**
The rationale for developing a guideline, as stated in the "*Choice of Topic*" section of the report, is clear.	40 (98)	0	1 (2)
There is a need for a guideline on this topic.	36 (89)	3 (7)	2 (5)
The literature search is relevant and complete.	32 (80)	8 (20)	0
I agree with the overall interpretation of the evidence.	35 (88)	5 (13)	0
The draft recommendations in this report are clear.	40 (98)	1 (2)	0
I agree with the draft recommendations as stated.	35 (85)	3 (7)	3 (7)
This draft report should be approved as a practice guideline	32 (80)	6 (15)	2 (5)
	Rated "likely" or "very likely"	**Rated "unsure"**	**Rated "not at all likely" or "unlikely"**
If this draft report were to become a practice guideline, how likely would you be to make use of it in your own practice?	33 (83)	4(3.5)	2(2)

Summary of Written Comments

Eighteen respondents (44%) provided comments. The main points contained in the written comments were:

1. Several practitioners (7) felt that primary care providers require more education on the use of proper screening techniques and need more information on how to better recognize melanoma, BCC, SCC, or dysplastic nevi in their patients.
2. Two respondents felt that only dermatologists (or dermatology nurses) should perform full-body exams and counsel patients at risk. Five practitioners commented on the lack of dermatologists in the province, pointing out that those currently practicing will be unlikely to take on new patients due to their already overburdened workloads. One practitioner stated that "the reference to dermatologists' surveillance are irrelevant and may cause anxiety."
3. Four practitioners felt that skin cancer screening and counselling should be recommended for the whole population, regardless of risk. These respondents

suggested that primary care physicians should screen patients during annual physicals since it is an easy and inexpensive form of cancer prevention.

4. A few (3) practitioners pointed out that the guideline has no mention of certain high risks such as previous exposure to ionizing radiation, particularly x-ray treatment on acne; exposure to arsenic, including as an insecticide; the use of cyclosporine prior to PUVA; and what one respondent termed as exposure to "high risk activities," which include wintering away, tanning beds, hobbies (e.g. golf or the use of a swimming pool), and outdoor work.
5. Four comments addressed concerns regarding knowledge transfer and the dissemination of information to physicians and patients.
6. Two practitioners stated that it will be challenging to obtain repeated, clinically satisfactory full-body photos from their patients, especially since many do not have access to digital cameras.
7. One practitioner commented that many pathologists are perhaps "overcalling" melanoma in situ or atypical melanocytic lesions and wondered if these patients should be included in the very-high-risk group. A second practitioner also wondered if a transplant patient who sees his transplant physician frequently should have his family physician refer him to a dermatologist.
8. Finally, six respondents commented that the guideline is well written and that they agree with and endorse the recommendations.

Modifications/Actions

The Skin Cancer Screening Guideline Panel discussed the comments resulting from practitioner feedback and has provided the following responses:

1. The panel strongly agrees that more education on skin screening is needed and hopes that this guideline will aid in knowledge transfer. The paragraph on Teaching Skin Self-Examination has been modified to better explain the tools currently available for assisting in proper skin examination. In order to offer further screening tools, the panel has decided to provide the Internet address for the Canadian's Dermatology Association's Guide to Skin Cancer Self-Examination pamphlet.
2. The panel realizes that the recommendations in this guideline will undoubtedly increase the already overstretched dermatologists' workload; however, this is true of any screening guideline and should not be seen as a barrier. In order to avoid focusing solely on dermatologists, it was decided to amend the first recommendation to include the words "…dermatologist or a trained health care provider…"
3. Although there may be a morbidity or mortality benefit from screening average- or low-risk people, there is no evidence of either benefit or harm from such screening. We have inserted a clear statement about the lack of evidence in Section 1, Recommendations. Although the panel did not undertake an economic analysis, the cost of full-population screening would likely be great and so cannot be justified in the absence of strong evidence.
4. The choice of risk factors was based on data found in an extensive literature review, and the panel thinks that, at the present time, there is insufficient evidence to recommend any other susceptibility factors. The panel agrees that ionizing radiation is a serious risk factor and in response to Practitioner Feedback and Report Approval Panel feedback, it has been decided to add a section discussing patients who have been exposed to ionizing radiation and to acknowledge these patients in the recommendations. The panel would also like to point out that the issue of prevention will be addressed in a future guideline.
5. The main dissemination of our guideline documents is through the Web site of the provincial cancer agency, Cancer Care Ontario. Guideline-indexing groups such as the

National Guidelines Clearinghouse and the Canadian Medical Association Infobase, also post our full guidelines or abstracts of our documents on their Web sites. In addition, condensed versions of the completed documents are published in peer-reviewed journals. The completed guideline will be forwarded to Health Knowledge Central, which produces pamphlets and brochures for physicians.

6. One of the panel members clarified that patients only need to have one set of photographic prints to serve as a baseline measurement for future comparisons. It was also clarified that this was not a recommendation but rather a suggested approach that might help high-risk patients monitor changes in their skin.
7. The group thinks that, at the present time, 'melanoma in situ' or 'atypical melanocytic lesions' imply a high risk, and, thus, no changes were made to the document. The issue of transplant patients has been acknowledged by the panel and a statement has been added to the Interpretive Summary addressing surveillance practices within this high-risk subgroup.

Report Approval Panel

The final practice guideline report was reviewed and approved by the PEBC Report Approval Panel (RAP) in February 2006. The Panel consists of two members, including an oncologist, with expertise in clinical and methodology issues. One member approved the guideline as written, with no comments, while the second member had minor suggestions. Key issues raised included the following:

1. The panel has overstated the need for survival data. Since an RCT powered to detect differences in survival, has not, and likely will not, be completed, survival may be "setting the bar too high."
2. The panel has downplayed the importance of ionizing radiation as a risk, particularly in the Practitioner Feedback section, where it is indicated that use is "rarely seen."

Modifications/Actions:

The Skin Screening Panel agreed with the issues raised by the member of the RAP and made the following changes to the report:

1. In response to comment 1, the following changes have been made:
   Page 12, paragraph 2 has been changed to state:
   In addition to considering the impact of screening on melanoma mortality reduction, the guideline panel considered other potential benefits from detecting skin cancer early through screening. They noted that non-melanoma skin cancer, which is not usually lethal except in transplant patients, if diagnosed earlier results in less extensive surgery and/or radiation therapy on highly visible sites such as the head and neck.

   Page 12, paragraph 4 has been changed to state:
   Even without evidence of mortality reduction, the guideline panel thought that surveillance by dermatologists of individuals who are at very high risk has the potential to reduce morbidity and mortality. Earlier detection of smaller lesions should lead to less extensive surgical procedures and/or radiation therapy. In malignant melanoma, the panel assumes that surveillance will result in detection of thinner lesions, therefore leading to a better prognosis. The very high-risk group….

   Page 12, paragraph 5 has been changed to state:
   Due to the lack of strong evidence for or against screening, the panel has…

2. The panel agrees with this comment and, in response, has modified question number 4 in the Practitioner Feedback section to recognize ionizing radiation as a potential risk

factor. A section discussing patients who have been exposed to ionizing radiation has also been added under the Medical Conditions/ Treatments section.

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