Wehner et al. 2012 Indoor Tanning and NMSC Analysis

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MH Wehner, a medical student at Stanford University School of Medicine, and E Linos, an assistant professor in dermatology at University of California San Francisco, conducted a systematic review and meta-analysis of the literature on indoor tanning and non-melanoma skin cancer.[1] Indoor tanning was defined by the authors as use of sunlamps in any venue at any time in history. The authors' findings and conclusions were published in 2012 in the British Medical Journal (345:e5909). The basic results reported were values obtained from a statistical meta-analysis of six epidemiological studies on squamous cell carcinoma (summary odds ratio 1.67; 95% CI, 1.29-2.17) and eight studies on basal cell carcinoma (summary odds ratio 1.29; 95% CI, 1.08-1.53) that the authors considered appropriate.

In meta-analysis work, adherence to certain principles is required. The most fundamental of these principles are (i) the data from the constituent studies included in the meta-analysis must relate to the same risk factor, (ii) the data from the constituent studies included in the meta-analysis must relate to the same outcome and (iii) crude odds ratios cannot be combined with adjusted odds ratios. The authors' failure to follow these principles renders their work invalid. No public health authority or any other person or organization charged with a duty to protect the public health should rely on this study.

Squamous Cell Carcinoma

Of the six epidemiological studies on SCC[2], three presented data on the risk of SCC from the use of sunlamps manufactured before 1980[3]. These data should not have been used in the Wehner et al. 2012 meta-analysis on the risk of SCC from modern sunlamps. Sunlamps manufactured before 1980 were principally mercury vapor lamps emitting a UV spectrum of 20% UVC, 30% - 50% UVB and 30% - 50% UVA. These lamps were banned in most countries around 1980[4]. Modern sunlamps emit a UV spectrum of 1-5% UVB, 95-99% UVA and no UVC. UVC in natural sunlight is absorbed in the atmosphere and does not reach the earth's surface. UVC is highly carcinogenic. Wehner 2012 should not have used the data from Aubrey1985, Bajdik 1996 and Han 2006 in the meta-analysis of risk of SCC associated with modern sunlamps.

The fourth study, Asgari et al. 2011, was a study of tea consumption and SCC risk and did not present any odds ratios assessing the risk of SCC from sunlamps. The

[1] Other authors included ML Shrive, a medical student at University of California San Francisco School of Medicine, MM Chren, professor of dermatology at University of California San Francisco, J Han, associate professor dermatology and epidemiology at Harvard Medical School and AA Qureshi, associate professor of dermatology at Harvard Medical School.

[2] Asgari et al. 2011, Aubrey et al. 1985, Bajdik et al. 1996, Han et al. 2006, Karagas et al. 2002 and Zhang et al. 2012.

[3] Aubrey et al. 1985, Bajdik et al. 1996 and Han et al. 2006

[4] IARC Working Group on Risk of Skin Cancer and Exposure to Artificial Ultraviolet Light, page 3 (2005 : Lyon, France)

authors of Wehner et al. 2012 apparently calculated their own crude odds ratios from data in Asgari 2011 but were unable to make any adjustments for confounders even though many confounders were present. Asgari 2011 noted that, compared to controls, cases were more likely to report red or blond hair, blue or gray eyes, lighter skin, a family history of skin cancer, childhood freckles and severe sunburns. Wehner et al. 2012 should not have conflated the crude odds ratios calculated from Asgari et al. 2011 with the adjusted odds ratios of Karagas et al. 2002 and Zhang et al. 2012.

The fifth study, Zhang et al. 2012, adjusted its crude odds ratios for a number of confounders, but failed to adjust them for cumulative lifetime sun exposure or for sunburns, the two leading risk factors for SCC. This failure renders the data from Zhang et al. 2012 invalid and unusable in a meta-analysis assessing the risk of SCC from sunbeds

The foregoing errors are sufficiently serious to question the results of Wehner et al. 2012's meta-analysis.

Since only one study remains unaddressed, a note on Karagas et al. 2002 is in order. Karagas 2002 studied data for the risk of SCC associated with the use of sunlamps before and after 1975. The data for use of sunlamps after 1975 show an adjusted odds ratio of OR=1.7 (95% CI, 0.9-3.5) for the risk of SCC from sunlamps. Since the lower confidence interval is less than 1.00, this result is not statistical significant. Additionally, these data included five years of data for use of pre-1980 sunlamps, rendering the results of Karagas unreliable. Karagas 2002 notes that three prior studies also found no association between exposure to artificial sources of UVR and non-melanoma skin cancer.

One further note: it is logical that there should be little or no risk of SCC from use of modern sunlamps in a tanning salon. Studies on risk of SCC from sun exposure indicate that cumulative lifetime sun exposure in excess of 20,000 hours for northern Europeans[5] and in excess of 50,000 hours for southern Europeans[6,7] is associated with significant risk of SCC. Tanning salon customers average 15-20 sessions per year with each session involving 20-30 minutes of equivalent sun exposure. A typical customer using tanning salons for 15 years from ages 20-35 receives about 150 hours of equivalent sun exposure. Thus while use of tanning salons cannot be said to be without risk of SCC, the risk is in the proportion of 150 to 20,000 or 50,000 depending on skin type.

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[5] Kennedy C, Bajdik CD, Willemze R, de Gruijl FR, Bavinck JNB. The Influence of Painful Sunburns and Lifetime Sun Exposure on the Risk of Actinic Keratoses, Seborrheic Warts, Melanocytic nevi, Atypical Nevi, and Skin Cancer. J Invest Dermatol 2003; 120:1087-1093.

[6] Rosso S, Joris F, Zanetti R. Risk of Basal and Squamous Cell Carcinoma of the Skin in Sion, Switzerland: A Case-Control Study. Tumori 1999; 85:435-442.

[7] Rosso S, Zanetti R, Martinez C, Tormo MJ, Schraub S, Sancho-Garnier H, Franceschi S, Gafa L, Perea E, Navarro C, Laurent R, Schrameck C, Talamini R, Tumino R, Wechsler K. The multicentre south European study "Helios" II: different sun exposure patterns in the aetiology of basal cell and squamous cell carcinomas of the skin. Brit J Cancer 1996; 73:1447-1454.

An analysis of each of the six constituent studies used by Wehner 2012 in its meta-analysis on the risk of SCC from sunlamps is attached as Appendix I.

Basal Cell Carcinoma

Of the eight epidemiological studies on BCC[8], one presented data on the risk of BCC from the use of sunlamps manufactured before 1980[9] (Bajdik et al. 1996). These data should not have been used in the Wehner et al. 2012 meta-analysis on the risk of BCC from modern sunlamps. Sunlamps manufactured before 1980 were principally mercury vapor lamps emitting a UV spectrum of 20% UVC, 30% - 50% UVB and 30% - 50% UVA. These lamps were banned in most countries around 1980. Modern sunlamps emit a UV spectrum of 1-5% UVB, 95-99% UVA and no UVC. UVC in natural sunlight is absorbed in the atmosphere and does not reach the earth's surface. UVC is highly carcinogenic. For this reason, Wehner 2012 should not have used the data from Bajdik et al. 1996 in its meta-analysis of risk of BCC associated with modern sunlamps.

The second study, Corona 2001, found an OR = 0.60 (95% CI, 0.30-1.20)

The third study, Ferrucci 2011, examined the risk of early-onset BCC diagnosed before age 40 from the use of sunlamps. Data from this study should not have been used in Wehner 2012's meta-analysis because such data related to a different outcome (early-onset BCC) than the other constituent studies.

The fourth study, Gon 2011, found an OR = 0.31 (95% CI, 0.07-1.35).

The fifth study, Han 2006, examined BCC cases diagnosed between 1989 and 1998, and the average age at diagnosis was 64. Data were not collected for sunlamp use before and after 1980, and the authors stated that it was possible that the majority of their study was of pre-1980 sunlamps, rendering the data collected unusable in a meta-analysis of the risk of BCC from use of post-1980 sunlamps.

The sixth study, Karagas 2002, studied data for the risk of BCC associated with the use of sunlamps before and after 1975. The data for use of sunlamps after 1975 an adjusted odds ratio of OR=1.4 (95% CI, 0.8-2.2) for risk of BCC from sunbeds. Since the lower confidence interval is less than 1.00, this result is not statistical significant. Additionally, these data included five years of data for use of pre-1980 sunlamps, rendering the results of Karagas unreliable. Karagas 2002 notes that three prior studies also found no association between exposure to artificial sources of UVR and nonmelanoma skin cancer.

The seventh study, Rosso 1999, was a low-power study with only 10 sunlamp users. Further, the study concluded that use of sunlamps was not associated with any increased risk of BCC, casting further doubt on the usability of the Rosso data in Wehner

[8] Bajdik 1996, Corona 2001, Ferrucci 2011,Gon 2011, Han 2006, Karagas 2002, Rosso 1999 and Zhang 2012.
[9] Bajdik 1996.

2012's meta-analysis. Thus the data from Rosso 1990 should be accorded little weight in a meta-analysis.

The eighth study, Zhang 2012, adjusted its crude odds ratios for a number of confounders, but failed to adjust them for sunburns, a leading risk factor for BCC. This failure renders the data from Zhang 2012 invalid and unusable in a meta-analysis assessing the risk of BCC from tanning beds.

Conclusion

Wehner 2012 is a seriously flawed meta-analysis. The CDC should not rely on Wehner 2012 and should remove all reference to it from the CDC's website.

Of the six constituent studies on the risk of SCC from modern (post-1980) sunbeds, three examined a different risk factor (pre-1980 sunbeds) and two failed to adjust for critical confounders, making a meta-analysis of the six studies impossible. The only remaining study, standing on its own, found no statistically significant association between SCC and sunbeds.

Of the eight constituent studies on the risk of BCC from modern (post-1980) sunbeds, two (Bajdik 1996 and Han 2006) examined a different risk factor (pre-1980 sunbeds), one (Ferrucci 2011) examined a different outcome (early-onset BCC vs. BCC at any age), and one (Zhang 2012) failed to adjust for a critical confounder. Of the four remaining studies, one (Corona 2001) found an OR = 0.60 (95% CI, 0.30-1.20), one (Gon 2011) found an OR = 0.31 (95% CI, 0.07-1.35), one (Karagas 2002) included some pre-1980 sunbed data and found an OR = 1.4 (95% CI, 0.8-2.2), and one (Rosso 1999) was a low-power study with only 10 sunlamp users that found an OR = 1.24 (95% CI, 0.53-2.88). A meta-analysis of these four studies with appropriate weighting shows an OR = 0.74 (95% CI, 0.42-1.05).

Use of the Wehner 2012 meta-analysis to discourage people from using tanning salons is not without risk to the public. In addition to driving tanning salon customers to use of tanning beds in gyms, apartments, homes, clubs and other venues where the tanning beds are self-operated and thus more likely to result in UV burns, discouraging the public from receiving non-burning UV exposure exacerbates the severe public health problem of inadequate sun exposure described in Hoel et al. 2016[10]. The U.S. Government recommending that tanning salons and sun exposure should be avoided only worsens the U.S. public's health.

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[10] Hoel DG, Berwick M, de Gruijl FR, Holick MF. The Risks and Benefits of Sun Exposure 2016. Dermatoendocrinol 2016; 8:e1248325

APPENDIX I

Asgari 2011

Summary: Case-control (415 v 415) in California of SCC with a focus on tea consumption. The study did report a highly significant effect of sunburns as well as regular peak hour sun exposure. Although the authors did not discuss it, the ever use of sunbeds was shown in their table to be 11.8% among cases and 8.7% among controls. The difference was not significant (p=0.137).

Comment: The authors did not present an odds ratio for ever use of sunbeds. Wehner 2012 apparently calculated a crude odds ratio of 1.41 (95% CI, 0.9-2.22) for this study from the numbers given in the authors' Table 1, but this odds ratio should not be used in a meta-analysis because no adjustments for confounding by other risk factors can be calculated from the data presented.

Aubry 1985

Summary: Case-control (92 v 172) in Montreal Canada reported a large OR = 13.42 (95% CI, 1.38-130.48) for SCC based on the ever use of long-tube sunlamps.

Comment: The SCC diagnoses were made in 1977 & 1978 that well predate the post-1980 modern sunbed with low UVB and no UVC. Therefore this study should not have been included in Wehner 2012's meta analysis assessing the risk of SCC from post-1980 sunbeds.

Bajdik 1996

Authors' Summary: "A case-control study of non-melanocytic skin cancer was conducted among men in the province of Alberta, Canada. Two hundred and twenty-six cases of basal cell carcinoma (BCC), 180 cases of squamous cell carcinoma (SCC) and 406 age-matched controls provided information concerning skin and hair color, ethnic origin and lifetime occupational sun exposure, but not sunburn history. Our results do not show any evidence of a significant risk of BCC or SCC associated with NSUVR exposure."

Authors' Results: "Only 8% of controls, 9% of BCC cases and 10% of SCC cases reported ever having used a sunlamp (Table I). Sunlamp use was associated with a slightly increased risk of both BCC and SCC, but neither risk was statistically significant. A dose-response model was fitted based on the cumulative number of occasions a subject was exposed and no relationship was observed for sunlamp use and either BCC or SCC (results not shown)."

Authors' Discussion: "Sunlamp use was the most common non-occupational source of NSUVR reported in our study, however the total number of users was small. Most of the sunlamp use reported in this study took place before 1980 when sunlamps emitted far more UVB than modern sunlamps and even some UVC."

Comment: Since most of the sunlamp use in this study took place before 1980, this study should not have been included in Wehner 2012's meta analysis assessing the risk of SCC or BCC from post-1980 sunbeds.

Han 2006

Summary: A nested case-control within Harvard's prospective 1976 Nurses Health Study had 275 SCC cases and 283 BCC cases diagnosed between 1989 and 1998 and 804 controls. The study found large risk effects for sun exposure but non-significant effects for the use of sunlamps or tanning salon use (BCC OR = 1.32 (95% CI, 0.87-2.03); SCC OR = 1.44 (95% CI, 0.93-2.24)). "There were non-significant associations of sunlamp usage or tanning salon attendance with increased risk of SCC or BCC."

Authors' Discussion: "The ratio of UVB to UVA emitted by indoor tanning devices was greatly reduced around 1980….Because the age of our study population at baseline (1976) ranged from 30 to 55, it is possible that the majority in this study was of older UVB-emitting devices."

Comment: Since the biannual questionnaires began in 1976 and ended in 1989-98, a significant amount of data from sunlamp use before 1980 was likely, rendering the data in Han 2006 improper for Wehner 2012's meta analysis assessing the risk of SCC from post-1980 sunbeds.

Karagas 2002

Summary: Case-control study of 603 cases of BCC and 293 cases of SCC in New Hampshire (540 controls) reported a significant increased risk for the use of a tanning device (BCC OR = 1.5 (95% CI, 1.1-2.1) and SCC OR = 2.5 (95% CI, 1.7-3.8)). The effects were reduced and no longer significant if the case did not first use a tanning device until after 1975.

Comment: The majority of the data on use of tanning devices in Karagas 2002 was for use prior to 1980, rendering the results of Karagas 2002 unusable in a meta analysis assessing the risk of SCC from use of tanning devices after 1980. Also, Karagas 2002 did not adjust its odds ratios for cumulative lifetime sun exposure, the leading environmental risk factor for SCC, rendering the results of Karagas 2002 unusable in a meta-analysis assessing the risk of SCC from tanning devices.

Zhang 2012

Summary: A cohort study of BCC and SCC within Harvard's prospective 1989 Nurses Health Study II. There were 5506 cases of BCC and 403 cases of SCC resulting in an RR for BCC of 1.15 (95% CI, 1.11-1.19) and for SCC 1.15 (95% CI, 1.20-1.78) for the use of tanning beds. This was based upon an average usage of 4 times per year. The usage was for those under the age of 35 with a division between high school/college and ages 25-35. The authors of Wehner et al. 2012 contacted Zhang et al. to obtain the unpublished RR for ever versus never use of tanning beds and obtained RRs for BCC and SCC of 1.29 (95% CI, 1.22-1.35) and 1.50 (95% CI, 1.20-1.78), respectively.

Comment: Zhang 2012 adjusted its crude odds ratios for a number of confounders, but failed adjust them for cumulative lifetime sun exposure (adjustments were made only for sun exposure between ages 15 and 30) or for sunburns (adjustments were made only for sunburns between ages 15 and 20). Since cumulative lifetime sun exposure and sunburns are the two leading risk factors for SCC, this failure renders the results of Zhang 2012 invalid and unusable in a meta analysis assessing the risk of SCC from tanning devices.

APPENDIX II

Bajdik 1996

Authors' Summary: A case-control study of non-melanocytic skin cancer was conducted among men in the province of Alberta, Canada. Two hundred and twenty-six cases of basal cell carcinoma (BCC), 180 cases of squamous cell carcinoma (SCC) and 406 age-matched controls provided information concerning skin and hair color, ethnic origin and lifetime occupational sun exposure, but not sunburn history. "Our results do not show any evidence of a significant risk of BCC or SCC associated with NSUVR exposure."

Results: "Only 8% of controls, 9% of BCC cases and 10% of SCC cases reported ever having used a sunlamp (Table I). Sunlamp use was associated with a slightly increased risk of both BCC and SCC, but neither risk was statistically significant. A dose-response model was fitted based on the cumulative number of occasions a subject was exposed and no relationship was observed for sunlamp use and either BCC or SCC (results not shown)."

Authors' Discussion: "Sunlamp use was the most common non-occupational source of NSUVR reported in our study, however the total number of users was small. Most of the sunlamp use reported in this study took place before 1980 when sunlamps emitted far more UVB than modern sunlamps and even some UVC."

Comment: Since most of the sunlamp use in this study took place before 1980, this study should not have been included in Wehner 2012's meta analysis assessing the risk of SCC from post-1980 sunbeds.

Corona 2001

Summary: Case-control (166 v 158) study of BCC in the Mediterranean reported a significant dose response for reported weeks spent at the beach before age 20 years. No effect was observed from non-solar UV exposures. The ever use of sunbeds or sunlamps yielded a confounder adjusted OR of 0.6 (95% CI, 0.3-1.2).

Comment: No problem was seen other than sunbed and sunlamp exposures were not separated. Also this was not a study in North America.

Ferrucci 2011

Summary: Case control (375 v 382) study of early-onset BCC (BCC diagnosed before age 40) conducted between 2004 and 2010 in Connecticut. Persons who used sunlamps exclusively in "businesses" (not defined) were at increased risk of early onset BCC (OR=1.69, 95% CI, 1.15–2.48) compared to non-users.

Comment: Data from this study should not have been used in Wehner 2012's meta-analysis because such data related to a different outcome (early-onset BCC) than the other constituent studies.

Gon 2011

Summary: Case-control (127 v 280) of BCC in Brazil reported an insignificant effect of artificial tanning OR = 0.31 (0.07, 1.35) using hospital based controls having non-cancerous dermatological conditions.

Comment: Only 3 of the 127 cases (25 of the 280 controls) reported artificial tanning which is evidently uncommon in southern Brazil. This is a low-power study which should accorded little weight in a meta-analysis.

Han 2006

Summary: A nested case-control within Harvard's prospective 1976 Nurses Health Study had 275 SCC cases and 283 BCC cases diagnosed between 1989 and 1998 and 804 controls. The study found large risk effects for sun exposure but non-significant effects for the use of sunlamps or tanning salon use (BCC OR = 1.32 (95% CI, 0.87-2.03); SCC OR = 1.44 (95% CI, 0.93-2.24)). "There were non-significant associations of sunlamp usage or tanning salon attendance with increased risk of SCC or BCC."

Authors' Discussion: "The ratio of UVB to UVA emitted by indoor tanning devices was greatly reduced around 1980….Because the age of our study population at baseline (1976) ranged from 30 to 55, it is possible that the majority in this study was of older UVB-emitting devices."

Comment: Since the biannual questionnaires began in 1976 and ended in 1989-98, a significant amount of data from sunlamp use before 1980 was likely, rendering the data in Han 2006 improper for Wehner 2012's meta analysis assessing the risk of BCC from post-1980 sunbeds.

Karagas 2002

Summary: Case-control study of 603 cases of BCC and 293 cases of SCC in New Hampshire (540 controls) reported a significant increase risk for the use of a tanning device (BCC OR = 1.5 (95% CI, 1.1-2.1) and SCC OR = 2.5 (95% CI, 1.7-3.8)). The effects were reduced and no longer significant if the case did not first use a tanning device until after 1975.

Comment: The majority of the data on use of tanning devices in Karagas 2002 was for use prior to 1980, rendering the results of Karagas unusable in a meta analysis assessing the risk of BCC from tanning devices after 1980.

Rosso 1999

Summary: Case-control of BCC and SCC in Switzerland (25 SCC cases, 120 BCC cases and 144 controls). For ever use of sunlamps the estimated OR for BCC was 1.24 (95% CI, 0.53-2.88). For SCC the OR was not reported because there no reported use of sunlamps among the 25 cases but 9 of the 144 controls reported use. This was a low-power study with only 10 sunlamp users. The study concluded that use of sunlamps was not associated with any increased risk of BCC.

Comment: This was a low-power study with only 10 sunlamp users. The data from Rosso 1999 should be accorded little weight in a meta-analysis.

Zhang 2012

Summary: A cohort study of BCC and SCC within Harvard's prospective 1989 Nurses Health Study II. There were 5506 cases of BCC and 403 cases of SCC resulting in an RR for BCC of 1.15 (95% CI, 1.11-1.19) and for SCC 1.15 (95% CI, 1.20-1.78) for the use of tanning beds. This was based upon an average usage of 4 times per year. The usage was for those under the age of 35 with a division between high school/college and

ages 25-35. The authors of Wehner et al. 2012 contacted Zhang et al. to obtain the unpublished RR for ever versus never use of tanning beds and obtained RRs for BCC and SCC of 1.29 (95% CI, 1.22-1.35) and 1.50 (95% CI, 1.20-1.78), respectively.

Comment: Zhang 2012 adjusted its crude odds ratios for a number of confounders, but failed adjust them for sunburns occurring before age 15 or after age 20. Failure to adjust for this widely accepted risk factor for BCC renders the results of Zhang 2012 unusable in a meta-analysis assessing the risk of BCC from use of sunbeds.