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Evidence-Based Series 8-8 IN REVIEW

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

The Use of Indoor Tanning Devices and the Risk of Developing Cutaneous Malignant Melanoma: A Systematic Review and Clinical Practice Guideline

E. McWhirter, L.H. Souter, R.B. Rumble, C.F. Rosen, T. Tenkate, J. McLaughlin, A. Mamelak, F. Wright, T. Petrella, and the Use of Indoor Tanning Devices Expert Panel

Report Date: August 6, 2014

An assessment conducted in November 2024 placed Guideline 8-8 IN REVIEW. This means that it is undergoing a review for currency and relevance. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

EBS 8-8 is comprised of 3 sections. You can access the summary and full report here:

https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/1166

Section 1:	**Guideline Recommendations**
Section 2:	**Evidentiary Base**
Section 3:	**Development Methods, Recommendations Development and External Review Process**

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Evidence-Based Series 8-8

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The Use of Indoor Tanning Devices and the Risk of Developing Cutaneous Malignant Melanoma: A Systematic Review and Clinical Practice Guideline

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Evidence-Based Series 8-8: Section 1

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

The Use of Indoor Tanning Devices and the Risk of Developing Cutaneous Malignant Melanoma: A Systematic Review and Clinical Practice Guideline: Guideline Recommendations

E. McWhirter, L.H. Souter, R.B. Rumble, C.F. Rosen, T. Tenkate, J. McLaughlin, A. Mamelak, F. Wright, T. Petrella, and the Use of Indoor Tanning Devices Expert Panel

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GUIDELINE OBJECTIVES

To determine the risk of cutaneous malignant melanoma (herein referred to as melanoma) associated with use of indoor tanning devices, including impact of age at first use and frequency of use on the relative risk of developing melanoma.

TARGET POPULATION

All users of indoor tanning beds are the target population of this guideline.

INTENDED USERS

This guideline is intended for use by clinicians, other health care providers, users and potential users of indoor tanning devices in Ontario.

RECOMMENDATIONS, KEY EVIDENCE, AND JUSTIFICATION

RECOMMENDATION 1
Use of indoor tanning devices should be avoided to reduce risk of melanoma.

Summary of Key Evidence for Recommendation 1

A systematic review with meta-analysis (1) based on pooling of 27 cohort and case-control studies found a significant association between ever use of indoor tanning devices and increased risk of developing melanoma (relative risk [RR], 1.25: 95% confidence interval [CI], 1.09-1.43; $p<0.05$).

Justification for Recommendation 1

There is strong evidence linking the use of indoor tanning devices to an increased risk of developing melanoma. Although the meta-analysis (1) lacked detail on some elements of interest for the included studies, the current systematic review of the literature verified the clinical homogeneity of the pooled studies. The Use of Indoor Tanning Devices Guideline

Development Group (GDG) believes that the current evidence informs a strong recommendation.

Qualifying Statements for Recommendation 1

The International Agency for Research on Cancer (IARC) recently declared solar ultraviolet radiation (UVR) from indoor tanning devices a carcinogen (2). Both UVA and UVB have been shown to cause direct DNA damage through production of DNA mutations (UVA at a lower level than UVB), as well as indirect DNA damage via production of reactive oxygen species. Although UVB radiation can initiate the production of vitamin D in the skin, there are no data to support that artificial UVR is superior to oral supplementation with vitamin D to increase serum levels of this vitamin. Given the significant risk of melanoma as a consequence of using tanning devices, the GDG concludes that risks that arise from the use of tanning devices far outweigh any perceived benefit to their use.

This systematic review evaluated studies from 2000 to present with the goal of capturing the impact of modern tanning beds, which have been designed to more accurately mimic UVR. However, the identified meta-analysis conducted by Boniol et al (1) included studies published from 1981 through 2012 and evaluated an older generation of tanning beds. It is hypothesized that future studies assessing the impact of modern tanning beds could potentially amplify the effects found in the current review.

RECOMMENDATION 2
All individuals should avoid use of indoor tanning devices, especially those at a younger age.

Summary of Key Evidence for Recommendation 2

A recent and comprehensive systematic review with meta-analysis (1) found an increased risk of melanoma in those who initiated tanning devices use at a younger age (RR, 1.59: 95%CI, 1.36-1.85; $p<0.05$). Data were pooled from 13 studies, 12 of which adjusted for confounders related to sun exposure and sun sensitivity.

Justification for Recommendation 2

Both the rate of tanning device use in youths, as well as the incidence of melanoma diagnosis in 15 to 34 year olds has been increasing. Moreover, the meta-analysis by Boniol et al (1) demonstrated that the younger a person starts using indoor tanning devices, the higher the risk of developing melanoma in their lifetime. These are concerning statistics, and the GDG concludes that the current evidence informs a strong recommendation.

Qualifying Statements for Recommendation 2

Based on the evidence, the GDG has not set an age cut-off for "younger age." The identified meta-analysis defined young age as under age 35 (1). However, not all the studies included in the analysis defined an age for younger age; in those that did, younger age was defined as anywhere from 18 to 35. In the three included case-control studies that found an increased risk of melanoma with a definitive age cut-off, younger age was defined as less than 25 years (3), less than 35 years (4) and less than 18 years (5). The GDG concludes that these data point to an association between tanning bed use and increased risk of developing melanoma at any younger age of first use: defining a specific age cut-off would only be speculative and would not add to the recommendation.

RECOMMENDATION 3
There is no safe lower limit of exposure to artificial UVR from indoor tanning devices.

Summary of Key Evidence for Recommendation 3

When evaluating the risk associated with frequent use of indoor tanning devices, both number of sessions and length of tanning sessions were considered. The meta-analysis conducted by Boniol et al (1) found a 1.8% increased risk of developing melanoma for each additional session of tanning device use per year (95%CI, 0.0-3.8%; $p<0.05$). Additionally, when Boniol et al (1) conducted an analysis of 14 studies that reported relative risks with frequent tanning bed use, they found a 42% increased risk of developing melanoma with high tanning bed use (RR, 1.42; 95%CI, 1.15-1.74; $p<0.05$). One additional case-control study (6), which was not included in the Boniol et al meta-analysis (1), similarly found an association between increased risk of melanoma and both the number of sessions and length of sessions ($p=0.04$).

Justification for Recommendation 3

Based on the association between ever use of indoor tanning devices and increased risk of developing melanoma, plus the greater risk associated with frequent use of indoor tanning devices, the evidence indicates that there is no safe lower limit of exposure to artificial UVR from indoor tanning devices.

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Updating

All PEBC documents are maintained and updated through an annual assessment and subsequent review process. This is described in the PEBC Document Assessment and Review Protocol, available on the CCO website at:
https://www.cancercareontario.ca/sites/ccocancercare/files/assets/CCOPEBCDARP.pdf?redirect=true

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Evidence-Based Series 8-8: Section 2

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The Use of Indoor Tanning Devices and the Risk of Developing Cutaneous Malignant Melanoma: A Systematic Review and Clinical Practice Guideline: Evidentiary Base

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1.0 INTRODUCTION

Melanoma is the most lethal form of skin cancer, and the seventh most common malignancy in Canada. In 2013, there were an estimated 6000 new cases (3300 males; 2700 females) (1). Approximately 49% of these (2950) were diagnosed in Ontario (1). Of significant concern is the increasing incidence in 15 to 34 year olds, with females having a notably higher age-standardized rate (2).

Ultraviolet Radiation (UVR) was deemed a carcinogen in 2009 by both the World Health Organization (WHO) and the International Agency for Research on Cancer (IARC) for its causative role in skin cancer, including both melanoma and non-melanoma skin cancers (NMSC), basal cell carcinomas (BCC), and squamous cell carcinomas (SCC). This declaration applied to both solar UVR and UV-emitting tanning devices (3). Non-melanoma skin cancers are the most common form of skin cancer; while they cause patient morbidity, along with costs to the health care system, they are typically curable. In contrast, melanoma caused an estimated 1030 deaths in 2013 (1). Thus, it was decided to restrict this systematic review and guideline to cutaneous melanoma. It is beyond the scope of this paper to systematically review the association between NMSC and use of indoor tanning devices. This has recently been reviewed by Gallagher and McLaughlin (4). Similarly, risk of ocular melanoma is not being addressed in this review: data for this have recently been summarized in an IARC monograph (3).

The solar UV spectrum is divided into short-wavelength UVC (100-280 nm), mid-wavelength UVB (>280-315 nm) and long-wavelength UVA (>315-400 nm). The entire UVC fraction and the majority of the UVB fraction are absorbed and filtered by stratospheric ozone; consequently, the UV wavebands reaching the earth's surface are composed of 95% UVA and 5% UVB (3). Both UVB and UVA have been implicated in DNA damage [reviewed in (5)]. UVB is well absorbed by DNA, leading to the formation of cyclobutane pyrimidine dimers (CPDs) and pyrimidine(6-4)pyrimidone photoproducts. When DNA repair mechanisms fail, cytosine (C) to thymine (T) "signature mutations" persist through subsequent cell divisions. While UVA is less well absorbed by DNA, it can also lead to C to T and guanine (G) to adenine (A) transitions. In addition, UVA and UVB can induce DNA damage indirectly via formation of

reactive oxygen species. The rare genetic disorder xeroderma pigmentosum (XP) is characterized by a deficiency in nucleotide excision repair. Patients with this disease are at a dramatically increased risk of skin cancers, including melanoma, supporting the role of pyrimidine dimers in the development of skin cancer [reviewed in (3)]. Furthermore, experiments with human volunteers have detected these types of DNA damage in skin exposed to indoor tanning devices [reviewed in (6)].

There are also data from genomic analysis that underpin the role of UVR in mutagenesis. Berger et al (7) undertook the sequencing of genomes from 25 metastatic melanomas and matched germline DNA. They found a wide range of point mutations, from 3-14 per megabase (Mb) of genome on non-UV exposed hairless skin of the extremities (acral sites), to 5-55 per Mb for metastases from primary tumours arising on hair-bearing skin of the trunk, and up to 111 per Mb on a tumour with a documented history of chronic sun exposure. While the mutation rate in acral melanomas was similar to other solid tumour types, the rate from the truncal melanomas was considerably greater. Significantly, in tumours with elevated mutation rates, most nucleotide substitutions were C to T transitions, consistent with UV irradiation effect. Moreover, variations in mutations rate correlated with frequency of the UV mutational signature. For example, 93% of mutations in the chronic sun-exposed tumours were C to T transitions, while only 36% of mutations in tumours in acral sites were C to T transitions.

The UV emission spectra of indoor tanning devices have evolved over time. Until the mid-1960s, mercury lamps were popular as artificial tanning devices and these emitted UVC, UVB and UVA wavelengths (8). Fluorescent tubes were then introduced in the 1960s and these could also have a substantial UVB emission [reviewed in (6,9)]. Due to the carcinogenic effects observed from the early generation UVB and UVC emitting tanning bulbs, the emission spectra of tanning devices shifted towards the reportedly primarily UVA bulbs in the 1970s and 1980s in an effort to improve safety [reviewed in (9)]. Consequently much higher UVA exposures are needed to produce the same degree of tanning as produced by UVB exposure (8). However, later studies discovered that supposedly pure UVA bulbs still emitted 0.5 to 2% UVB [reviewed in (6,9)]. In the 1990s, the UV spectra from tanning bulbs were altered again in an effort to mimic natural sunlight by increasing the UVB output to around 4%, thereby increasing tanning effectiveness (8). Gerber et al (10) found that the UVA from indoor tanning beds is 10-15 times greater than the noon sun, corresponding to a solar UV index of 13 ("very high"; the UV index of high noon summer sun at intermediate latitudes is 8.5). In addition, it is estimated that two to 10 times more skin is exposed in tanning devices than with solar UV exposure (11). In an informative assessment of 20 different indoor tanning devices in Sydney and Melbourne, Australia, Gies et al (12) performed detailed spectral measurements of UV emissions from the devices. They found that 15 of the units emitted greater than a UV index of 20, and three had intensities above a UV index of 36.

The 2006 Second National Sun Survey (13) demonstrated that 9% (range 7%-12%) of Canadians use indoor tanning devices (this term will be used to encompass tanning beds, sunlamps and solaria). Of those using tanning devices, just over one third (36%) use them more than 12 times per year. In Ontario, 8% of adults had used an indoor tanning device over a one-year period. Using 2010 data, the overall age-adjusted proportion of adults using tanning beds in the preceding 12 months was 5.6% in the United States (14), while in Europe, prevalence of ever-use of indoor tanning varies greatly with country (6).

The causative role of indoor tanning devices in increasing the risk of cutaneous malignant melanoma (herein referred to as melanoma) has been reviewed extensively in the mid-2000s (6,15,16). Given the increasing incidence of melanoma, and high prevalence of indoor tanning device use, the Melanoma Disease Site Group (Melanoma DSG) sought to systematically review more recent literature and to establish a clinical practice guideline.

In order to make recommendations as part of a clinical practice guideline, the working group of the Melanoma DSG developed this evidentiary base upon which the recommendations are based. Based on the objectives of the guideline, the Working Group (WG) derived the research questions outlined below.

1.1. RESEARCH QUESTIONS

1. Does the use of indoor tanning devices increase the risk of developing melanoma?
    a. Does age at first use of indoor tanning device affect the relative risk of developing melanoma?
    b. Does the frequency of indoor tanning device use affect the relative risk of developing melanoma?

2.0. METHODS

This evidentiary base was developed using a planned two-stage method, summarized here and described in more detail below.

1. Search and evaluation of existing systematic reviews: If one or more existing systematic reviews are identified that address the research questions and are of reasonable quality, then those systematic reviews would form the core of the evidentiary base.
2. Systematic review of the primary literature: This review would focus on those areas not covered by existing reviews if any are located and accepted.

The Program in Evidence-Based Care (PEBC) is supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC and any associated Programs is editorially independent from the Ministry.

2.1. Search for Existing Clinical Practice Guidelines and Systematic Reviews

An electronic search employing OVID was used to systematically search the MEDLINE and EMBASE databases for systematic reviews and clinical practice guidelines. OVID was searched from 2000 to week 6 of 2013 using the following keywords: “melanoma,” “skin tumor,” “sun tan,” “sun bathing,” “sunlight” and “ultraviolet radiation”. In addition, websites/databases of specific guideline developers and systematic review producers were searched, using the same keywords and for the same time period. These websites/databases included: Inventory of Cancer Guidelines, the National Guidelines Clearinghouse, Cochrane Database of Systematic Reviews (CDSR), Scottish Intercollegiate Guideline Network (SIGN), American Society of Clinical Oncology (ASCO), European Society of Clinical Oncology (ESMO), National Comprehensive Cancer Network (NCCN), National Institute for Health and Care Excellence (NICE), Australian National Health and Medical Research Council, New Zealand Guideline Group, and IARC. Only the most recent clinical practice guidelines from each organization, as well as the most recent systematic review when multiple reviews were found with overlapping outcomes, were chosen for further evaluation. The Appraisal of Guidelines for Research and Evaluation (AGREE II) Instrument (17) would be applied to any clinical practice guideline considered for inclusion. Identified systematic reviews that required further consideration based on the above criteria would be assessed using the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tool (18). The results of the AMSTAR assessment would be used to determine whether or not an existing review could be incorporated as part of the evidentiary base. Any identified reviews that did not meet the criteria above, whose AMSTAR assessment indicated important deficiencies in quality, or that were otherwise not incorporated as part of the evidence base would be reported in the reference list, but not further described or discussed.

2.2. Primary Literature Systematic Review

Assuming that no existing systematic review was identified, or that identified reviews were incomplete in some fashion, a systematic review of the primary literature was also planned. This review would be reduced in scope, such as a reduction in subject areas covered, time frames covered, etc., based on the scope of incorporated existing reviews. The criteria described below are written assuming no existing reviews would be incorporated.

2.2.1. Literature Search Strategy

OVID was used to systematically search the MEDLINE and EMBASE databases for evidence in May of 2011. The search was updated on Sept 7, 2012 and again on Feb 4, 2013. A complete literature search strategy can be found in Appendix 2. In addition to the MEDLINE and EMBASE database searches, reference lists of included systematic reviews and primary literature were scanned for potentially useful studies, and four papers were forwarded for consideration by the lead author (EM) from her personal files.

2.2.2. Study Selection Criteria and Protocol

Articles were selected based on the following criteria:

1. Studies that compare indoor tanning history versus no indoor tanning history, and studies for which the primary focus was tanning device use and incidence of melanoma including:
    a. Evidence-Based Clinical Practice Guidelines
    b. Systematic Reviews with and without meta-analyses
    c. Cohort and case-control studies
2. Studies were conducted post-2000 (to focus evidence when possible on most recent tanning devices)
3. Reports published in English only
4. Reports published in peer-reviewed journals

2.2.3. Data Extraction and Assessment of Study Quality and Potential for Bias

Data were extracted from all studies that passed full-text review by methodologists (BR and LS) and the lead author (EM). All extracted data and information were audited by an independent auditor.

The quality of the included primary evidence was assessed as follows. Randomized controlled trials (RCT) would be assessed for quality by examining the following seven criteria: the method of randomization, reporting of blinding, the power and sample size calculation, length of follow-up, reporting details of the statistical analysis, reporting on withdrawals from treatment and other losses to follow-up, and reporting on the sources of funding for the research. Comparative, but non-randomized, evidence would be assessed according to full reporting of: patient selection criteria, all relevant outcomes, and the source of funding.

2.2.4. Synthesizing the Evidence

The WG planned to pool the data if a current meta-analysis was not identified.

3.0. RESULTS

3.1. Search for Existing Clinical Practice Guidelines and Systematic Reviews

Two clinical practice guidelines (19,20), one position statement (21) and five systematic reviews (6,15,16,22,23) were identified by the search for existing systematic reviews (Appendix 3).

3.1.1. Quality of Clinical Practice Guidelines

Identified clinical practice guidelines were published by groups affiliated with the WHO (19) and collaboration between the Australian Cancer Network and the New Zealand Guideline Group (20). As neither of the two clinical practice guidelines retained (19,20) were suitable for adapting, no formal assessment of quality was performed, and they will not be discussed further.

A position statement published by the Canadian Paediatric Society (21) was also retained. Since the position statement (21) was not considered a suitable source of evidence on which to base recommendations, no formal assessment of quality was performed, and it will not be discussed further.

3.1.2. Quality of Systematic Reviews

Of the 16 systematic reviews identified by the literature search, only five specifically addressed the outcomes of interest and were considered for inclusion. Four of the systematic reviews included a meta-analysis (6,15,16,22) and one did not (23).

3.1.2.1. Systematic reviews with meta-analyses

As is illustrated in Appendix 4, there was significant study inclusion overlap between all the systematic reviews with meta-analysis. Additionally, all four evaluated similar outcomes of ever versus never use of indoor tanning devices, age at first use and frequency of use. The reviews by Gordon et al (16) and Boniol et al (22) updated the IARC (6) literature search. Since the Boniol et al meta-analysis (22) was the most recent and complete (Appendix 4), it was the only systematic review quality assessed using the AMSTAR tool (Appendix 5) and included in our evidence base. The remaining three systematic reviews with meta-analysis (6,15,16) will not be discussed further, as they did not add any information over the Boniol et al review (22).

The Boniol et al review (22) scored highly using the AMSTAR assessment criteria (Appendix 5). The only important missed AMSTAR criterion was no reporting of study detail. Since study details are necessary when developing clinical practice guideline recommendations, we extracted study details for the studies included in Boniol et al (22).

3.1.2.2. Systematic reviews without meta-analyses

The one identified systematic review without meta-analysis (23) included many of the studies analyzed in the meta-analyses (Appendix 4), with only two included studies (24,25) that were excluded in the current Boniol et al meta-analysis (22). However, since the systematic review was older than the Boniol et al review (22) and did not include a meta-analysis, the review did not add any information over Boniol et al (22) and will not be discussed further.

3.2. Primary Literature Systematic Review

When the original literature search for this systematic review was conducted, there was no current meta-analysis available on the most recent tanning bed studies. Since the tanning bed emissions changed in the 1990s, the primary literature systematic review was designed to cover studies published between 2000 and May 2011 (original search date), in an effort to analyze the new generation of beds and to allow for the estimated 15-year lag for those exposed to tanning beds and development of melanoma (16). When the literature search was updated in September of 2012, the Boniol et al meta-analysis (22) was identified. At that point, the Boniol et al meta-analysis (22) became the core evidence base for this systematic review. Since Boniol et al (22) did not provide in depth information on the

included studies, it was deemed incomplete, and the updated primary literature systematic review was used to analyze the studies included and excluded from Boniol et al (22). Any identified studies included in Boniol et al (22) are described at an adequate level to better understand the population under investigation and to verify that the studies were clinically homogenous. Additional studies identified by the primary literature systematic review that were not included in Boniol et al (22) are added to the evidentiary base and described in detail.

3.2.1. Literature Search Results

A total of 40 primary literature studies underwent full-text review by the lead author (EM) and methodologists (BR, LS) (Figure 1). Of these, 13 papers were retained (24,26-37) (Appendix 3).

The meta-analysis conducted by Boniol et al (22) pooled 27 studies. Thirteen of the included studies were published before the year 2000. The remaining 14 studies [four cohort (33-35,37) and 10 case control (26-29,31,32,36,38-40) studies] were originally identified by the current systematic review of the primary literature. Three of the case-control studies did not meet the current inclusion criteria, as two were correspondence documents (38,40) and one did not assess ever use compared with never use of indoor tanning devices (39).

Two additional case-control studies (24,30), not included in Boniol et al (22), were identified by the literature search and retained.

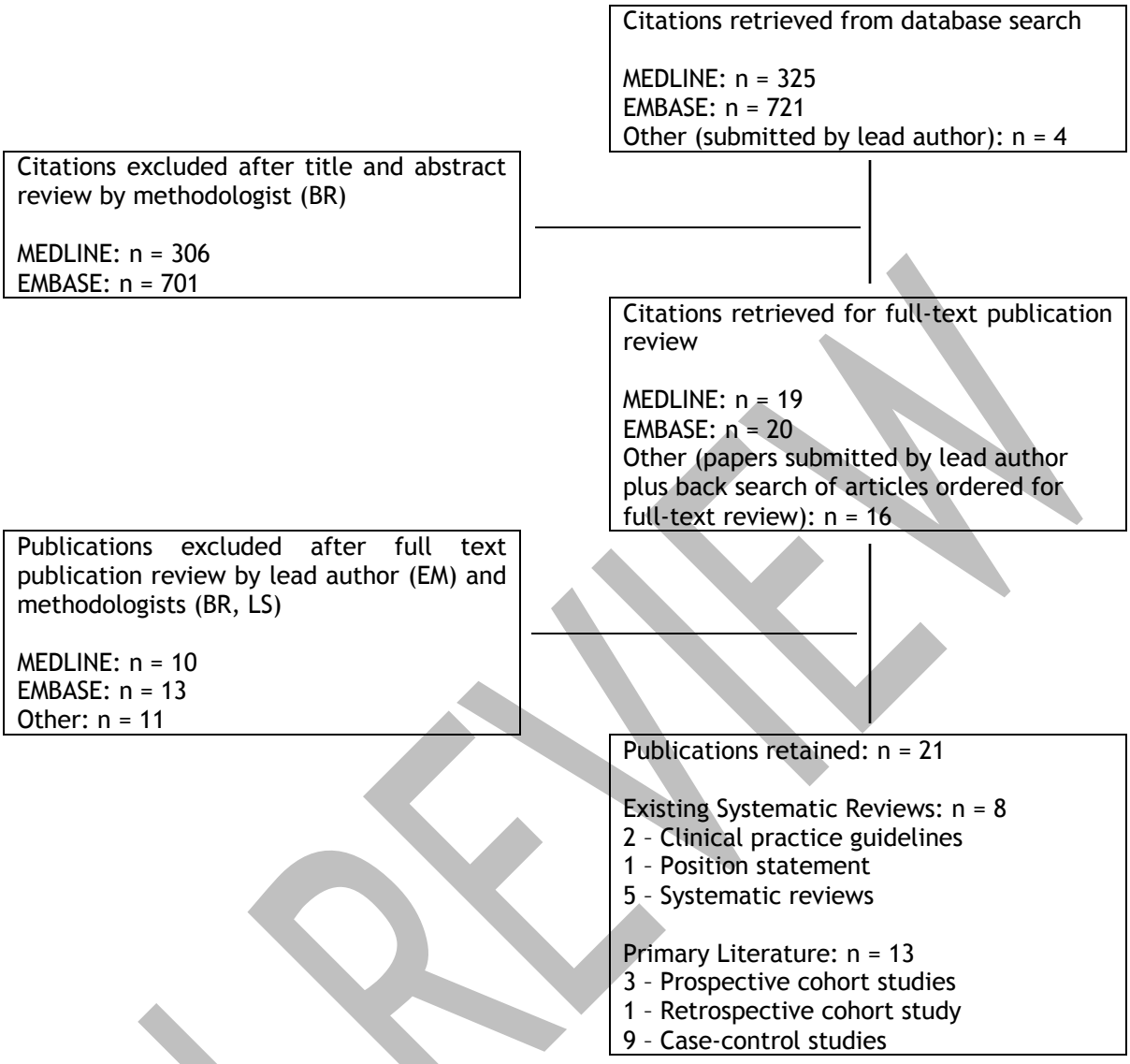

Figure 1. Selection of clinical practice guidelines, systematic reviews and primary literature from the search results of MEDLINE and EMBASE databases.

3.2.2. Study Design and Quality

The included cohort and case-control studies were all assessed for quality according to the following criteria: full reporting of the patient selection criteria and relevant outcomes, and the source of funding. A summary of the quality findings can be found in Appendix 6.

3.2.2.1. Studies included in Boniol et al (22)

The three prospective cohort studies (33,35,37) and one retrospective cohort study (34) pooled by Boniol et al (22) were assessed for quality. All three prospective cohort studies were of acceptable quality; however, the potential for recall bias associated with any self-reported baseline characteristic, exposure, or outcome is acknowledged as a potential limitation in all three. Also, both the Zhang et al and Nielsen et al studies are subject to demographic bias based on gathering data solely from a female nursing population (37) and solely Caucasian (33), respectively. The retrospective cohort study by Ting et al (34) had

several limitations resulting in it being considered of low quality and it will not be discussed further within these results.

A total of seven (26-29,31,32,36) case-control studies included in Boniol et al (22) were quality assessed. All the studies were of adequate quality, but were limited by either, or both, recall and selection bias (Appendix 6).

3.2.2.2. Additional case-control studies

The two case-control studies (24,30) identified outside of the Boniol et al meta-analysis (22) were also quality assessed. As with the other case-control studies, these studies were of adequate quality, but the Fears et al study (30) was limited by recall bias, while the Parr et al study (24) was limited by both recall and selection bias (Appendix 6).

3.3. Question 1. Does the use of indoor tanning devices increase the risk of developing melanoma?

Studies that assessed ever compared with never use of indoor tanning devices were identified to inform this research question. The meta-analysis conducted by Boniol et al (22) plus two additional case-control studies (24,30) reported on this outcome.

3.3.1. Boniol et al (22) *Meta-Analysis*

The meta-analysis by Boniol et al was calculated from a random effects model and pooled data from 17 cohort or population-based case-control studies and 10 other case-control studies, totalling 11,428 cases of melanoma (22). Heterogeneity was assessed by Higgins and Thompson's I^2 statistic, where I^2 scores range from zero to 100%, with zero indicating that the relative risks across studies within the meta-analysis are homogeneous. Our in-depth evaluation of the study details also confirmed that the studies were clinically homogeneous and pooling of the data was appropriate. Of the 27 studies pooled, 18 were conducted in European countries, seven in North America and two in Australia. Findings show a clear association between the use of tanning beds and the subsequent development of melanoma (Figure 2). When all studies were pooled, the summary relative risk (RR) of developing melanoma after ever use of tanning beds was 1.20 (95% confidence interval [CI] 1.08-1.34, $p<0.05$) with some heterogeneity (I^2, 56%) detected between studies (Figure 2). A Macaskill test (41) detected no publication bias when the studies were pooled ($p=0.99$). When only population-based cohort and case-control studies were analyzed, the summary relative risk was slightly higher (RR, 1.25; 95%CI, 1.09-1.43; $p<0.05$) (Figure 2). The study also separately analyzed the 18 studies that adjusted for confounders related to sun exposure and sun sensitivity and found a significant risk of developing melanoma after ever use of tanning beds (RR, 1.29; 95%CI, 1.13-1.48; $p<0.05$). Finally, the paper compared relative risks for developing melanoma as a consequence of tanning bed use in populations living at different latitudes and found that relative risks for ever versus never use did not differ (22).

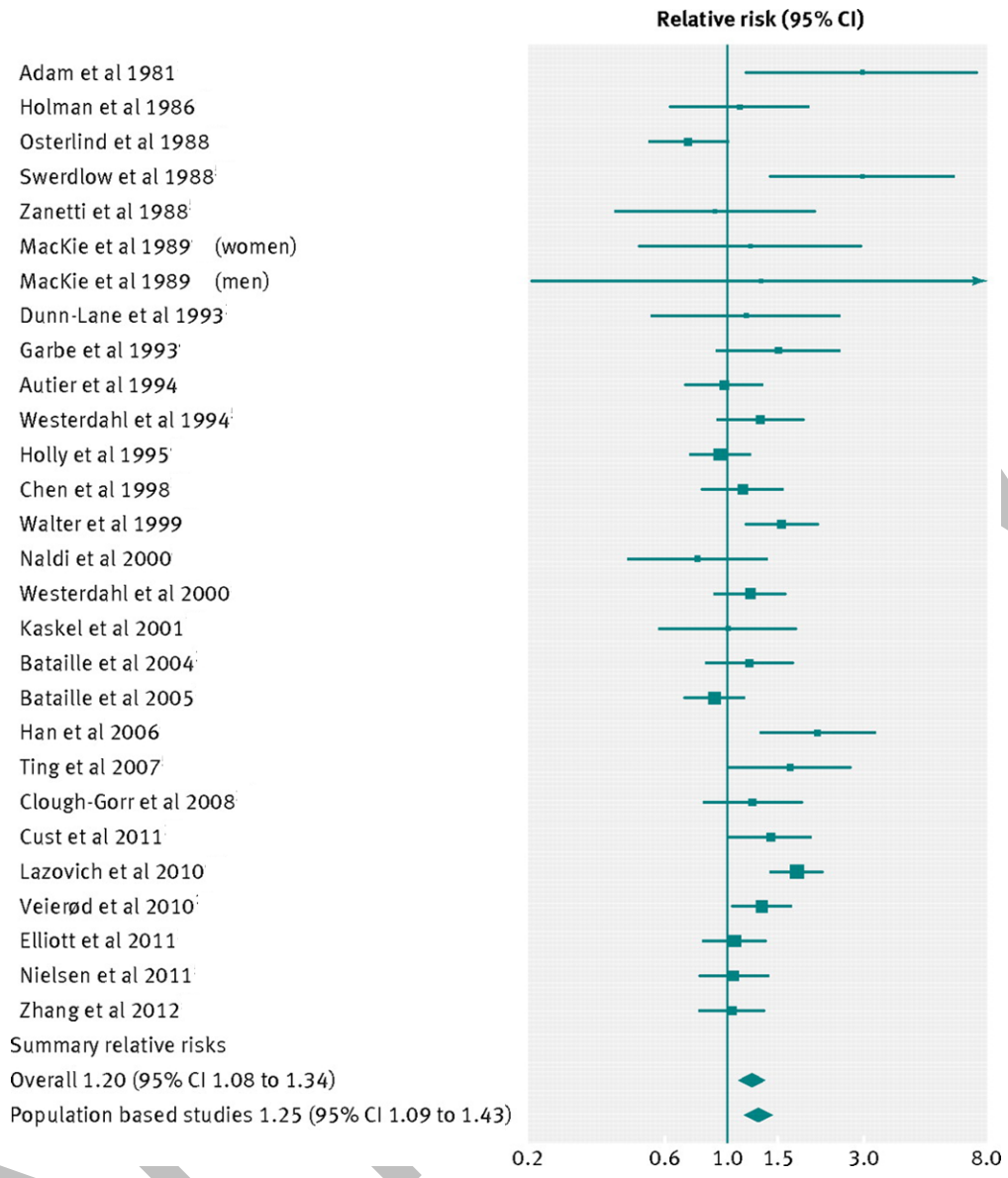

Figure 2. Forest plot of relative risk for melanoma associated with ever compared with never use of indoor tanning devices. Figure reproduced from Boniol et al (22) with permission under the terms of the Creative Commons Attribution Non-Commercial License, permitting reproduction of the open-access article (http://creativecommons.org/licenses/by-nc/2.0/). Figure was modified to remove the reference numbering that pertained to the Boniol et al (22) reference list.

3.3.1.1. Studies included in Boniol et al (22)

Of the 14 studies included in Boniol et al (22) that were published after the year 2000, 11 were evaluated in depth by the present reviewers. As was outlined above (section 3.2.1.), three of the case-control studies pooled by Boniol et al did not meet the current inclusion criteria. The study conducted by Kaskel et al (39) did not assess ever use compared with never use of indoor tanning devices so was excluded from our systematic review; however, Boniol et al (22) chose to include data closest to ever versus never use from this case-control study for this analysis. Additionally, the retrospective cohort study by Ting et al (34) was

excluded from the current systematic review as per the previous quality assessment description (section 3.2.2.1.).

Since the Boniol et al review (22) did not provide adequate descriptions of the pooled studies, the studies identified by the current systematic review are summarized in Table 1 in an effort to provide the dates when indoor tanning devices were used, information on the population under investigation and detail on the comparison used by Boniol et al since most studies included multiple comparisons. Additionally, given that the Boniol et al (22) forest plot (Figure 2) does not include a number value for the relative risks of each study, Table 1 includes the appropriate comparison and relative risk data for the studies. The current reviewers are aware that for every study, Boniol et al (22) transformed measures of association (adjusted for the maximum number of confounding variables and 95% confidence intervals) into logarithms of relative risk and then calculated the corresponding variance, so it is recognized that the relative risk data in Table 1 may be speculative for some comparisons.

Participants in the three cohort studies were from Sweden, Norway and the United States of America and were all women. These studies reported 976 cases of melanoma in 209,380 females. The largest cohort study (35), which compared never, rarely, and once per month or more indoor tanning device use across-age groups (10-19, 20-29, 30-39, 40-49 and 10-39 years of age), found a significantly increased risk for melanoma with ever versus never use of indoor tanning devices (Table 1). The two smaller cohort studies (33,37) did not find a correlation between indoor tanning device use and melanoma (Table 1). The cohort study conducted by Nielsen et al (33) separately analyzed use of sun lamps and sunbeds and compared 25 to 39 year olds with 40 to 64 year olds, while the cohort study by Zhang et al (37) evaluated the risk of tanning bed use on skin cancers among teenage and young women enrolled in the Nurses' Health Study II cohort. The seven case-control studies included in the Boniol et al (22) meta-analysis included melanoma cases from across Europe and North America. Three case-control studies (29,31,32), including the largest (32), found a significantly increased risk for melanoma with ever use of indoor tanning devices (Table 1). The remaining four case-control studies were unable to correlate indoor tanning device use to increased risk of melanoma (26-28,36).

Table 1. Studies included in Boniol et al (22) assessing risk of melanoma with ever versus never use of indoor tanning devices.

Study	Population	Tanning Device Use (TDU)	Relative Risk (RR) included in Boniol et al meta-analysis (22)
Prospective Cohort Studies			
Veierod et al, 2010 (35)	• 30-50 year-old Swedish and Norwegian females • n = 106,366	• 1962–2005 • TDU reporting from 1962 to study inception (1991-1992) was retrospective	• Age-adjusted significant risk for ever use vs. never use for 10-39 year olds ○ RR = 1.31; 95%CI, 1.03-1.33; p=0.03 (Figure 2)
Nielsen et al, 2012 (33)	• Swedish cohort of randomly chosen women aged 25-64 • n = 29,520	• TDU collected retrospectively in 1990-1991 • Cohort then followed until 2007	• Multivariate analysis could not confirm a correlation between ever use of sun lamps and risk of melanoma ○ HR = 1.0; 95%CI, 0.6-1.6 (Figure 2)
Zhang et al, 2012 (37)	• 25-42 year-old female nurses enrolled in Nurses' Health Study II cohort in the United States of America	• TDU reported retrospectively in 2005 on TDU in high school or college and at ages 25-35	• No significant difference in risk for melanoma from tanning bed exposure when comparing between never to ever use, separated by age groups (during

Study	Population	Tanning Device Use (TDU)	Relative Risk (RR) included in Boniol et al meta-analysis (22)
	• n = 73,494	• Cohort then followed until 2009	high school/college and ages 25-35) ○ HR = 1.11; 95%CI, 0.97-1.27; p=0.13 (Figure 2)[I]
Case-Control Studies			
Westerdahl et al, 2000 (36)	• Cases from Swedish population-based tumour registry ○ n = 571 ○ AOD: 16-80 • Controls from National Population registry	• Melanoma diagnosed in 1995-1997 with TDU collected retrospectively	• No significant association when comparing never use to 'sometime' use ○ OR = 1.1; 95%CI, 0.8-1.4 (Figure 2)[II]
Bataille et al, 2004 (27)	• Cases and controls from hospitals and general practitioners in the United Kingdom ○ Cases: n = 413 • Cases and controls were 16-75 years old	• Melanoma diagnosed in 1989-1993 • Retrospective collection of TDU	• After adjusting for age and gender, risk of developing melanoma after ever exposure to tanning beds was not significant ○ OR = 1.19; 95%CI, 0.84-1.68; p=0.33 (Figure 2)[II]
Bataille et al, 2005 (26)	• Cases from clinics and hospitals in Sweden, the Netherlands, the United Kingdom, Belgium and France ○ n = 597 ○ AOD: 18-49 • Controls from population registries, general practice and neighbourhoods, matched to country, age and gender	• Melanoma diagnosed in 1998-2001 with TDU collected retrospectively	• No significant difference was found when looking at age-adjusted ever vs. never use ○ OR = 0.90; 95%CI, 0.71-1.14 (Figure 2)
Han et al, 2006 (31)	• Cases and controls from the Nurses' Health Study cohort ○ Cases: n = 200 • Women were aged 30-55 at study inception in 1976	• Melanoma diagnosed in 1989 and 2000 • Cases and controls filled out questionnaires in 2002 on UV exposure retrospectively	• OR = 2.06; 95%CI, 1.30-3.26; p<0.05) (Figure 2)
Clough-Gorr et al, 2008 (28)	• Cases from New Hampshire state cancer registry ○ n = 423 ○ AOD: 20-69 • Controls from state driver's licence registry, matched by age and gender	• Melanoma diagnosed in 1995-1998 • Retrospective collection of UVB tanning lamp use before 1980 and UVA tanning bed use after 1980, to one year prior to diagnosis	• No significant difference was found when analyzing ever use vs. never use of tanning beds ○ OR = 1.14; 95%CI, 0.80-1.61 (Figure 2)[II]
Cust et al, 2011 (29)	• Cases from population-based registries in Brisbane, Sydney and	• Melanoma diagnosed in 2000-2002 with TDU collected	• OR = 1.41; 95%CI, 1.01-1.96; p=0.04 (Figure 2)

Study	Population	Tanning Device Use (TDU)	Relative Risk (RR) included in Boniol et al meta-analysis (22)
	Melbourne, Australia ○ n = 604 ○ AOD: 18-39 • Controls from electronic roll, matched by city, gender and age	retrospectively	
Lazovich et al, 2010 (32)	• Cases from Minnesota state cancer registry ○ n = 1,167 ○ AOD: 25-29 • Age and gender matched controls from driver's licence registry	• Melanoma diagnosed in 2004-2007, retrospective collection of TDU during adolescence	• OR = 1.74; 95%CI, 1.42-2.14; p=0.006 (Figure 2)

Note: AOD, age of diagnosis; HR, hazard ratio; OR, odds ratio; RR, relative risk; TDU, tanning device use; vs, versus.

[I] In the Zhang et al study (37), the RR values for the individual groups comparisons (during high school/college and aged 25-35), as well as an average of four times a year in both periods, were very similar, making it difficult for the current reviewers to speculate on the comparison used by Boniol et al (22) (Figure 2). The RR included in this table is the RR calculated for average use in both periods as it most closely represented the forest plot RR (Figure 2).

[II] In addition to the non-significant risk recorded by these three studies and used by Boniol et al (22) (Figure 2), all three studies also found a significant risk for ever use of tanning devices. Westerdahl et al (36) found significantly increased risk of melanoma with regular tanning device use (OR, 1.8; 95%CI, 1.2-2.7; p=0.05). In the Clough-Gorr et al (28) study, a significantly increased risk of melanoma with ever use was found when analyzing both tanning bed and tanning lamp use together (OR, 1.96; 95%CI, 1.00-1.96; p<0.05). The 2004 Bataille et al study (27) reported an age-adjusted significant difference between ever and never use for those under 45 when combined with skin type I and II (OR, 2.25; 95%CI, 1.10-5.02; p<0.05).

3.3.2. Additional Case-Control Studies

Two additional small case-control studies were identified by the current systematic review of the primary literature (24,30). These two studies fall within the search dates of Boniol et al (22), but that review does not mention exclusion of the studies, so it is unclear whether the Boniol et al search did not identify these studies or if they were excluded based on specific criteria.

The case-control study conducted by Fears et al (30) assessed only 188 cases of melanoma. This study analyzed data obtained through a large case-control study conducted in 1991-1992 (42). Fears et al examined ever use versus never use, total number of sessions, whether the enrollee was a current user and number of years tanning beds had been used. The study did not find a significant difference between ever use and never use of tanning devices.

The smallest case-control study identified was conducted by Parr et al (24) and assessed 162 cases of melanoma. This nested case-control study analyzed women in the Norwegian Women and Cancer Study cohort and was designed to assess recall bias. Information about melanoma risk factors was collected at study enrollment, in 1991-1992 when cases and controls were 24-49 year old, or in 1996-1997 and again in 2004, after some women had developed melanoma. Parr et al examined never versus rarely and/or more than or equal to once/month use of tanning devices in 10 to 19, 20 to 29, 30 to 39 and 40 to 49 year olds. There were no significant differences found for any comparison. However, a trend approaching significance was found for 20-29 year old women who had used tanning devices compared with those who had no exposure (odds ratio [OR], 1.73; 95%CI, 0.99-3.02; p=0.06).

3.3.3. Summary

The systematic review with meta-analysis conducted by Boniol et al (22) found a significantly increased relative risk for melanoma after ever use of indoor tanning devices (RR, 1.25; 95%CI, 1.09-1.43; $p<0.05$). Neither of the additionally identified case-control studies found an association between ever use of indoor tanning devices and increased melanoma diagnosis (24,30).

3.4. Question 1a. Does age at first use of indoor tanning device affect the relative risk of developing melanoma?

Studies that compared age of indoor tanning device use initiation and risk of developing melanoma were included for this research question. The meta-analysis conducted by Boniol et al (22) and one additional case-control study (24) were included.

3.4.1. Boniol et al (22) *Meta-Analysis*

The Boniol et al meta-analysis (22) assessed age of initiation and heightened risk of developing melanoma. Thirteen of the included 27 studies included evaluations for first tanning bed use in youth compared with never use. Relative risks from the 13 studies were pooled to determine the overall RR (Figure 3). Relative risks were adjusted for confounders related to sun exposure and sun sensitivity in 12 of the 13 studies. The analysis found that use before the age of 35 increased the risk of developing melanoma compared with tanning device use after the age of 35 (RR, 1.59; 95%CI, 1.36-1.85; $p<0.05$) (Figure 3) with no heterogeneity (I^2, 3%).

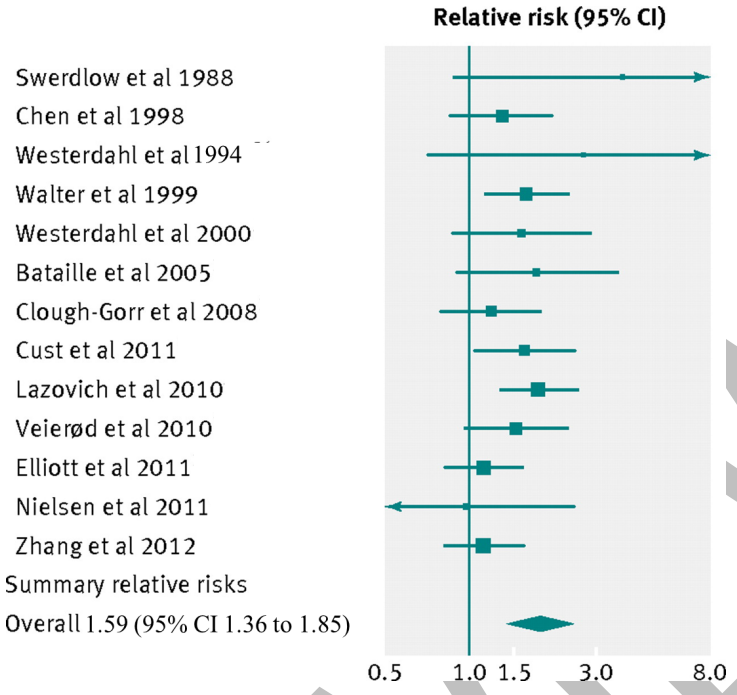

Figure 3. Forest plot of relative risk for melanoma associated with ever use of indoor tanning devices when first use was before age of 35. Figure reproduced from Boniol et al (22) with permission under the terms of the Creative Commons Attribution Non-Commercial License, permitting reproduction of the open-access article (http://creativecommons.org/licenses/by-nc/2.0/). Figure was modified to incorporate the RR correction published after the initial release of the Boniol et al review (22). Additionally, the reference numbering that pertained to the Boniol et al reference list was removed from the figure.

3.4.1.1. Studies included in Boniol et al (22)

Of the 13 studies pooled for this analysis, all nine studies published after 2000 were identified by the current systematic review with eight (26,28,29,32,33,35-37) meeting the inclusion criteria. Once again, since the Boniol et al review (22) did not provide adequate descriptions of the pooled studies, Table 2 summarizes the dates when indoor tanning devices were used, information on the population under investigation and details on the age of initiation comparison for the identified studies. Additionally, given that the Boniol et al (22) forest plot (Figure 3) does not include a number value for the relative risks of each study, Table 2 includes the appropriate comparison and relative risk data for the studies, recognizing that due to data transformation by Boniol et al (22), relative risk data may be speculative for some comparisons.

The largest cohort study, which grouped women by age decade to determine if age of indoor tanning device use affected the risk of developing melanoma, found a trend towards increased risk for 20 to 29 year olds that was not statistically significant (35) (Table 2). The other two cohort studies did not find a link between age of indoor tanning device use initiation and increased risk of melanoma (33,37). Of the five case-control studies that analyzed age of initiation, three studies found an increased risk of developing melanoma when indoor tanning device use was initiated at an earlier age (Table 2). The study by Westerdahl et al (36) compared tanning device use before and after age 35, while the study by Cust et al (29) compared use before and after age 25, and Lazovich et al (32) compared usage before and after age 18. The Boniol et al (22) meta-analysis did not include data from

the 2004 Bataille et al (27) case-control study. However, the case-control study reported an age-adjusted significant difference between ever and never use for those under 45 when combined with skin type I and II (OR, 2.25; 95%CI, 1.10-5.02; p<0.05).

Table 2. Studies included in Boniol et al (22) assessing risk of melanoma with ever use of indoor tanning devices based on age of initiation.

Study	Population	Tanning Device Use (TDU)	Relative Risk (RR) Included in Boniol et al Meta-analysis (22)
Prospective Cohort Studies			
Veierod et al, 2010 (35)	• 30-50 year-old Swedish and Norwegian females • n = 106,366	• 1962–2005 • TDU reporting from 1962 to study inception (1991-1992) was retrospective	• No significant difference between age decades of 10-19, 20-29, 30-39 and 40-49 • A trend towards risk was reported for TDU of at least once per month vs. never use for 20-29 year olds compared to 10-19, 30-39 and 40-49 year olds ○ RR = 1.39; 95%CI, 0.90-2.14; p=0.13 (Figure 3) [I]
Nielsen et al, 2012 (33)	• Swedish cohort of randomly chosen women aged 25-64 • n = 29,520	• TDU collected retrospectively in 1990-1991 • Cohort then followed until 2007	• Significantly increased risk for users that use tanning devices more than 10 times per year vs. never use for 25-39 year olds compared with 40-64 year olds ○ HR = 2.5; 95%CI, 1.0-6.2; p=0.05 [II]
Zhang et al, 2012 (37)	• 25-42 year-old female nurses enrolled in Nurses' Health Study II cohort • n = 73,494	• TDU reported retrospectively in 2005 on TDU in high school or college and at ages 25-35 • Cohort then followed until 2009	• No significant difference in risk when comparing TDU in female in high school/college vs. 25-35 years old who both used tanning devices more than six times per year ○ HR = 1.23; 95%CI, 0.69-2.20; p=0.37 (Figure 3)
Case-Control Studies			
Westerdahl et al, 2000 (36)	• Cases from Swedish population-based tumor registry ○ n = 571 ○ AOD: 16-80 • Controls from National Population registry	• Melanoma diagnosed in 1995-1997 with TDU collected retrospectively	• Increased risk of melanoma as a consequence of TDU for those under the age of 35 vs. those over 35 when comparing ever to never use ○ OR = 2.3; 95%CI, 1.2-4.2; p=0.05 (Figure 3)
Bataille et al, 2005 (26)	• Cases from clinics and hospitals in Sweden, the Netherlands, the United Kingdom, Belgium and France ○ n = 597 ○ AOD: 18-49 • Controls from population registries, general practice and neighbourhoods, matched to country,	• Melanoma diagnosed in 1998-2001 with TDU collected retrospectively	• No significant difference when comparing age of first use before age 15 and after age 15 ○ OR = 1.82; 95%CI, 0.92-3.62 (Figure 3)

Study	Population	Tanning Device Use (TDU)	Relative Risk (RR) Included in Boniol et al Meta-analysis (22)
	age and gender		
Clough-Gorr et al, 2008 (28)	• Cases from New Hampshire state cancer registry ○ n = 423 ○ AOD: 20-69 • Controls from state driver's licence registry, matched by age and gender	• Melanoma diagnosed in 1995-1998 • Retrospective collection of UVB tanning lamp use before 1980 and UVA tanning bed use after 1980, to one year prior to diagnosis	• No difference detected when comparing age of TDU initiation before age 20 and after age 20 ○ OR = 1.78; 95%CI, 0.76-4.15; p=0.42 (Figure 3) [II]
Cust et al, 2011 (29)	• Cases from population-based registries in Brisbane, Sydney and Melbourne, Australia ○ n = 604 ○ AOD: 18-39 • Controls from electronic roll, matched by city, gender and age	• Melanoma diagnosed in 2000-2002 with TDU collected retrospectively	• Increased risk for melanoma with TDU for those less than 25 years old, compared with older than 25 years ○ OR = 1.64; 95%CI, 1.07-2.51; p<0.05 (Figure 3) [III]
Lazovich et al, 2010 (32)	• Cases from Minnesota state cancer registry ○ n = 1,167 ○ AOD: 25-29 • Age and gender matched controls from driver's licence registry	• Melanoma diagnosed in 2004-2007, retrospective collection of TDU during adolescence	• Significantly increased risk of melanoma when TDU initiation occurs before age 18 ○ OR = 1.85; 95%CI, 1.33-2.57; p≤0.05 (Figure 3)

Note: AOD, age of diagnosis; HR, hazard ratio; OR, odds ratio; RR, relative risk; TDU, tanning device use; vs, versus.

[I] In addition to the non-significant risk reported by Veierod et al (35) and included in the Boniol et al meta-analysis (22) (Figure 3), Veierod at et also reported a significantly increased risk for melanoma for frequent users (at least once per month) of tanning beds in two or three decades when ages 10-39 were combined (age-adjusted RR, 2.13; 95%CI, 1.25-3.64; p=0.004).

[II] For both these studies, the RR value listed in the table could not be linked to the RR value used in the Boniol et al (22) forest plot (Figure 3). These risk values are those reported by the individual studies for their age of initiation comparison.

[III] In the Cust et al study (29), age of initiation for TDU compared use before age 25 and after age 25 (OR, 1.64; 95%CI, 1.07-2.51; p<0.05); however, when younger ages were examined, the OR for tanning bed use initiation before age 20 was 1.88 (95% CI, 0.99-3.57; p=0.02) and the OR for between ages 20 and 24 was 1.50 (95%, CI 0.88-2.55; p=0.02). Since these OR values are very similar, the current reviewers are merely speculating that the OR comparing TDU before age 25 to after age 25 is the risk value used in the Boniol et al meta-analysis (22) (Figure 3).

3.4.2. Additional Case-Control Study

The Parr et al case-control study (24) compared never versus rarely and at least once a month use of indoor tanning beds across age ranges of 10 to 19, 20 to 29, 30 to 39 and 40 to 49, and did not find a difference in melanoma risk between the age groups.

3.4.3. Summary

The Boniol et al meta-analysis (22) determined that indoor tanning device use before the age of 35 increased the risk of developing melanoma compared with tanning device use after the age of 35 (RR, 1.59; 95%CI, 1.36-1.85; p<0.05). The additional case-control study by

Parr et al did not find a significantly increased risk for developing melanoma when tanning device use was initiated at a younger age.

3.5. Question 1b. Does the frequency of indoor tanning device use affect the relative risk of developing melanoma?

When assessing the risk of melanoma in relation to tanning device use frequency, studies that included both session length and number of tanning sessions were considered. The Boniol et al meta-analysis (22), as well as two additional case-control studies (24,30), informed this research question.

3.5.1. Boniol et al (22) *Meta-Analysis*

The systematic review with meta-analysis conducted by Boniol et al (22) found an increased risk of melanoma development for each additional session of tanning device use per year (RR, 1.8%; 95%CI, 0.0-3.8%; $p<0.05$). This analysis included four studies that reported data on risk associated with the number of tanning bed sessions per year. Additionally, analysis of 14 studies that reported relative risks with frequent tanning bed use (Figure 4) found a 42% increased risk of developing melanoma with high tanning bed use (RR, 1.42; 95%CI, 1.15-1.74; $p<0.05$; I^2, 47%). High tanning bed use was defined as the highest category of sunbed use reported in each study (22).

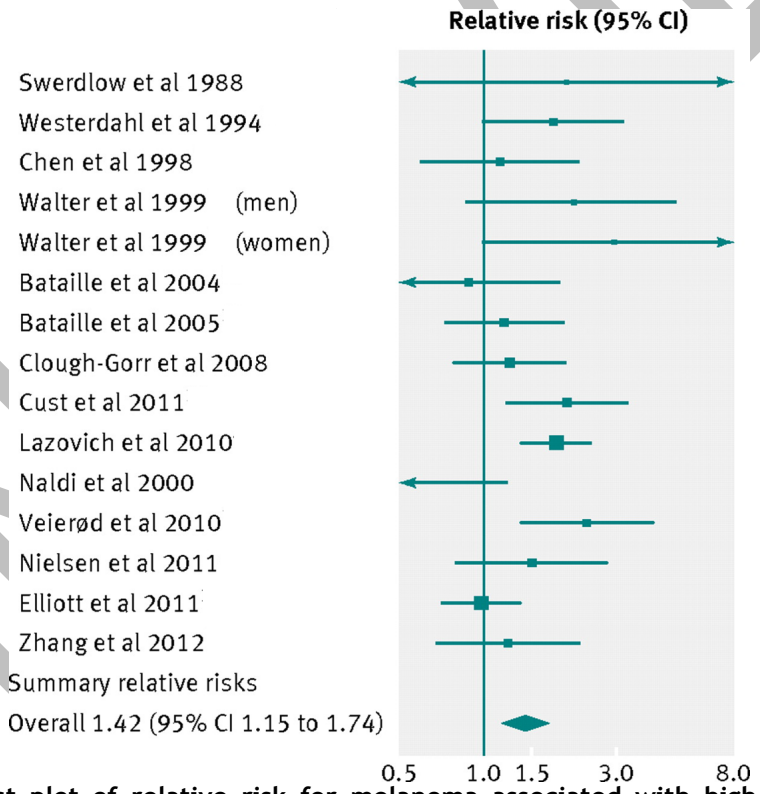

Figure 4. Forest plot of relative risk for melanoma associated with high use of indoor tanning devices. Figure reproduced from Boniol et al (22) with permission under the terms of the Creative Commons Attribution Non-Commercial License, permitting reproduction of the open-access article (http://creativecommons.org/licenses/by-nc/2.0/). Figure was modified to remove the reference numbering that pertained to the Boniol et al reference list. For this analysis, "high use" was defined as the highest use condition for each individual study.

3.5.1.1. Studies included in Boniol et al (22)

Of the 14 studies pooled for this analysis, all 10 studies published after 2000 were identified by the current systematic review, with eight (26-29,32,33,35,37) meeting the inclusion criteria. Since the Boniol et al review (22) did not provide adequate descriptions of the pooled studies, the studies identified by the current systematic review are summarized in Table 3 in an effort to provide the dates when indoor tanning devices were used, information on the population under investigation and details on the frequency of indoor tanning devices use in each study. Additionally, given that the Boniol et al (22) forest plot (Figure 4) does not include a number value for the relative risks of each study, Table 3 includes the appropriate comparison and relative risk data for the studies, recognizing that this may be speculative for some comparisons.

Of the three cohort studies, the largest study found an increased risk of melanoma with frequent use of indoor tanning devices (35) (Table 3). When ages 10 to 39 were combined, a significantly increased risk for melanoma was found with at least once a month use of tanning devices in two or three decades. Neither the cohort study by Nielsen et al (33) nor the cohort study by Zhang et al (37) found an association between high frequency of indoor tanning device use and increased risk of melanoma. Five case-controls studies published after 2000 were pooled in the Boniol et al meta-analysis (22) (Table 3). Two of these case-control studies found an increased risk for melanoma with frequent use of indoor tanning devices. Lazovich et al (32) found that the odds ratios for developing melanoma increased with number of lifetime sessions, with the highest risk being associated with more than 100 sessions (Table 3). Similarly Cust et al (29) assessed number of lifetime indoor tanning sessions and found a significantly increased risk of melanoma with more than 10 sessions compared with no tanning device use (Table 3). The case-control studies conducted by Clough-Gorr et al (28) and by Bataille et al (26,27) did not find an association between melanoma risk and increased frequency of tanning device use (Table 3).

Table 3. Studies included in Boniol et al (22) assessing risk of melanoma with high use of indoor tanning devices.

Study	Population	Tanning Device Use (TDU)	Relative Risk (RR) Included in Boniol et al Meta-analysis (22)
Prospective Cohort Studies			
Veierod et al, 2010 (35)	• 30-50 year-old Swedish and Norwegian females • n = 106,366	• 1962–2005 • TDU reporting from 1962 to study inception (1991-1992) was retrospective	• Significantly increased risk for melanoma in 10-39 year olds who use tanning devices at least once a month in two or three decades compared with never use ○ RR = 2.37; 95%CI, 1.37-4.08; p=0.003 (Figure 4)
Nielsen et al, 2012 (33)	• Swedish cohort of randomly chosen women aged 25-64 • n = 29,520	• TDU collected retrospectively in 1990-1991 • Cohort then followed until 2007	• No significantly increased risk for all women (aged 25-64) who used tanning devices more than 10 times per year ○ HR = 1.5; 95%CI, 0.8-2.8; p=0.2 (Figure 4) [I]
Zhang et al, 2012 (37)	• 25-42 year-old female nurses enrolled in Nurses' Health Study II cohort • n = 73,494	• TDU reported retrospectively in 2005 on TDU in high school or college and at ages 25-35 • Cohort then	• No significantly increased risk for women in high school/college or those 25-35 years old when using tanning devices more than six times per year

Study	Population	Tanning Device Use (TDU)	Relative Risk (RR) Included in Boniol et al Meta-analysis (22)
		followed until 2009	○ High school/college: HR = 1.23; 95%CI, 0.69-2.20 (Figure 4) [II] ○ 25-35 years old: HR = 1.31; 95%CI, 0.90-1.91 (Figure 4) [II]
Case-Control Studies			
Bataille et al, 2004 (27)	• Cases and controls from hospitals and general practitioners in the United Kingdom ○ Cases: n = 413	• Cases and controls were 16-75 years old • Melanoma diagnosed in 1989-1993 • Retrospective collection of TDU	• No significant difference in risk when comparing number of cumulative lifetime hours of TDU (0, 1-9, 10-19, 20-99, >100 hours) ○ OR = 0.92; 95%CI, 0.43-1.91 (Figure 4)
Bataille et al, 2005 (26)	• Cases from clinics and hospitals in Sweden, the Netherlands, the United Kingdom, Belgium and France ○ n = 597 ○ AOD: 18-49 • Controls from population registries, general practice and neighbourhoods, matched to country, age and gender	• Melanoma diagnosed in 1998-2001 with TDU collected retrospectively	• No significant difference in risk when comparing cumulative lifetime TDU in hours (0, <10, 10-30, 31-60, 61-100, >100 hours) ○ OR = 1.19; 95%CI, 0.73-1.93 (Figure 4)
Clough-Gorr et al, 2008 (28)	• Cases from New Hampshire state cancer registry ○ n = 423 ○ AOD: 20-69 • Controls from state driver's licence registry, matched by age and gender	• Melanoma diagnosed in 1995-1998 • Retrospective collection of UVB tanning lamp use before 1980 and UVA tanning bed use after 1980, to one year prior to diagnosis	• No significant difference in risk when comparing frequency of use (never, less than 10 times, at least 10 times) or years of use (never, less than 1 year, more than 1 year) ○ RR = 1.25; 95%CI, 0.79-1.98; p=0.42 (Figure 4)
Cust et al, 2011 (29)	• Cases from population-based registries in Brisbane, Sydney and Melbourne, Australia ○ n = 604 ○ AOD: 18-39 • Controls from electronic roll, matched by city, gender and age	• Melanoma diagnosed in 2000-2002 with TDU collected retrospectively	• Significantly increased risk of melanoma with more than 10 TDU sessions compared with never use ○ OR = 2.01; 95%CI, 1.22-3.31; p=0.01 (Figure 4)
Lazovich et al, 2010 (32)	• Cases from Minnesota state cancer registry ○ n = 1167 ○ AOD: 25-29 • Age and gender	• Melanoma diagnosed in 2004-2007, retrospective collection of TDU during adolescence	• Risk for developing melanoma increased with number of lifetime TDU sessions with highest risk associated with more than 100 sessions

Study	Population	Tanning Device Use (TDU)	Relative Risk (RR) Included in Boniol et al Meta-analysis (22)
	matched controls from driver's licence registry		○ OR = 2.72; 95%CI, 2.01-3.63; p=0.0002 (Figure 4)

Note: AOD, age of diagnosis; HR, hazard ratio; OR, odds ratio; RR, relative risk; TDU, tanning device use; vs, versus.

[I] In addition to the non-significant risk due to more frequent TDU in all women in the Nielsen et al study (33) that was used in the Boniol et al meta-analysis (22) (Figure 4), Nielsen et al also reported a significantly increased risk for 25-39 year olds. After adjusting for host factors, sunburns and sun exposure, the authors reported a significant increase in risk of melanoma among younger women (25-39 years at enrolment) who used sunbeds more than 10 times per year (HR = 2.5; 95%CI, 1.0-6.2; p=0.05).

[II] Since these risks are very close in value, the current reviewers are unable to speculate on which was used in the Boniol et al meta-analysis (22) (Figure 4).

3.5.2. Additional Case-Control Studies

The Fears case-control study (30) found that longer session times and more frequent tanning device use was associated with an increased risk of melanoma compared with shorter session times and less frequent use (OR not provided; p=0.04).

The case-control study by Parr et al (24) did not find an association between melanoma risk and increased frequency of tanning device use when comparing never to rarely and at least once per month use.

3.5.3. Summary

The meta-analysis by Boniol et al (22) reported both an 8% increased risk of melanoma development for each additional session of tanning device use per year (RR, 1.8%; 95%CI, 0.0-3.8%; p<0.05), as well as a 42% increased risk of developing melanoma with high tanning bed use (RR, 1.42; 95%CI, 1.15-1.74; p<0.05). The case-control study by Fears et al (30) also found that frequent use of indoor tanning devices and longer tanning session resulted in an increased risk for melanoma (p=0.04). The case-control study by Parr et al (24) did not find an association when comparing never to rarely and at least once per month indoor tanning device use.

3.6. Ongoing Trials

The clinical trials database at http://www.clinicaltrials.gov was searched for relevant active and closed trials on February 18, 2013 using the keywords "tan", "tanning", and "melanoma". No studies were found in this search.

4.0. DISCUSSION

Worldwide, the incidence of melanoma is increasing, with older males having a higher incidence in North America and Australia, and females of all ages in Europe (43). Globally, among the fair-skinned Caucasian population, the annual rate of increase in melanoma ranges from 3% to 7% [reviewed in (44)]. In Ontario, the incidence rates have more than doubled since 1971 (2). Of concern is the increased incidence in youth and young adults, and females in particular (2,45). In Ontario, melanoma accounts for 10% of malignancies among 15 to 34 year olds, the fourth most common malignancy in this age group (2).

In Canada, from 1996 to 2006, there was a statistically significant increase in indoor tanning, from 7.7% to 9% of adults (13). From the 2006 National Sun Survey (13), the most frequent users of tanning beds were 16 to 24 year olds, with 27% of young women, and 8% of young men reporting use. Similar findings were reported in the United States, with the highest rates of indoor tanning in white females aged 18 to 21 (32%), with 67% of these reporting tanning at least 10 times in the past 12 months (46). Ontario data from the 2006 National Sun Survey (13) reported that 2.1% of females in Grades 7/8, and 11.4% of those in

Grades 11/12 had ever used a tanning bed. Significantly, an Ipsos Reid poll (47) commissioned by the Canadian Cancer Society in 2012 reported a near-doubling in use, with 21% of Grade 12 students having used a tanning bed. From 2006 to 2012, overall use had increased from 5% to 8% of the Grade 7 to 12 students surveyed. Similarly, the Youth Risk Behaviour Survey (YRBS), conducted by the United States Centers for Disease Control (CDC), examined the self-reported use of indoor tanning devices by public and private high school students in Grades 9 through 12. As reviewed in Watson (48), the 2011 national survey found that 13.3% of high school students used an indoor tanning device in the previous year. For females, the prevalence of indoor tanning increased from 11.7% in Grade 9 to 31.8% in Grade 12 (for males, 4.5% and 8.5%, respectively) (48).

When work began on this guideline in May 2011, there had been no recent systematic review, meta-analysis or guideline regarding use of indoor tanning devices. Recognizing the recent publication of several studies assessing the relationship between use of indoor tanning devices and risk of melanoma, the Melanoma DSG of Cancer Care Ontario's PEBC sought to conduct an updated systematic review and establish a clinical practice guideline. In an effort to capture the impact of more modern tanning beds, which were developed in the 1990s and emit UVA plus approximately 4% UVB, compared to the earlier generation of primarily UVA emitting beds, we elected to date the start of our literature review in 2000. In the meta-analyses identified by the original literature search in 2011 (6,15,16), approximately half of the pooled studies were published between 1981 and 2004, likely reflecting the earlier generation of tanning devices. In order to incorporate studies analyzing the new generation of indoor tanning devices and in order to allow for the estimated 15-year lag for those exposed to tanning beds and development of melanoma (16), a complete primary literature systematic review was conducted from 2000 onwards. The meta-analysis conducted by Boniol et al (22) was identified in a literature search update in 2012 and thus became the core for this evidentiary base. Boniol et al (22) included all of the studies analyzed in the older meta-analyses plus studies conducted up until 2012. When compared with the primary literature systematic review originally conducted for this report, Boniol et al (22) included all the identified studies since 2000, with the exception of Parr et al (24) and Fears et al (30).

The Boniol et al meta-analysis (22) was a strong report that pooled data from 27 cohort and case-control studies, totalling 11,428 international cases of melanoma. Although, it was recognized that Boniol et al (22) was the best available evidence and it did score highly on the AMSTAR, the lack of detail on the included studies was considered a shortcoming of the review. Providing an in-depth assessment of the included studies allowed us to determine the included study quality, population recruitment details, decade of tanning bed use and the clinical homogeneity of studies. The current systematic review sought to assess the post-2000 studies included in the Boniol et al meta-analysis (22). Additionally, we attempted to link the relative risks reported in the Boniol et al (22) forest plots (Figures 2-4) to the appropriate analysis in each of the included studies in order to better understand which data were pooled by Boniol et al. Even though Boniol et al (22) completed data transformation on the pooled relative risks, this link was generally easy to determine. In a few notable cases, the current reviewers were unable to identify the appropriate data pooled and were only able to speculate (Table 1-3).

The substantial strength of the Boniol et al meta-analysis (22) is in the consistent and significant findings of an increased risk of melanoma with the use of indoor tanning devices across numerous studies. When all 27 studies were pooled, the meta-analysis found a significant 20% increased risk of melanoma for ever versus never use of indoor tanning devices (RR, 1.20; 95%CI 1.08-1.34; $p<0.05$). A further strength of Boniol et al (22) is the inclusion of more recent studies, which used in depth questionnaires to assess for additional risk factors of melanoma, in terms of both constitutional host factors and sun exposure history. Blonde or

red hair, light eye colour, freckles, nevi, Fitzpatrick skin types I and II and family history of melanoma are important risk factors for melanoma [reviewed in (49)]. Other potentially confounding risk factors, assessing the degree of solar UV exposure, including outdoor recreational or employment exposure, sunbathing vacation and a history of sunburns and blistering, were also more commonly taken into account with the recent publications. One critique of early studies, in particular, is the lack of control for these confounding risk factors for melanoma. Boniol et al (22) undertook an analysis restricted to the 18 studies that adjusted for such confounders, which yielded a similar summary relative risk of 1.29 (95%CI, 1.13-1.48; $p<0.05$). Unfortunately, the Boniol et al report (22) did not include a forest plot for this analysis, nor a list of the 18 studies that were pooled. However, from our in-depth review of the post-2000 studies included in Boniol et al (22), the current reviewers speculate that all three included prospective cohort studies [Nielsen et al (33), Veierod et al (35), Zhang et al (37)], as well as the case-control studies by Westerdahl et al (36), Bataille et al in 2005 (26), Clough-Gorr et al (28) and Lazovich et al (32) were included in this analysis, as they all controlled for host susceptibility factors and sun exposure variables, such as routine exposure, outdoor activity exposure and sunburns.

Two additional case-control studies that assessed the risk of developing melanoma with ever versus never use of indoor tanning devices were identified by the primary literature systematic review. Both the Fears et al (30) and Parr et al (24) studies were small studies, which may have contributed to their finding no association between indoor tanning device use and risk of melanoma. Fears et al (30) included only 188 cases of melanoma and was limited by recall bias and limited data on indoor tanning use. Similarly, the case-control study by Parr et al (24) included only 162 cases of melanoma and was limited by recall bias. Parr et al (24) was also limited by selection bias, as the population was solely female; however, this was minimized by the population-based design of the study. Neither of these case-control studies were included in the Boniol et al meta-analysis (22). Boniol et al (22) does indicate exclusion of a few studies based on study design and lack of estimates of relative risk for melanoma associated with use of indoor tanning devices. Since both Fears et al (30) and Parr et al (24) would pass these selection criteria and they were not mentioned in Boniol et al (22), it is unclear whether the studies were not picked up by the literature search or if they were excluded based on undisclosed criteria. Given the relatively small number of cases included in Fears et al (30) and Parr et al (24) compared with the size and significance of a number of well conducted studies included in Boniol et al (22), it is extremely unlikely that their inclusion would have greatly impacted the results of the meta-analysis.

Another negative case-control study, that was included in Boniol et al (22), warrants closer investigation. Bataille et al in 2005 (26) was the largest of the negative case-control studies (n=597). The authors noted limitations of the study, including its multi-centre design (across six countries in Europe), with different health systems and UV awareness, as well as difficulties in standardizing methods of recruitment. In a follow-up report analyzing the findings of this study, De Vries et al (50) reviewed in detail the potential for selection bias, with subjects potentially self-selecting as the study ethics board mandated that participants were aware of the purpose of the study. Additionally, the study found no association between solar UV exposure and melanoma, a well-documented association, leading the authors to speculate that cases may have under-reported both their solar UV and indoor tanning device exposure. Finally, there was also significant use of tanning devices, found in 53% of cases and 57% of controls, indicating possible recruitment bias in this study. The current reviewers hypothesize that inclusion of this large case-control study with known study limitations in the Boniol et al meta-analysis (22) may have led to a lower estimation of indoor tanning device risk.

The current systematic review is the only published review that has endeavored to identify the generation of tanning bed use within the individual studies contained therein. Although we designed the current literature search with a year 2000 starting point, in an effort to capture the impact of more modern tanning beds, the Boniol et al meta-analysis (22) was included in the evidentiary base as the most up-to-date and comprehensive data available. In an effort to still identify the generation of tanning beds used in the Boniol et al meta-analysis (22), our in-depth analysis of the pooled studies included extracting tanning device usage dates. All of the prospective cohort studies included in Boniol et al (22) assessed tanning device usage that took place in the 1980s, while a number of the case-control studies evaluated cases whose diagnosis of melanoma occurred in the 1980s and 1990s (26-28,31,36). This identifies a gap in the current research, as our in-depth analysis of the studies demonstrated that the included studies evaluated the older generation of primarily UVA emitting beds. It is hypothesized that future studies, assessing the impact of modern indoor tanning devices, aimed to mimic solar UVR, including approximately 4% UVB, may amplify the relative risk found by Boniol et al (22).

The Boniol et al meta-analysis (22) also found a significantly increased risk of melanoma in those whose first use of tanning devices occurred before the age of 35 (RR, 1.59; 95%CI, 1.36-1.85; $p<0.05$). This summary relative risk was determined from pooling of 13 studies that included evaluations for tanning bed use in youth compared with never use. Boniol et al (22) defined younger age as before age 35; however, not all the studies included in the analysis defined an age for younger age. From the in-depth review of the included studies, we know that the three included prospective cohort studies did not use a definitive younger age cut-off but instead a younger age range. Veierod et al (35) compared age groups of 10 to 19, 20 to 29, 30 to 39 and 40 to 49, plus a combined group of age 10 to 39. Nielsen et al (33) compared women who were 25 to 39 years old with women who were 40 to 69 years old. Finally, the prospective short study by Zhang et al (37), which found a non-significant trend for melanoma with younger age, compared women in high school or college to women who were 25 to 36 years old. In the three included case-control studies that found an increased risk of melanoma with a definitive age cut-off, younger age was defined as less than 25 years (29), less than 35 years (36) and less than 18 years (32). The lack of a definitive "younger age" in the literature does not constitute a limitation of the evidence, but rather points to an association between tanning bed use and increased risk of developing melanoma at any younger age of first use.

When analysing the frequency of tanning device use on the risk of developing melanoma, the Boniol et al meta-analysis (22) calculated a relative risk for frequent use of tanning device and one specifically for number of sessions in a year. The meta-analysis found a significantly increased risk of 42% (95%CI, 1.15-1.74) with higher use of indoor tanning devices (22). For this analysis, Boniol et al (22) pooled data from 14 studies that reported relative risks with high tanning bed use. For each of the studies, Boniol et al used the highest category of tanning device use reported (22). When attempting to link the appropriate primary literature data to the forest plot (Figure 4) for this analysis, the current reviewers did not identify any notable issues. Based on four studies that reported an increased risk of melanoma with increased number of tanning bed sessions per year, Boniol et al (22) found a 1.8% increased risk of melanoma for each additional session of sunbed use per year (95%CI, 0.998-1.038). Unfortunately, Boniol et al (22) does not indicate which four studies were used for this analysis. From the in-depth review of the included studies, the current reviewers speculate that the four studies included Veierod et al (35), Nielsen et al (33), Cust et al (29) and Lazovich et al (32), as these four studies reported an increased risk of melanoma with frequent tanning bed sessions. Additionally, the case-control study conducted by Fears et al (30) that was not included in Boniol et al (22) found that longer session times and frequent

use was associated with an increased risk of melanoma compared with shorter session times and less frequent use.

As illustrated in the footnotes of Tables 1 through 3, our independent evaluations of the studies included in Boniol et al (22) identified some discrepancies between the comparisons pooled in the meta-analyses and those the current reviewers would have included. It should be noted that all discrepancies point to Boniol et al (22) providing a conservative estimate of the risk of indoor tanning device use and does not challenge our conclusion.

A final strength of the Boniol et al meta-analysis (22) is the translatability of the findings. In addition to pooling data from studies conducted in Europe, North America and Australia, Boniol et al (22) sought to compare relative risks at different latitudes. The analysis compared relative risks for developing melanoma as a consequence of tanning bed use in populations living at different latitudes and found that relative risks for ever versus never use did not differ (22). Thus, the findings from Boniol et al (22) can appropriately be used to inform guidance for our target population in Ontario.

5.0. CONCLUSIONS

There is strong evidence associating the use of indoor tanning devices and the risk of developing melanoma. A comprehensive meta-analysis that included several well-designed, case-control and cohort studies demonstrated a significant and consistent increased risk of melanoma with ever versus never use of tanning beds.

Solar UVR was first declared a carcinogen in 1992 by the IARC, and in 2009, they expanded the definition of UVR to include UVA, UVB and UVC, as well as UVR from indoor tanning devices. Given that the amount of UVR generated by indoor tanning devices far exceeds that of solar UVR (10-12), the increased frequency of tanning bed use by youth and young adults, and the increasing incidence of melanoma in 15 to 34 year olds, this is a particularly pressing issue.

The global increase in use of indoor tanning devices, along with increasing rates of melanoma, has prompted numerous countries to legislate a ban on their use, particularly for youths. Internationally, Brazil has completely banned use of tanning beds, while many European countries and Australia have banned youth under the age of 18. In North America, many states in the U.S.A. have some form of restricted access. In Canada, four provinces, including Nova Scotia, P.E.I., Quebec, and parts of British Columbia, have bans for those under the age of 18; Manitoba and Saskatchewan require parental consent for under-18s. More recently, in early October 2013, the Skin Cancer Prevention Act was passed, banning indoor tanning device use for youth under 18 years of age in Ontario. Based on an Australian study that estimated 281 of 8,682 total new cases of melanoma diagnosed annually could be attributed to indoor tanning devices (51), it is hypothesized that this ban in Ontario could potentially reduce the number of annually diagnosed cases of melanoma by a similar factor.

There are perceived postulated benefits to the use of indoor tanning devices, including obtaining adequate amounts of vitamin D, as well as psychological benefits. The issue of vitamin D has been extensively assessed by the Institute of Medicine (IOM) (52). While UVB radiation, both solar and from indoor tanning devices, can initiate the production of vitamin D in the skin, there are no data to support that UVR is superior to oral supplementation of vitamin D in increasing serum levels of this vitamin. The IOM does not view indoor tanning devices as an important source of vitamin D. Given the risk of skin cancer from indoor tanning devices, the IOM (52), Canadian Dermatology Association (53) and Ontario Division of the Canadian Cancer Society (54) all recommend oral supplementation to increase vitamin D levels. While there are studies suggesting indoor tanning devices promote

an overall sense of well-being (55), this review demonstrates that the potential risk of indoor tanning devices use far outweighs any of these potential benefits.

We recommend that all tanning bed use should be avoided to decrease the risk of developing cutaneous malignant melanoma. As there is a clear association between earlier age of first use of indoor tanning devices, although there were some differences used in the age cut-offs across the studies, the summation of evidence suggests that there is a particularly elevated risk in those under the age of 35 (22). Lastly, given that there is an increased risk of melanoma with increasing frequency of tanning device use, there is no safe minimum exposure to artificial UVR from indoor tanning devices.

6.0. CONFLICT OF INTEREST

Information regarding conflict of interest declarations can be found at the end of Section 3.

7.0. ACKNOWLEDGEMENTS AND AUTHORSHIP

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A complete list of the members of the Expert Panel and the Working Group, with their affiliations and conflict of interest information, is provided in Section 3, Appendix 1.

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Evidence-Based Series 8-8: Section 3

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

The Use of Indoor Tanning Devices and the Risk of Developing Cutaneous Malignant Melanoma: A Systematic Review and Clinical Practice Guideline: Development Methods, Recommendations Development and External Review Process

E. McWhirter, L.H. Souter, R.B. Rumble, C. Rosen, T. Tenkate, J. McLaughlin, A. Mamelak, F. Wright, T. Petrella, and the Use of Indoor Tanning Devices Expert Panel

Report Date: August 6, 2014

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, 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, termed Disease Site Groups (DSGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC produces evidence-based and evidence-informed guidelines, known as Evidence-Based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

This EBS is comprised of the following sections:

- *Section 1: Guideline Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.

- *Section 2: Evidentiary Base*. Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: Development Methods, Recommendations Development, and External Review Process*. Summarizes the EBS development process, the recommendations development process and the results of the formal external review of the draft version of the EBS.

FORMATION OF WORKING GROUP

The Melanoma Disease Site Group (Melanoma DSG) asked the PEBC to develop a guideline on the association between cutaneous malignant melanoma (herein referred to as melanoma) and tanning bed usage. In consultation with the Melanoma DSG, a Working Group (WG) was identified from the Melanoma DSG membership, plus prevention and public health contacts provided by CCO's Prevention Program. This Working Group consisted of two medical oncologists, one dermatologist, one surgeon, one epidemiologist, one public health scientist and two methodologists. The WG, Melanoma DSG, and public health contacts also formed the Use of Indoor Tanning Devices Guideline Development Group. This group would take responsibility for providing feedback on the guideline as it was being developed and acted as an Expert Panel for the document at Internal Review, reviewing the document and requiring changes as necessary before approving it.

OBJECTIVES AND RESEARCH QUESTIONS

This WG developed the following objective for this guideline in consultation with the Use of Indoor Tanning Devices Expert Panel.

1. To determine the risk of melanoma associated with use of indoor tanning devices, including if age at first use affects the relative risk of developing melanoma and if increased use affects the relative risk of developing melanoma.

From this objective, the following research questions were derived to direct the search for available evidence to inform recommendations to meet the objectives.

1. **Does the use of indoor tanning devices increase the risk of developing melanoma?**
    a. **Does age at first use of indoor tanning device affect the relative risk of developing melanoma?**
    b. **Does the frequency of indoor tanning device use affect the relative risk of developing melanoma?**

GUIDELINE REVIEW

Almost all PEBC document projects begin with a search for existing guidelines that may be suitable for adaptation. The PEBC defines adaptation, in accordance with the ADAPTE Collaboration, as "the use and/or modification of (a) guideline(s) produced in one cultural and organizational setting for application in a different context" (3). This includes a wide spectrum of potential activities, from the simple endorsement, with little or no change, of an existing guideline, to the use of the evidence base of an existing guideline with *de novo* recommendations development.

For this document, a search was conducted of the Inventory of Cancer Guidelines (www.cancerguidelines.ca) and the National Guidelines Clearinghouse (www.guideline.gov). In addition, the websites of several known high-quality guideline developers, including Scottish Intercollegiate Guideline Network (SIGN), American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), National Institute for Health and Care Excellence (NICE), Australian National Health and Medical Research Council, New Zealand Guideline Group and International Agency for Research on Cancer (IARC) were

searched. Finally, an electronic search employing OVID was used to systematically search the MEDLINE and EMBASE databases from 2000 to week 6 of 2013 using the following keywords: "melanoma," "skin tumor," "sun tan," "sun bathing," "sunlight," and "ultraviolet radiation." Only guidelines published after 2000 were considered. Guidelines that were considered relevant to the objectives and the research questions were then evaluated for quality using the Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument.

Two clinical practice guidelines were retained from the literature search. As neither of the two clinical practice guidelines was suitable for adaptation, neither was included in the evidentiary base.

EVIDENTIARY BASE DEVELOPMENT

Using the research questions described above, a search for existing systematic reviews and a systematic review of the primary literature were conducted, as described in Section 2 of this EBS.

INITIAL RECOMMENDATIONS

Using the evidentiary base in Section 2, the WG developed a set of initial recommendations. These initial recommendations were developed through a consideration of the aggregate evidence quality and the potential for bias in the evidence and the likely benefits and harms of using indoor tanning devices. The WG considered the values they used in weighing benefits compared with harms and then made a considered judgement. This process is described in detail for each topic area described below.

Main Research Question – Risk of melanoma with tanning device use

Key Evidence for Benefits and Harms

A systematic review with meta-analysis (4) based on pooling of 27 cohort and case-control studies found a significant association between indoor tanning device use and increased risk of developing melanoma (relative risk [RR], 1.25; 95% confidence interval [CI], 1.09-1.43; $p<0.05$).

Aggregate Evidence Quality and Potential for Bias

The meta-analysis conducted by Boniol et al (4) was of fairly good quality. The lack of detail on the included studies was a limitation of the review; however, the in-depth review of the studies in the current systematic review verified the clinical homogeneity of the pooled studies.

Values of the Working Group

This systematic review evaluated studies from 2000 to present with the goal of capturing the impact of modern tanning devices, which have been designed to more accurately mimic solar UVR. However, all of the cohort studies assessed tanning device usage that took place in the 1980s, and a number of the case-control studies looked at cases whose diagnosis of melanoma occurred in the 1980s and 1990s. Thus, future studies assessing the impact of the modern tanning beds could potentially amplify the effects found in the current review.

Considered Judgement

There is strong evidence associating the use of indoor tanning devices and the risk of developing melanoma. Although both the prospective cohort studies and case-control studies are subject to several forms of bias, the findings of these studies are consistent and

significant. The Melanoma DSG feels that the current evidence informs a strong recommendation.

Initial (DRAFT) Recommendation 1
Use of indoor tanning devices should be avoided to reduce risk of melanoma.

Sub-question a. – Age at first use
Key Evidence for Benefits and Harms

A recent and comprehensive systematic review with meta-analysis (4) found an increased risk of melanoma in those who initiated tanning device use at a younger age (RR, 1.59; 95%CI, 1.36-1.85; $p<0.05$). Data were pooled from 13 studies, 12 of which adjusted for confounders related to sun exposure and sun sensitivity.

Aggregate Evidence Quality and Potential for Bias

The meta-analysis conducted by Boniol et al (4) was of fairly good quality. The lack of detail on the included studies was a limitation of the review; however, the in-depth review of the studies in the current systematic review verified the clinical homogeneity of the pooled studies.

Values of the Working Group

Given that both the rate of tanning device use in youths and the incidence of melanoma diagnosis in 15 to 34 year olds are increasing, use of indoor tanning devices by youths is of great concern.

Considered Judgement

Based on the evidence, the Melanoma DSG has not set an age cut-off for "younger age." The identified meta-analysis defined 'young age' as under age 35 (4). However, not all the studies included in the analysis defined an age for younger age; in those that did, 'younger age' was defined as anywhere from age 18 to age 35. In the three included case-control studies that found an increased risk of melanoma with a definitive age cut-off, younger age was defined as less than 25 years (5), less than 35 years (6) and less than 18 years (7). The Melanoma DSG believes these data point to an association between tanning bed use and increased risk of developing melanoma at any younger age of first use; defining a specific age cut-off would only be speculative and would not add to the recommendation.

Initial (DRAFT) Recommendation 2
All individuals should avoid use of indoor tanning devices, especially those at a younger age.

Sub-question b. – Frequency of use
Key Evidence for Benefits and Harms

The meta-analysis conducted by Boniol and colleagues (4) found a 1.8% increased risk of developing melanoma for each additional session of tanning device use per year (95%CI, 0.0-3.8%; $p<0.05$). Additionally, when Boniol et al (4) conducted an analysis of 14 studies that reported relative risks with frequent tanning bed use, they found a 42% increased risk of developing melanoma with high tanning bed use (RR, 1.42; 95%CI, 1.15-1.74; $p<0.05$). One additional case-control study (8), which was not included in the Boniol et al meta-analysis (4), similarly found an association between increased risk of melanoma and both number of sessions and length of sessions ($p=0.04$).

Aggregate Evidence Quality and Potential for Bias

The meta-analysis conducted by Boniol et al (4) was of fairly good quality. The lack of detail on the included studies was a limitation of the review; however, the in-depth review of the studies in the current systematic review verified the clinical homogeneity of the pooled studies. The case-control study conducted by Fears et al (8) was a very small study of acceptable quality that was limited by recall bias.

Values of the Working Group

The 2006 Second National Sun Survey (9) demonstrated that 9% of Canadians use indoor tanning devices. Of those using tanning devices, 36% use them more than 12 times per year (9).

Considered Judgement

When evaluating the risk associated with frequent use of indoor tanning devices, both number of sessions and length of tanning sessions were considered. Based on the association between both number of indoor tanning device sessions and length of sessions, and the increased risk of developing melanoma, the evidence indicates that there is no amount of safe exposure to tanning beds.

Initial (DRAFT) Recommendation 3
There is no safe lower limit of exposure to artificial UVR from indoor tanning devices.

INTERNAL REVIEW

Almost all PEBC documents undergo internal review. This review is conducted by the Expert Panel and the Report Approval Panel. The WG was responsible for incorporating the feedback and required changes of both of these panels, and both panels had to approve the document before it could be sent to External Review.

Expert Panel Review and Approval

The Melanoma DSG plus prevention and public health contacts provided by CCO's Prevention Program acted as the Use of Indoor Tanning Devices Expert Panel for this document. The members of this group were required to submit conflict of interest declarations prior to reviewing the document. These declarations are described in Appendix 1. The document must be approved by formal vote. In order to be approved, 75% of the Use of Indoor Tanning Devices Expert Panel members must cast a vote or abstain, and of those who voted, 75% must approve the document. At the time of the voting, the Use of Indoor Tanning Devices Expert Panel members could suggest changes to the document, and possibly make their approval conditional on those changes. In those cases, the WG was responsible for considering the changes, and if those changes could be made without substantially altering the recommendations, the altered draft would not need to be resubmitted for approval again.

The Use of Indoor Tanning Devices Expert Panel reviewed the document at several draft stages during the Melanoma DSG meetings that were held in the spring and fall of 2011, 2012 and 2013. In October of 2013, the Use of Indoor Tanning Devices Expert Panel was emailed a complete draft that the WG believed was ready for Expert Panel approval. During this review, the Use of Indoor Tanning Devices Expert Panel provided the following key feedback.

1. Expert Panel members raised concern about the inclusion of the Boniol et al meta-analysis (4) in addition to individual studies included within.
2. Expert Panel members suggested that studies on DNA damage by UVR be added to the introduction and discussion of Section 2.

3. Expert Panel members were concerned that the data may be providing an underestimate of the risk as most studies evaluated the older generation of beds. Expert Panel members believed that this concern should be included in Section 1.
4. Recommendation 2 wording was debated as the original recommendation did include a definition for younger age. Expert Panel members believed that defining a younger age cut-off did not add to the recommendation.
5. Wording for Recommendation 3 was also debated, although the message remained the same.

In response to this feedback, the WG made the following changes.

1. WG members explained the need for the in-depth analysis of the studies included in Boniol et al (4), which the Expert Panel accepted. Guideline text was then altered to more clearly explain the in-depth analysis.
2. The provided studies on DNA damage were added to the introduction and discussion of Section 2. Additionally, statements explaining DNA damage by UVR were added to the Qualifying Statement for Recommendation 1.
3. Although the hypothesis that the data provide an underestimation of risk was originally included in the discussion of Section 2, further statements were added to the Qualifying Statements for Recommendation 1.
4. Recommendation 2 was altered to remove a younger age definition. A Qualifying Statement section was added to Recommendation 2, which outlined the age definitions in the included studies.
5. The text for Recommendation 3 was altered to incorporate concerns.

On November 1, 2013 at the Melanoma DSG fall meeting, the Use of Indoor Tanning Devices Expert Panel considered a draft of the document incorporating the changes described above, and formally approved the document by vote. Of the 17 members of the Use of Indoor Tanning Devices Expert Panel, 15 members cast votes and two abstained, for a total of 88.2% response. Of those that cast votes, 15 approved the document (100%).

Report Approval Panel Review and Approval

The purpose of the Report Approval Panel (RAP) review is to ensure the methodological rigour and quality of PEBC documents. The RAP consists of nine clinicians with broad experience in clinical research and guideline development, and the Director of the PEBC. For this document, two RAP members review the document; the Director and one other. RAP members must not have had any involvement in the development of the guideline prior to Internal Review. Both RAP members must approve the document, although they may do so conditionally. If there is a conditional approval, the WG is responsible for ensuring the necessary changes are made, with the Assistant Director of Quality and Methods, PEBC, making a final determination that the RAP's concerns have been addressed.

In November 2013 the RAP reviewed this document. The RAP approved the document in January 2014. Key issues raised by the Report Approval Panel included the following:

1. RAP reviewers raised concern about the inclusion of both the Boniol et al meta-analysis (4) and the studies included within.
2. One RAP reviewer found the multiple layers of subheading in Section 2 confusing.
3. One RAP reviewer believed that the Justification for Recommendation 1 was awkward to read and difficult to understand.
4. One RAP reviewer believed that the guideline would benefit from a lay summary.
5. The original version of the guideline included recommendations and a conclusion for the identified clinical practice guidelines and position statement in an appendix. One

RAP reviewer believed that since the identified clinical practice guidelines and position statement were not adapted, that there was no need to include the appendix.

The Working Group made the following changes in response to the RAP review:

1. The Working Group reframed the guideline to focus more on the results of the Boniol et al meta-analysis (4), while better clarifying the need for the in-depth analysis of the included studies. Additionally data from the included studies that were not pertinent to better understanding the meta-analysis or the population under investigation were removed from the evidence base.
2. Section 2 was reorganized using a number-based subheading system.
3. Justification for Recommendation 1 was rewritten for clarity.
4. The Working Group agreed that the guideline would benefit from a lay summary for this guideline. Unfortunately, neither the Working Group, nor the PEBC have the resources or experience to produce a lay summary.
5. The appendix was removed from the guideline.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following approval of the document at Internal Review, the Melanoma DSG circulated the draft document with recommendations modified as noted under Internal Review, above, to external review participants for review and feedback.

Methods

Targeted Peer Review: During the guideline development process, 13 targeted peer reviewers from Ontario, Nova Scotia, British Columbia and Quebec, considered to be clinical and/or methodological experts on the topic were identified by the WG. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Three reviewers agreed, and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on April 9, 2014. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The Use of Indoor Tanning Devices Expert Panel reviewed the results of the survey.

Professional Consultation: Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. The PEBC database was used to identify professionals who had reported being interested in both melanoma or skin cancer and either systemic therapy, radiation, surgery or primary care. Additionally, public health individuals were identified through the UV Network ListServ. All identified professionals were contacted by email to inform them of the survey. All 70 individuals informed of the survey were from Ontario. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). The notification email was sent on April 9, 2014. The

consultation period ended on May 9, 2014. The Use of Indoor Tanning Devices Expert Panel reviewed the results of the survey.

Results

Targeted Peer Review
Three responses were received from three reviewers. Key results of the feedback survey are summarized in Table 1.

Table 1. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=3)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. **Rate the guideline development methods.**				2	1
2. **Rate the guideline presentation.**				2	1
3. **Rate the guideline recommendations.**			1	2	
4. Rate the completeness of reporting.				2	1
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?			1	2	
6. Rate the overall quality of the guideline report.				3	
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.			2	1	
8. I would recommend this guideline for use in practice.			2	1	

9. What are the barriers or enablers to the implementation of this guideline report?
The targeted peer reviewers did not define any barriers or enablers for this guideline.

Summary of Written Comments

The main points contained in the written comments were:

1. All three reviwers felt that although the available evidence does not allow for a definition for "younger age," a lack of definition makes Recommendation #2 difficult to apply. Additionally, one reviewer was concerned that those 25-35 would be missed as this age bracket is not generally considered "younger."
2. One reviewer is concerned that the recommendations do not provide action guidance for clinicians and only further support what clinicians and nurses already know, leading the reviewer to speculate that peers will not make use of the guideline.
3. One reviewer suggested a rewrite for Recommendation 3 to instead state, "There is no safe limit of exposure to artificial ultraviolet radiation related to the use of indoor tanning devices."
4. Two reviewers suggested inclusion of discussion surrounding duration and cumulative dose of UVR when discussing the studies. They believed that the importance of these factors were implied by Recommendation 3, but felt that the idea could be made clearer. One additionally pointed out that cumulative dose has significant implications in cancer

development, behavioural modification, and risk assessment at a clinical level. Finally, the other reviewer was concerned that a discussion about frequency of use is not complete without including comment on dose and duration of UVR.
5. One reviewer would have liked the guideline to address the expected reduction in melanoma if we intervene on the use of indoor tanning.

Professional Consultation
Five responses were received. Key results of the feedback survey are summarized in Table 2.

Table 2. Responses to four items on the professional consultation survey.

	Number (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.				4 (80%)	1 (20%)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.				2 (40%)	3 (60%)
3. I would recommend this guideline for use in practice.				3 (60%)	2 (40%)

4. What are the barriers or enablers to the implementation of this guideline report?
The Professional Consultation reviewers identified public education as the main barrier to implementation of this guideline. The reviewers identified the precise sun safety direction and inclusion of discussion on obtaining adequate levels of vitamin D as an enabler for implementation.

Summary of Written Comments
The main point contained in the written comments was:
1. Several reviewers pointed to a need for public dissemination of this guideline. The reviewers were concerned that simple publishing as per usual PEBC channels would result in missing the most important target audience.

Modifications/Actions
1. Recommendation 3 was lengthened to state that there is no lower limit of exposure to artificial UVR.
2. The Justification for Recommendation 2 was altered to include the point that the younger a person starts using indoor tanning devices, the higher the risk of developing melanoma. A definition for "younger age" was not added to the Recommendation as the Expert Panel stands behind their original belief that an age would not add to the recommendation.
3. The Expert Panel is comfortable with the Recommendations not being action statements as they believe the action is implicit.
4. In terms of UVR duration and cumulative dose, the Expert Panel feels that the issues were thoroughly explained in Section 2 and that inclusion in Section 1 is unnecessary.
5. A study from Australia, which addressed the expected reduction in melanoma incidence if tanning device use is lowered, was added to the Discussion of Section 2 to address the comment on intervention benefit.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Use of Indoor Tanning Devices Expert Panel and the Report Approval Panel of the PEBC. Updates of the report will be conducted in accordance with the PEBC Document Assessment and Review Protocol.

Conflict of Interest

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, Use of Indoor Tanning Device Expert Panel members, and internal and external reviewers were asked to disclose potential conflicts of interest. All authors except for AM and CR reported that they had no conflict of interest. AM reported that he runs a private practice dermatology clinic, and that he was interviewed by the Ottawa Sun about skin cancer and risk factors. CR reported that she has also been involved in media interviews where she has voiced her views on the risk of indoor tanning. All Melanoma DSG members, except for AJ reported no conflict of interest. AJ published on opinion piece on the risk of indoor tanning in Current Oncology in 2012. All RAP members reported no conflict of interest. All external reviewers except for CM reported no conflict of interest. CM reported that he runs a private practice dermatology clinic. The COI declared above did not disqualify any individuals from performing their role in the development on this guideline, in accordance with the PEBC COI policy. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi@mcmaster.ca.

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Appendix 1: Members of the Use of Indoor Tanning Devices Guideline Development Group.

Working Group Members

Name and Affiliation	Contact Information	Conflict of Interest
Elaine McWhirter, MD Assistant Professor, McMaster University	Juravinski Cancer Centre 699 Concession St. Hamilton, ON L8V 5C2	None
Lesley H Souter, PhD Health Research Methodologist, Cancer Care Ontario's Program in Evidence-Based Care	Dept. of Oncology, McMaster University, Juravinski Hospital Site 711 Concession St. Hamilton, ON L8V 1C3	None
R. Bryan Rumble, MSc Health Research Methodologist, Cancer Care Ontario's Program in Evidence-Based Care	Dept. of Oncology, McMaster University, Juravinski Hospital Site 711 Concession St. Hamilton, ON L8V 1C3	None
Cheryl F. Rosen, MD Head, Division of Dermatology	Toronto Western Hospital and University Health Network Hospitals 399 Bathurst St. Toronto, ON M5T 2S8	Has voiced her views on risk of indoor tanning in media interviews
Thomas Tenkate, PhD Associate Professor and Director	School of Occupational and Public Health Ryerson University 350 Victoria St. Toronto, ON M5B 2K3	None
John McLaughlin, PhD Professor, Dalla Lana School Of Public Health and Senior Investigator, Lunenfeld-Tanenbaum Research Institute	Lunenfeld-Tanenbaum Research Institute Mount Sinai Hospital 600 University Ave. Toronto, ON M5G 1X5	None
Adam Mamelak, MD Sanova Dermatology	12319 North Mopac Expressway, Suite 100 Austin, TX 78758	Runs a private practice dermatology clinic. Has been interviewed by the Ottawa Sun about skin cancer and risk factors.
Frances Wright, MD Co-Chair, Melanoma Disease Site Group	Division of General Surgery, Sunnybrook Health Sciences Centre 2075 Bayview Avenue Toronto, ON M4C 5T2	None
Teresa Petrella, MD Co-Chair, Melanoma Disease Site Group	Sunnybrook Health Sciences Centre 2075 Bayview Avenue Toronto, ON M4C 5T2	None

Report Approval Panel Members

Name	Contact Information	Conflict of Interest
Dr Melissa Brouwers	Dept. of Oncology, McMaster University, Juravinski Hospital Site 711 Concession St. Hamilton, ON L8V 1C3	None
Dr Sebastien Hotte	Juravinski Cancer Centre 699 Concession St. Hamilton, ON L8V 5C2	None

Expert Panel Members

Name	Contact Information	Conflict of Interest
Melanoma DSG Members		
Dr Tara Baetz	Cancer Centre of Southeastern Ontario, Kingston General Hospital	None
Dr Pablo Cano	Northeastern Ontario Regional Cancer Centre	None
Annette Cyr	Melanoma Network of Canada	None
Dr Alexandra Easson	Princess Margaret Hospital	None
Dr Danny Ghazarian	Toronto General Hospital	None
Dr Caroline Hamm	Windsor Regional Cancer Centre	None
Dr Anthony Joshua	Princess Margaret Hospital	Published an opinion piece on the risk of indoor tanning in Current Oncology, 2012
Dr Jadranka Jambrosic	Dermatology Practice, Brampton	None
Dr David McCready	Princess Margaret Hospital	None
Dr Christian Murray	Skin Surgery Centre, University of Toronto	None
Dr Xinni Song	The Ottawa Hospital Cancer Centre	None
Dr Sudha Rajagopal	Credit Valley Hospital	None
Dr Alexander Sun	Princess Margaret Hospital	None
Dr John Toye	Plastic Surgery Practice, Orillia	None
Public Health Members		
Dr Loraine Marrett	Cancer Care Ontario	None
Dr David Mowat	Region of Peel Health Services	None
Dr Dan Smith	Family Practice, Ottawa	None

Appendix 2: Literature Search Strategies.

Database: Ovid MEDLINE(R) <1946 to Week 6 2013>
Search Strategy:
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1 exp Suntan/
2 exp Sunbathing/
3 exp Heliotherapy/
4 exp Sunlight/
5 *Ultraviolet Rays/ae [Adverse Effects]
6 1 or 2 or 3 or 4 or 5
7 exp Melanoma/
8 exp Skin Neoplasms/
9 7 or 8
10 6 and 9
11 exp Evidence-Based Medicine/
12 exp Practice Guideline/
13 exp Meta-Analysis/
14 exp Randomized Controlled Trial/
15 exp Clinical Trial/
16 exp Prospective Studies/
17 Comparative Study/
18 11 or 12 or 13 or 14 or 15 or 16 or 17
19 10 and 18
20 exp Letter/
21 exp Editorial/
22 exp Comment/
23 20 or 21 or 22
24 19 not 23
25 limit 24 to (English language and humans and yr="2000 -Current")

Database: Embase <1996 to 2013 Week 6>
Search Strategy:
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1 exp suntan/
2 exp sunbathing/
3 exp phototherapy/
4 exp sunlight/
5 exp ultraviolet radiation/
6 1 or 2 or 3 or 4 or 5
7 exp melanoma/
8 exp skin tumor/
9 7 or 8
10 6 and 9
11 exp "systematic review"/
12 exp practice guideline/
13 meta analysis/
14 randomized controlled trial/
15 clinical trial/
16 exp prospective study/
17 exp comparative study/
18 11 or 12 or 13 or 14 or 15 or 16 or 17
19 10 and 18
20 letter/
21 editorial/
22 comment.mp.
23 exp photodynamic therapy/
24 exp psoriasis/
25 20 or 21 or 22 or 23 or 24
26 19 not 25
27 limit 26 to (human and English language and yr="2000 -Current")

Appendix 3: Study Designs and Publication Types of Identified Evidence

Author, year published	Years of study	Total included N	Sponsorship
Clinical Practice Guidelines			
Australian Cancer Network Melanoma Guidelines Revision Working Party, 2008 (20)	N/A	NR	Cancer Council Australia, Australia Ministry of Health, Melanoma Network, Cancer Institute NSW
World Health Organization, 2003 (19)	N/A	NR	World Health Organization
Position Statements			
Taddeo et al, 2012 (21)	N/A	NR	Canadian Paediatric Society, Adolescent Health Committee
Systematic reviews with meta-analyses			
Boniol et al, 2012 (22) [an update of IARC 2006 (6)]	1981-2012	27 studies including 232,356 patients	International Prevention Research Institute, European Institute of Oncology
Gordon et al, 2007 (16)	1981-2006	20 studies including 123.282 patients	Queensland Institute of Medical Research
IARC 2006 (6)	1979-2006	19 studies including 122,278 patients	International Agency for Research on Cancer
Gallagher et al, 2005 (15)	1984-2004	10 studies including 115,926 patients	Michael Smith Foundation for Health Research Infrastructure
Systematic reviews without meta-analyses			
Lin et al, 2011 (23)	2001-2010	12 studies including 119,027 patients (Indoor tanning studies only)	Agency for Healthcare Research and Quality
Prospective cohort studies			
Veierod et al, 2010 (35)	1991-1992	106,366 women	Swedish Board of Science, Swedish Cancer Society
Nielsen et al, 2012 (33)	1990-2007	29,520 women	The Skane County Council's Research and Development Foundation, The Swedish Cancer Society, The Welander and Finsen Foundation and The Gyllenstiernska Krapperup Foundation
Zhang et al, 2012 (37)	1989-2009	73,494 women	National Institutes of Health
Retrospective cohort studies			
Ting et al, 2007 (34)	NR	501 patients (with complete medical records out of 1518 respondents)	Skin Cancer Foundation
Case-control studies			
Fears et al, 2011 (30)	1991-1992	Cases: 188	None

Author, year published	Years of study	Total included N	Sponsorship
		Controls: 282	
Cust et al, 2011 (29)	2000-2005	Cases: 604 Controls: 479	National Health and Medical Research Council of Australia, The Cancer Council New South Wales, The Cancer Council Victoria, The Cancer Council Queensland, U.S. National Institutes of Health, NHMRC, Victorian Cancer Agency, University of Sydney Medical Foundation
Lazovich et al, 2010 (32)	2004-2007	Cases: 1167 Controls: 1101	American Cancer Society, National Cancer Institute
Clough-Gorr et al, 2008 (28)	1995-1998	Cases: 423 Controls: 678	National Cancer Institute
Parr et al, 2009 (24)	1991-2004	Cases: 162 Controls: 1242	Norwegian Cancer society, Norwegian Foundation for Health and Rehabilitation
Westerdahl et al, 2000 (36)	1995-1997	Cases: 571 Controls: 913	Swedish Cancer Society
Han et al, 2006 (31)	1989-2000	Cases: 200 Controls: 804	National Institute of Health, The Harvard SPORE in Skin Cancer
Bataille et al, 2005 (26)	1999-2001	Cases: 597 Controls: 622	European Commission
Bataille et al, 2004 (27)	1989-1993	Cases: 413 Controls: 416	Cancer Research UK

Note: Included reference numbers are in accordance with numbering from Section 2.

Appendix 4: Studies Included in each of the Obtained Systematic Reviews

Study, year	**IARC, 2006** (6)	**Gallagher et al, 2005** (15)	**Gordon and Hirst, 2007** (16)	**Boniol et al, 2012** (22)
Adam et al, 1981 *	✓		✓	✓
Holman et al, 1986 *	✓		✓	✓
Osterlind et al, 1988 *	✓	✓	✓	✓
Swerdlow et al,1988 *	✓	✓	✓	✓
Zanetti et al, 1988 *	✓		✓	✓
MacKie et al, 1989 *	✓		✓	✓
Dunn Lane et al, 1993 *	✓		✓	✓
Garbe et al, 1993 *	✓	✓	✓	✓
Westerdahl et al, 1994 *	✓	✓	✓	✓
Autier et al, 1994 *	✓	✓	✓	✓
Holly et al, 1995 *	✓	✓	✓	✓
Chen et al, 1998 *	✓	✓	✓	✓
Walter et al, 1999 *	✓	✓	✓	✓
Naldi et al, 2000 ¥ (40)	✓		✓	✓
Westerdahl et al, 2000 (36)	✓	✓	✓	✓
Kaskel et al, 2001 € (39)	✓		✓	✓
Veierod et al, 2003 £	✓	✓	✓	
Bataille et al, 2004 (27)	✓		✓	✓
Bataille et al, 2005 (26)	✓		✓	✓
Han et al, 2006 (31)			✓	✓
Clough-Gorr et al, 2008 (28)				✓
Ting et al, 2007 (34)				✓
Parr et al, 2009 (24)				
Veierod et al, 2010 (35)				✓
Lazovich et al, 2010 (32)				✓
Cust et al, 2011 (29)				✓
Elliott et al, 2011 ¥ (38)				✓
Fears et al, 2011 (30)				
Nielsen et al, 2012 (33)				✓
Zhang et al, 2012 (37)				✓
	19	**10**	**20**	**27**
	N=122,278	**N=115,926**	**N=123,282**	**N=232,356**

Note: Systematic review reference numbers are in accordance with numbering in Section 2.
* denotes studies excluded from the current systematic review due to publication before the inclusion date of 2000.
¥ denotes studies excluded due to being correspondence and thus not meeting the inclusion criteria.
£ denotes a study excluded as a newer publication by the same group, with updated and republished data.
€ denotes studies excluded due to a lack of ever versus never tanning bed use data.
All other studies were included in the current systematic review.

Appendix 5: AMSTAR Quality Assessment of Included Systematic Review

AMSTAR Tool:	Boniol et al, 2012 (22)
Q1. Was an *a priori* design provided?	Yes
Q2. Was there duplicate study selection and data extraction?	Yes
Q3. Was a comprehensive literature search performed?	Yes
Q4. Was the status of the publication used as an inclusion criterion?	No
Q5. Was a list of studies (included and excluded) provided?	Yes
Q6. Were the characteristics of the included studies provided?	Yes
Q7. Was the scientific quality of the included studies assessed and documented?	No
Q8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes
Q9. Were the methods used to combine the findings of studies appropriate?	Yes
Q10. Was the likelihood of publication bias assessed?	Yes
Q11. Was the conflict of interest stated?	Yes

Appendix 6: Quality of Included Cohort and Case-Control Studies

Study (ref)	Full Reporting of Patient Selection Criteria	Full Reporting of Outcomes	Sources of Funding	Limitations
Prospective Cohort Studies				
Nielsen et al, 2012 (33)	Randomly from Swedish Population/Census Registry	Yes	The Skane County Council's Research and Development Foundation, Swedish Cancer Society, The Welander and Finsen Foundation, The Gyllenstiernska Krapperup Foundation	• Age of questionnaire – developed in 1980s, provides limited data on frequency, time and amount of solar/outdoor UVR exposure • Demographic bias – solely white-skinned women • Recall bias – self-reported baseline characteristic, exposure or outcome
Veierod et al, 2010 (35)	Randomly selected from Norwegian National Population Register and Swedish National Population Register	Yes	Swedish Board of Science and Swedish Cancer Society	• Recall bias – self-reported baseline characteristic, exposure or outcome
Zhang et al, 2012 (37)	Women from Nurse's Health Study II (NHSII)	Yes	National Institutes of Health	• Non-significant melanoma trend due to small sample size • Tanning beds age – tanning beds prior to late 1970s had different UV-emitting tubes than those today • Demographic bias – solely female nurses • Recall bias – prospective-retrospective cohort mixed study design and fairly infrequent tanning bed use
Retrospective Cohort Studies				
Ting et al, 2007 (34)	Random sample of patients from academic dermatology clinic	Yes	Skin Cancer Foundation Photobiology grant	• Substantial missing data – only one third of survey entirely completed • Retrospective design – no way to control for other UV exposures or for any effects due to photosensitizing medications • Recall bias – self-reported • Demographic and geographic bias – patients all from single academic setting
Case-control Studies				
Bataille et al, 2004 (27)	Cases from hospitals and general practice centres in North East Thames region of the UK and controls from a list of patients in	Yes	Cancer Research UK (formerly Imperial Cancer Research Fund)	• Recall bias – self-reported and retrospective design

	same area			
Bataille et al, 2005 (26)	Patients from Sweden, the Netherlands, the U.K., Belgium, and France	Yes	BIOMED II (European Commission)	• Recall bias – self-reported and retrospective design • Selection bias – participants may have self-selected on the basis of tanning bed use during consent • Multinational study with difficulties standardizing recruitment methods
Clough-Gorr et al, 2008 (28)	Cases from New Hampshire State Cancer Registry matched to age and gender-matched controls from New Hampshire driver's licence lists	Yes	None reported	• Recall bias – self-reported via questionnaire and telephone
Cust et al, 2011 (29)	Cases and controls from Sydney, Melbourne and Brisbane, Australia	Yes	National Health & Medical Research Council of Australia	• Lacking data – no data available on type of tanning device or session duration • Recall bias – self-reported via telephone call • Selection bias – both cases and control had poor participation
Fears et al, 2011 (30)	Obtained patient data from large matched case-control study	Yes	None reported	• Impossible to separate effects caused by tanning beds, tanning lamps and outdoor exposure • Recall bias – self-reported
Han et al, 2006 (31)	Nurses enrolled in the Nurses' Health Study (NHS) in the U.S.A.	Yes	National Institutes of Health and The Harvard SPORE in Skin Cancer	• Misclassification – self-reported assessment on pigmentation phenotypes • Recall bias – self-reported • Selection bias- solely non-Hispanic white female nurses
Lazovich et al, 2010 (32)	Cases from Minnesota State Cancer Registry matched to age and gender-matched controls from Minnesota driver's licence lists	Yes	American Cancer Society and National Cancer Institute	• Recall bias – self-reported via questionnaire and telephone
Parr et al, 2009 (24)	Randomly selected from National Population Registry in Norway with follow-up and outcome data from Norway Cancer Registry	Yes	Norwegian Foundation for Health & Rehabilitation and Norwegian Cancer Society	• Recall bias – self-report but assessed by study • Selection bias – solely female participants, but minimized due to population-based design
Westerdahl et al, 2000 (36)	Matched cases and controls from National Population Registry of Sweden	Yes	Swedish Cancer Society	• Recall bias – self-reported and retrospective design • Selection bias minimized by population-based design

Note: Reference numbers are in accordance with numbering from Section 2.