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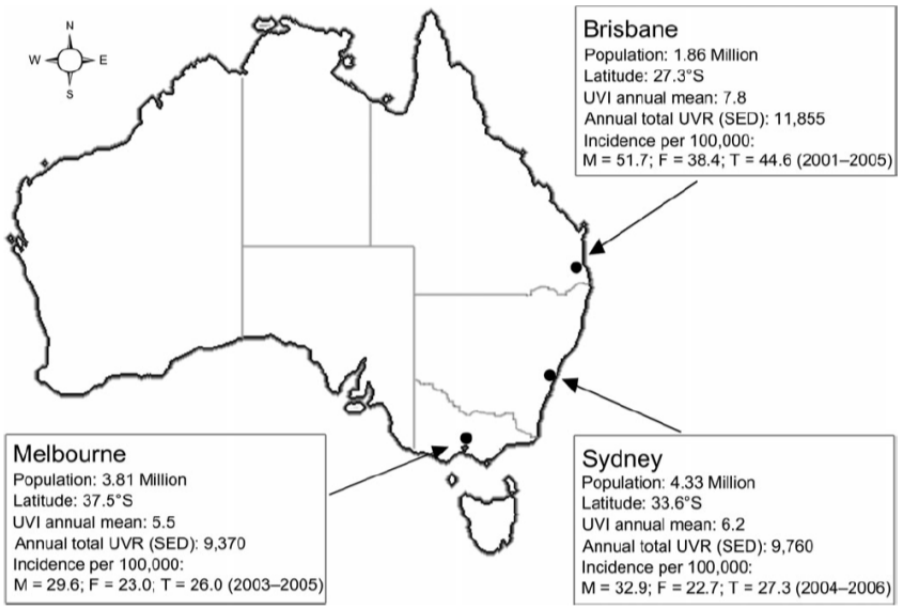
Review of Cust et al. 2011: Early-onset melanoma in relation to sunbed use during adolescence and early adulthood.

To investigate whether the use of sunbeds during early adolescence and early adulthood is associated with early-onset melanoma, Cust et al. 2011 analyzed data from the Australian Melanoma Family Study, a multicenter, population-based, case-control-family study conducted from 2001 through 2005 in three Australian cities: Sydney, Melbourne and Brisbane. Figure 1 shows a map of the study locations.

Figure 1 Map of Australia showing the location of major cities Brisbane, Sydney, and Melbourne.[1]



Based on their analysis, the investigators state that use of sunbeds by teens and young adults is associated with increased risk:

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[1] From Cust et al. 2009. Also shown are the population sizes, latitude, solar ultraviolet (UV) radiation estimates, and age-standardized melanoma incidence rates. Abbreviations: F, female; M, male; SED, standard erythemal dose; T, total; UVI, UV index; UVR, UV radiation. UVI is the maximum biologically effective solar UV radiation for the day, averaged over 10 or 30 minutes. SED is a measure of the cumulative ambient solar UVR; 1 SED is equivalent to an erythemally effective radiant exposure of 100 Joules/m^2.

> "Sunbed use is associated with increased risk of melanoma. Younger people might be more susceptible to the carcinogenic effects of ultraviolet radiation. We investigated the association between sunbed use and risk of early-onset cutaneous malignant melanoma. … Compared with having never used a sunbed, the OR [odds ratio] for melanoma associated with ever-use was 1.41 (95% confidence interval (CI) 1.01–1.96), and 2.01 (95% CI 1.22–3.31) for more than 10 lifetime sessions (P_{trend} 0.01 with cumulative use). The association was stronger for earlier age at first use (P_{trend} 0.02). The association was also stronger for melanoma diagnosed when aged 18–29 years (OR for more than 10 lifetime sessions = 6.57, 95% CI 1.41–30.49) than for melanoma diagnosed when 30–39 years (OR 1.60, 95% CI 0.92–2.77; $P_{interaction}$ 0.01). Among those who had ever used a sunbed and were diagnosed between 18 and 29 years of age, three quarters (76%) of melanomas were attributable to sunbed use. Sunbed use is associated with increased risk of early-onset melanoma, with risk increasing with greater use, an earlier age at first use and for earlier onset disease." (Cust et al. 2011, Abstract)

Despite the above-quoted summary of findings and the title of their article, Cust et al.'s analyses did not address the use of sunbeds, much less sunbed use in commercially-operated facilities that follow FDA regulations and guidance, or other national standards. What the investigators call "sunbed use" was in fact the use of sunlamps and/or sunbeds in a variety of locations, which included beauty salons (55% of users), gyms (72% of users), and private homes (60% of users). [2]

With regard to the use of tanning salons, reported by 83% of sunlamp and/or sunbed users in Cust et al.'s article, most of those persons must have used a so-called "sunbed" in one or more of the other venues noted above: beauty salons, gyms and private homes.

In brief, despite Cust et al.'s representations quoted above, their analyses do not address the use of sunbeds, regardless of location. More importantly, their analyses do not address the risk of early-onset melanoma in relation to use of sunbeds following U.S. regulations. The importance of this point concerns the intensity of the ultraviolet (UV) radiation exposures involved and the opportunity for UV burns, the latter a major risk factor for melanoma.

1. Background

The primary aims of the Australian Melanoma Family Study are to investigate the influence of genetic, phenotypic, and environmental factors and their interactions on melanoma risk, particularly before age 40. Research issues of interest include the characterization of melanoma risk associated with both rare high-risk genetic mutations, and common low-moderate risk genetic variants; assessing whether there are vulnerable periods in early life from sun exposure; estimating the effect of sun exposure on melanoma

[2] Cust et al. 2011, p. 2427

risk for genetically susceptible individuals; and determining whether modifiable risk factors for melanoma differ between carriers and non-carriers of genetic variants or by family history of melanoma (Cust et al. 2009, p. 1542).

2. Study methods

2.1 Cases Cases of melanoma were identified from 1 July 2000 to 31 December 2002 through population-based state cancer registries covering the three participating cities. During that time, study-eligible cases were required to have had a histopathologically confirmed first primary invasive cutaneous melanoma diagnosed between age 18 and 39 years; patients with a history of in situ melanoma (n = 5) were included.

A total of 1,211 apparently eligible cases were identified, but only 629 participated. The main reasons for nonparticipation were inability to contact cases (n = 247), refusal (n = 201), and doctors not giving permission for contact (n = 74). [3] The analysis by Cust et al. 2011 was based on 604 of the 629 participating cases, the other 25 being excluded because of missing data.[4]

2.2 Controls For purpose of analysis, Cust et al. pooled the data from two types of controls: population-based controls (n = 232) and spouse/friend controls (n = 247) … 479 controls in total.[5]

Population-based controls were selected from the electoral rolls in Brisbane, Sydney and Melbourne, and were frequency matched to the cases by age (within 5 years) and sex using proportional random sampling. Controls were study-eligible if they were age 18 to 39 years at the time of approach and had no history of melanoma, including in situ melanoma.

A total of 1,068 population-based controls were identified, but only 240 participated. The main reasons for nonparticipation were inability to contact controls (n = 458) and refusal to participate in the study (n = 330).[6]

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[3] Cust et al. 2009, Figure 2. Participation was 54% when calculated as a proportion of those apparently eligible, and 76% as a proportion of those who could be contacted.

[4] See Figure 2 in Cust et al. 2009, and p. 2427 in Cust et al. 2011.

[5] The authors state that "The risk estimates were similar in analyses that compared cases separately with each control group." Cust et al. 2011, p. 2429 The Australian Melanoma Family Study also had two other types of controls: adult first- and second-degree relatives of the study cases and population-based controls; and extended families. See Cust et al. 2009, p. 1543.

Although the Australian Melanoma Family Study enrolled 240 population controls, one control did not have a complete interview; excluding an additional 7 controls with missing data on key variables resulted in 232 population-based controls in the analysis by Cust et al.

Spouse/friend controls were a spouse, partner, or friend nominated by a case as a potential control. To be eligible for study, the potential control must have been at least 18 years of age and have had no history of melanoma, including in situ melanoma. There were no other age, sex, or residency restrictions.

There were 371 nominations made for spouse/friend controls, among which 75 refused or could not be contacted, and 1 was ineligible for study. Among the resulting 295 spouse/friend controls that participated, 289 had complete interviews. [7] Cust et al. excluded from analysis an additional 33 persons who were age ≥45 years, and 9 who had missing data. Thus, Cust et al.'s analysis of "sunbed" use included data on 247 spouse/friend controls from the 371 nominations made.

Comments The analyses by Cust et al. 2011 were based on 50% of their identified cases (604/1,211) and 33% of their identified controls (479/1,439). Not all of these persons were study eligible, however. Making allowance for ineligibility yields an estimate that the analysis was based on 52% of study-eligible cases, 604/(1,211 × 0.96), and 35% of study-eligible controls, 479/(1,439 × 0.96).[8]

The low participation rates for cases and controls give rise to substantial uncertainty about potential bias from selective enrollment in Cust et al.'s study. The investigators express their belief, however, that their estimates of relative risk of melanoma in relation to the use of "sunbeds" are likely to be unaffected, one reason being that:

> "the associations between known risk factors (hair color, ability to tan, mole count, family history) and melanoma are consistent with results of recent meta-analyses and were similar when analyzed separately by using population-based controls, spouse/ friend controls, and sibling controls." (Cust et al. 2009 p. 1550, references omitted)

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[6] Cust et al. 2009, Figure 2. Participation was 23% when calculated as a proportion of all apparently eligible controls and 42% as a proportion of those contacted.

[7] Cust et al. Figure 2

[8] Among the 865 cases that could be contacted (1,112 - 247), 830 (96%) were study-eligible. Among the 371 spouse/ friend controls that were nominated, 370 were study-eligible. Among the 610 population controls that could be contacted (1,068 – 458), 570 were study-eligible. Thus, the 940 study-eligible controls (370 + 570) represented 96%, 940/(371 + 610), of the controls that could be contacted. See Figure 2 in Cust et al. 2009.

The investigators' confirmation of the associations noted above, however, does not establish the reliability of their quantitative estimates of relative risk in relation to the use of "sunbeds," especially in circumstances involving weak associations, that is, estimates of relative risk which, for the most part, are ≤ 2.0, and in instances where RR > 2.0 involve relatively few cases and controls.[9] Such estimates are known to be susceptible to influences of bias, confounding and chance (Shapiro 2000, 2008). Thus, although Cust et al.'s *qualitative* assessment of melanoma risk factors may be sound, it does not establish the validity of their quantitative estimates of relative risk in relation to UV exposure, "sunbeds" in particular.

Cust et al. offer two other reasons to rule out enrollment bias / selection bias for their findings of increased risk associated with "sunbeds."

> "Selection bias might also be a problem due to poor participation by cases and controls, if participation of cases and controls was influenced by their past or current sunbed use. However, [1] collection of data on sunbed use was part of a larger study examining genetic and environmental risk factors for melanoma and thus sunbed use might be less likely to have influenced participation. [2] Data collection was also completed well before local news media coverage of cases of melanoma in young people who had used sunbeds." (Cust et al. 2011, p. 2433)

Both rationales cited above are plausible, but plausible reasoning is not a substitute for a well-conducted study. In this regard, Cust et al.'s reasoning does not incorporate any direct assessment by them of the potential effect of selection / enrollment bias on their resulting estimates of relative risk.

2.3 Data collection Although study cases were identified between July 2000 and December 2002, data were collected on cases (and controls) between January 2001 and December 2005. All cases were age <40 years at diagnosis, and all controls were <40 years when ascertained, but cases and controls could be as old as age 44 years at the time of interview. [10]

A trained interviewer administered a structured questionnaire to each participant by telephone. During the 45-minute telephone interview, participants were asked to recall their sun exposure at 10, 15, 20, 30 and 40 years of age.[11] Participants also reported their skin-, eye-, and natural hair color at age 18 years, usual

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[9] See Cust et al. 2011, Tables 2 – 4.

[10] For study cases, the median interval between diagnosis of melanoma and interview was 10 months; 25% of cases had interviews occurring 14 months or more after diagnosis. Corresponding information on controls (e.g., interval from electoral-roll selection to interview) was not reported: see Cust et al. 2009, p. 1544.

[11] In the attempt to improve recall, cases and controls were asked to complete before their telephone interview a lifetime calendar in which they indicated, for each year of life, their place of residence, place of work or study,

tanning and sunburn response to prolonged or repeated exposure of skin to sunlight, the number of moles (nevi) covering the body (none, few, some, many), freckling, and were also asked to have someone count the number of all moles on their back.

Estimates of lifetime total sun exposure were derived by assigning recall data for age 10 to each year from ages 5 to 12; for age 15 to each year from ages 13 to 17; for age 20 to years 18 to 24; for age 30 to years 25 to 34; and for age 40 to years 35 to 44.

Estimates of lifetime and age-specific ambient UV irradiation exposure were derived by combining information on annual place of residence with cloud-adjusted, monthly mean ambient erythemal UV radiation (kJ/m^2) at each residential location derived from published satellite observations. [12]

2.4 Exposure to "sunbeds" Data were collected on ever use of a sunlamp and/or sunbed, age at first use and last use, total number of lifetime sessions, and locations in which sunlamps and sunbeds were used. Cases were also asked how often the specific anatomical site of the melanoma was exposed to such light. For this question controls were assigned a pseudo-site of melanoma, frequency-matched based on the expected site distribution in the cases.

To estimate "sunbed" exposure to the specific anatomical site of melanoma in the cases or to the pseudo-site in the controls, Cust et al. multiplied the exposure estimates by a weighting factor based on the reported amount of time that the site / pseudo-site was exposed: 1.0 = always, 0.75 = more than half, 0.5 = about half, 0.25 = less than half, 0.0 = never.

Comments As noted earlier, Cust et al.'s analyses of melanoma in relation to the use of ''sunbeds'' do not relate to sunbeds, but rather to the use of sunlamps and/or sunbeds in a variety of locations. The investigators, moreover, did not collect information on the specific types of indoor tanning devices that were used, nor did they collect data on the durations of the sessions involved. [13]

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number of days spent at work or study each week in warmer months and in cooler months, and holiday locations. A summary of the completed residence calendar was sent to participants to refer to during the telephone interview.

[12] Such estimates, like those for lifetime total sun exposure, undoubtedly involve considerable error.

[13] Citing IARC 2006 and Lazovich et al. 2010, the investigators claim that "there is little evidence that the association between artificial UV exposure and melanoma differs by the type of indoor tanning appliance used [predominantly UVB- or UVA-emitting]." They also state their belief that "In our young study population, it is likely that most participants used more modern UVA-emitting devices." See Cust et al. 2011, p. 2433.

Although information was collected on locations of use, none of the analyses by Cust et al. addressed melanoma risk in relation to use of sunbeds restricted to commercial tanning facilities. Furthermore, and perhaps most importantly, none of their analyses of "sunbed" use considered whether such use was accompanied by burns, a major risk factor for melanoma, and an indication of the inappropriate use of an indoor tanning device.

In summary, none of the analyses by Cust et al. 2011 address whether persons who engage in proper use of sunbeds in commercial tanning facilities are at increased risk of early-onset melanoma.

2.5 Statistical analysis The relative risk of melanoma associated with "sunbed" use was estimated by Cust et al. by unconditional logistic regression. Estimates of relative risk, based on the odds ratio, were adjusted for age (continuous), sex, city of recruitment, usual skin response to sun exposure (never burns always tans, sometimes burns usually tans, usually burns sometimes tans, always burns never tans), confirmed family history of melanoma in first-degree relatives (none, any), skin color (very fair, fair, olive/brown/Asian/black), cumulative lifetime total sun exposure (quartiles), and education (junior high school, senior high school, vocational, university). [14]

Estimates of relative risk were tested for possible differences by sex, age, usual skin response to sun exposure, anatomical site of the lesion, number of nevi, ambient UV irradiance, and lifetime total sun exposure.

3. Main findings *Ever-use* of a sunbed or sunlamp was reported by 24% of female controls and 8% of male controls. Of those controls reporting "sunbed" use, the median number of lifetime sessions was 9 (interquartile range 4-18). [15]

The remainder of this section focuses on two key aspects of Cust et al.'s results: age at first use of a "sunbed," and the number of lifetime sessions reported.[16]

3.1 Age at first use Table 1 displays Cust et al.'s estimates of the relative risk (RR) of early-onset melanoma in relation to age at first use of a "sunbed." As compared to persons who had never used a "sunbed," persons whose first use was prior to age 25 were estimated to be at 64% increased risk of

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[14] Sun exposure-related variables were categorized using quartiles of the distribution in controls.

[15] Although the prevalence of "sunbed" use is best characterized by use in population-based controls, which are intended to represent the experience from which the study cases arise, Cust et al. report the prevalence of use based on their aggregation of population controls and spouse / friend controls.

[16] The main findings by Cust et al. 2011 are displayed in their Tables 2 – 4.

melanoma occurring before age 40 (RR = 1.64, 95% CI 1.07 – 2.51).[17] Persons with age at first use ≥25 years had no statistically significantly increased risk (RR = 1.06, 95% CI 0.66 – 1.72).

Table 1 Relative risk (RR) of early-onset melanoma in relation to age at first use of a "sunbed" [18]

Age at first use	CAs	COs	RR	L95	U95
Never	467	395	1.00		
≥25 years	46	39	1.06	0.66	1.72
<25 years	83	41	1.64	1.07	2.51

Because the number "sunbed" sessions was found to be associated with an increased risk of melanoma, discussed in section 3.2 below, and because earlier age at first use is expected to be associated with an increased number of sessions, Cust et al. attempted to assess whether age at first use *per se*, and not the number of "sunbed" sessions, was associated with increased risk of early-onset melanoma.

Table 2. Relative risk (RR) of early-onset melanoma in relation to age at first use of a "sunbed" [19]

			Adjusted for lifetime "sunbed" sessions					
			No			Yes		
Age at first use	CAs	COs	RR	L95	U95	RR	L95	U95
≥25 years	46	39	1.00			1.00		
<25 years	81	41	1.32	0.70	2.48	1.18	0.62	2.25
≥25 years	46	39	1.00			1.00		
20 -24	45	26	1.14	0.55	2.35	1.07	0.51	2.22
<20	36	15	1.63	0.72	3.70	1.39	0.59	3.23
			P_{trend} = 0.26			P_{trend} = 0.48		

Table 2 above shows Cust et al.'s analysis of this issue. In this instance the reference group consists of persons whose first use of a "sunbed" occurred at age ≥25 years, whereas in Table 1 the reference group consists of persons who had never used a "sunbed."

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[17] CI: confidence interval.

[18] From Cust et al. 2011, Table 2. CAs: cases, COs: controls. L95 and U95 are the lower and upper 95% confidence limits on the estimated relative risk (RR).

[19] From Cust et al. 2011, Table 3. Adjustment for number of lifetime sunbed sessions as a continuous variable.

Although Table 1 suggests that the relative risk of early-onset melanoma is RR = 1.64 when first use of a "sunbed" occurs before age 25, the upper-right panel of Table 2 indicates that if one accounts for the number of "sunbed" sessions, the relative risk is substantially diminished: estimated to be RR = 1.18, a result compatible with no increased risk, insofar as the lower 95% confidence limit (L95 = 0.62) lies below 1.0, the no-effect value of relative risk.

The lower panel of Table 2 displays additional details reported by Cust et al. 2011, who further considered first use before age 20 and between 20-24 years, as compared to first use at age 25 years or older. Although the estimate of relative risk associated with first use <20 years is 1.39 (lower-right panel), the result is not statistically significant (L95 = 0.59). Adjusted for the number of sessions, moreover, there is also no statistically significant trend of increasing relative risk with earlier age at first use: $P_{\text{trend}} = 0.48$.

Comments Putting aside the fact that Cust et al. do not specifically address the use of sunbeds, or proper use of these devices (e.g., use without burns), the results discussed above indicate that the number of "sunbed" sessions, not early age at first use, was the major determinant of Cust et al.'s finding of increased risk of early-onset melanoma.

The investigators' statement (Cust et al. 2011, Abstract) that

> "The association was stronger for earlier age at first use (P_{trend} 0.02)."

relies on an analysis that does not account for the number of sessions involved.[20]

3.2 Number of "sunbed" sessions Table 3 below, from Cust et al.'s analysis, displays estimates of relative risk in relation to the number of "sunbed" sessions (upper panel), and in relation to the number of sessions according to age at first use (lower panel).

[20] Cust et al. 2011, p. 2429.

Table 3. Relative risk of early-onset melanoma in relation to the number of lifetime sessions.

No. lifetime sessions	CAs	COs	RR	L95	U95
None	467	395	1.00		
1 - 10	72	57	1.08	0.72	1.61
>10	62	27	2.01	1.22	3.31
			P_{trend} = 0.01		
Age at first use, lifetime sessions					
Never	467	395	1.00		
<25, 1-10	42	26	1.30	0.75	2.24
≥25, 1-10	25	29	0.79	0.45	1.41
<25, >10	39	15	2.13	1.13	4.03
≥25, >10	21	10	1.88	0.85	4.19

The upper panel of Table 3 shows a statistically significant trend of increasing relative risk with increasing number of sessions. There is, however, no evidence of a statistically significantly increased relative risk of melanoma with 1-10 "sunbed" sessions, regardless of whether first use began at ages <25 or ≥25 years (see RR = 1.30 and 0.79 respectively in Table 3, lower panel).[21] There is, however, an approximately 2-fold increased risk associated with >10 sessions (Table 3, upper and lower panels). The estimates of relative risk do not differ statistically significantly by age at first use: see the overlapping 95% confidence limits for RR = 2.13 and RR = 1.88 in the lower panel.

Table 4 below, from Cust et al.'s Table 3 (lower panel), confirms what is shown in Tables 1 – 3 above: the number of sessions, not age at first use, is the important factor underlying Cust et al.'s findings.

Table 4. Relative risk of early-onset melanoma in relation to the number of lifetime sessions of "sunbed" use.

			Adjusted for age at first use					
			No			Yes		
No. lifetime sessions	**CAs**	**COs**	**RR**	**L95**	**U95**	**RR**	**L95**	**U95**
1 - 10	67	55	1.00			1.00		
>10	60	25	2.07	1.08	4.00	2.01	1.04	3.89
			P_{diff} = 0.03			P_{diff} = 0.04		

[21] Statements concerning no statistically significantly increased risk are based on the lower 95% confidence limits (L95) being < 1.0, the "no-effect value" of relative risk.

Cust et al. reported additional analyses of the number of lifetime sessions. These indicate that >10 sessions were associated with statistically significantly increased relative risk of melanoma occurring in persons with a number of characteristics; key results are displayed in Table 5. [22]

Table 5 Relative risk of early-onset melanoma in relation to >10 "sunbed" sessions, by characteristics of study subjects.

	RR	L95	U95
Age 18 – 29 years	6.57	1.41	30.5
Sometimes or never tan	3.18	1.16	8.75
No or few nevi	3.26	1.49	7.11
≤ median lifetime (27, 208 hours) sun exposure	5.06	2.02	12.7
Lifetime ambient UV irradiance ≤ median 42,004 kJ/m²	2.53	1.31	4.90

Table 6 displays Cust et al.'s estimates of relative risk of melanoma in relation to years since first use of a "sunbed." The estimates of increased relative risk, although not statistically significant, are approximately 1.40, regardless of whether first use had occurred within 1 - 4 years (RR = 1.35) or ≥15 years after first use of a "sunbed" (RR = 1.43).[23]

Table 6 Relative risk of early-onset melanoma in relation to years since first use

Years since first use	CAs	COs	RR	L95	U95
Never	467	395	1.00		
1 - 4	48	24	1.35	0.78	2.33
5 - 14	45	28	1.33	0.79	2.23
≥15	36	28	1.43	0.83	2.46

Comments The factors noted in Table 5 suggest several possibilities for increased risk of melanoma associated with >10 sessions: susceptibility to an adverse effect of cumulative exposure to UV-emitting devices, biased detection of melanoma, or improper use of sunlamps and/or sunbeds resulting in burns. None of the analyses by Cust et al. help to resolve these issues.

With regard to Table 6, one should note that exposure to a carcinogen often requires a long period of time before the adverse effect becomes evident, 20 to 30 years or more is common. Although none of the estimates of relative risk displayed in Table 6 rule out chance (i.e., L95 < 1.0 in all instances), much less

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[22] From Cust et al. 2011, Table 4. Relative risk in relation to >10 sessions was also greatest for lesions on the trunk: RR = 3.19, 95% CI 1.75 – 5.80.

[23] From Cust et al., Table 2. The estimates are adjusted for age, sex, city of recruitment, education, family history of melanoma, skin color, usual skin response to sun exposure, and cumulative lifetime total sun exposure.

bias or confounding, the estimates of increased relative risk suggest at least three possibilities, none of which were considered or investigated by Cust et al.

The first possibility is that UV irradiation of an already-existing pre-malignant or undetected malignant lesion may enhance its rate of growth; malignant melanoma, depending on subtype, can be a very fast-growing tumor (Liu et al. 2006). A second possibility is that the estimates of (non-statistically significant) increased relative risk displayed in Table 6 reflect biased surveillance for and detection of early-onset melanoma among persons who use indoor tanning devices. A third possibility is that the estimates of increased relative risk represent confounding by burns associated with improper use of sunlamps and/or sunbeds.

Cust et al. attempt to reconcile their results with those reported by the IARC in a 2006 Working Group report, which claimed by unreliable analysis that early age at first use of a "sunbed" was associated with a 75% increased risk of melanoma. Although Cust et al. state that their study supports the proposition that "sunbed use during adolescence and early childhood is associated with increased risk of early-onset melanoma," they nonetheless acknowledge that:

> "cumulative sunbed exposure is probably more important than age at first use, although cumulative exposure did not fully account for the association of earlier age at first use with melanoma risk." (Cust et al. 2011, p. 2432)

4. Discussion

Study strengths With regard to strengths, Cust et al.'s 2011 article relied on their population-based study of early-onset melanoma in Australia, which had some important details on indoor-tanning behavior: persons' age at start, the number of times a tanning device had been used, and the locations of use, e.g., in a tanning salon, gym, beauty salon, and at home.

The investigators collected information that is relevant to a person's risk of melanoma, and took account of this in their analyses: age, sex, sun exposure, usual skin response to sun exposure, skin color, number

of nevi, and family history of melanoma. Such factors, if not taken into account, may give rise to a spurious association between the use of tanning devices and the subsequent development of melanoma.[24]

The investigators also gave a thorough accounting of participation by study subjects, and discussed findings by other investigators that did or did not support their own results.

In many respects, Cust et al.'s 2011 article is exemplary, but not with regard to assessing the risk of melanoma in relation to the use of sunbeds.

Study weaknesses The above-noted strengths with regard to data collection and analysis are counter-balanced if not over-weighed by a number of substantial weaknesses. These include the low participation rates of cases and controls, the lack of information on the tanning devices that were used, whether burns had occurred from the use of sunlamps and/or sunbeds, and the failure to assess whether persons who had used modern fluorescent lamps in commercial facilities that follow regulatory guidance by the FDA or other national standards (e.g. in Australia) were at increased risk of early-onset melanoma.

Minimal information about the disease itself, namely the body site at which melanomas occurred, was addressed by Cust et al.'s analysis. Likewise, there was no consideration of possible biased surveillance for and detection of melanoma: see Appendix A for discussion of this issue.

Cust et al. did not address the intensity of UV exposures from the indoor tanning devices that were used, such as the doses of UV radiation involved and the cumulative exposure resulting therefrom. A surrogate endpoint that would be relevant to this issue, which was not considered by them, is the number of burns resulting from indoor tanning.

The above-noted weaknesses are further enhanced by the investigators' misrepresentation of what their study addressed … said in their article's title, abstract, tables and text, to be the use of "sunbeds," when in fact they acknowledge that so-called "sunbed use" does not refer specifically to the use of sunbeds. This conflation of different tanning devices and circumstances of UV exposure continues the practice of the IARC's Working Group (IARC 2006, 2007) and a recent update by Boniol et al. 2012.

Whether supported by facts or not, Cust et al. are apparently intent on promulgating their advocacy against the use of sunbeds:

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[24] For instance, if persons whose skin is light, and are thereby at increased risk of melanoma, preferentially use sunlamps and/or sunbeds, then an increased risk will be found if only because the devices are used by persons who are inherently at increased risk. The association would be a consequence of "confounding."

> "Our findings indicate that UV radiation exposure from sunbeds is a risk factor for early-onset melanoma, particularly melanoma diagnosed between ages 18 and 29 years. The increasing risk associated with an earlier age at first use adds further support to efforts to restrict minors and discourage young adults from using sunbeds." (Cust et al. 2011, p. 2433)

Summary Cust et al.'s estimates of increased relative risk of early-onset melanoma cannot be interpreted as evidence of a melanoma hazard incurred from use of sunbeds, whether as a teenager or young adult, in commercially-operated facilities that follow FDA regulations and guidance, or other national standards.

/S/

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Appendix A

Potential Bias from Surveillance and Detection of Melanoma [25]

The possibility of biased *surveillance for* and *detection of* melanoma in persons who use indoor tanning devices was not discussed or addressed by Cust et al. 2011. There are several reasons why methods of detecting melanoma are important. To begin, melanoma is not like a myocardial infarction or a stroke, which routinely lead to a trip to an emergency room, a stay in hospital, and eventual diagnosis. Melanoma has no symptoms of early disease, only signs: the appearance of a new lesion, i.e., a nevus or pigmented mole, or a change in the size, elevation or pigmentation of an existing lesion occurring on one's skin. [26] To be diagnosed with melanoma, one must therefore notice its signs, seek an exam, receive a biopsy, and then have that biopsy specimen examined by a pathologist, preferably one experienced with skin cancer. [i, ii, iii, iv, v]

Skin examinations for melanoma are not routinely done,[27] and if done tend to be targeted to individuals thought to be at increased risk of melanoma, which presumptively includes persons with a history of indoor tanning. [28] Furthermore, public-health activities such as skin-cancer screening initiatives in Scotland [vi] and unfavorable media attention to indoor tanning in Australia, [vii (p. 2433)] will increase the likelihood of detecting melanoma in persons who tan indoors, while missing the detection of melanoma in those who do not. With regard to the USA, the Centers for Disease Control and Prevention (CDC) and the FDA, to name two U.S. federal agencies, emphasize the presumptive hazards of indoor tanning. [viii, ix] The U.S. American Academy of Dermatology (AAD), moreover, has been a long-standing advocate of screening for skin cancer, with programs in place since the mid-1980s. [x] Like the CDC and the FDA, the AAD alerts persons to the presumptive hazard of indoor tanning devices.[xi]

An IARC Working Group noted the following: [xii (p. 3)]

> "In the 1980s and 1990s, amid growing concern about the carcinogenic potential of UVB, the UV output of low-pressure fluorescent lamps was shifted towards UVA, allowing so-called "UVA tanning"."

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[25] Adapted from Schlesselman - Use of Indoor Tanning Devices and Risk of Melanoma: Review of an Assessment by a Working Group of the International Agency for Research on Cancer. August 28, 2012.

[26] Bleeding and ulceration, which can arise later, are indicative of late-stage disease, which represented 13% of melanomas diagnosed in the USA between 2003 and 2009: http://seer.cancer.gov/statfacts/html/melan.html .

[27] http://www.cdc.gov/cancer/skin/basic_info/screening.htm

[28] http://www.cdc.gov/cancer/skin/basic_info/indoor_tanning.htm

Thus, concerns about skin cancer in relation to indoor tanning have apparently been expressed for many years.

Cust et al. (2011, p. 2433) refer explicitly to that study's avoidance of selection bias arising from media coverage. Such concern complements earlier remarks by de Vries et al. on their European population-based study, reported in 2005: [xiii (p. 2153)]

> "the indications for potential biases in recruitment and recall make it impossible to rely on risk estimates derived from our analyses. The data presented here highlight the need to be aware of potential recall and selection biases when studying an exposure for a disease in a well educated and informed population."

Another concern related to biased surveillance for and detection of melanoma is that persons who use indoor tanning devices may be more aware of the condition of their skin, and thus more likely to notice any changes on their body. The importance of this possibility is reinforced by a study of 471 patients newly diagnosed with melanoma between 1995 and 1998: 57% of patients detected their own melanoma; only 16% of melanomas were detected by physicians. [xiv]

With respect to screening for melanoma, Terushkin and Halpern note the following: [xv (p. 487)]

> "Despite the lack of official guidelines, numerous screening programs have been performed in an effort to diagnose earlier forms of melanoma. Screening efforts in the United States were initiated as early as 1985 by the American Academy of Dermatology (AAD) and continue to this day. In a survey of participants with suspected melanomas in the 1992 to 1994 programs, Koh and colleagues [x] showed that more than 90% of melanomas detected measured less than 1.5 mm in depth. Melanomas at a less advanced stage were found during screenings, in comparison to the 1990 Surveillance, Epidemiology and End Result Registry (SEERR) data."

Thus, persons who are preferentially screened for melanoma are expected to have earlier-stage disease and, as discussed above, persons with a history of indoor tanning may be more likely to have melanoma detected and diagnosed.

From an analysis of incidence data for melanoma in the Surveillance, Epidemiology and End Results Registry (SEER), and skin biopsy rates from Medicare claims in the USA, Welch et al. concluded that for the period 1986 to 2001: [xvi (Abstract)]

> "The incidence of melanoma is associated with biopsy rates. That the extra cases diagnosed were confined to early stage cancer while mortality remained stable suggests over diagnosis – the increased incidence being largely the result of increased diagnostic scrutiny and not an increase in the incidence of disease."

The implication of surveillance and detection bias is that epidemiologic studies may be destined to find a spuriously increased relative risk of melanoma in relation to indoor tanning, even if recall bias and self-selection bias are absent.

If surveillance and detection bias were present, then one would expect cases of melanoma with a history of indoor tanning to have smaller tumor size (T), less nodal involvement (N), and less metastatic (M) disease at diagnosis as compared to cases of melanoma with no history of indoor tanning. Comparisons of TNM stage for cases of melanoma with a history of indoor tanning, versus those without, would not rule out the possibility that differential biopsy rates led to more cases of melanoma being detected in persons with a history of indoor tanning. Comparisons of TNM stage would, however, provide the first step to address an important issue that should have been addressed by Cust et al. [29]

In summary, conducting epidemiologic studies in populations with haphazard screening for and detection of melanoma, or which target individuals thought to be at high risk of melanoma, increases the possibility of biased results. Analyses which consider TNM stage, and study participants' answers to questions about skin exams and melanoma detection, could address some of the issues discussed above.

[29] TNM stage has long been the de-facto standard of pathologic diagnosis of melanoma and other cancers.

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