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Nonmelanoma skin cancer in women

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ABSTRACT

Men continue to develop nonmelanoma skin cancer (NMSC) at higher rates than women, but the epidemiologic pattern of NMSC development is evolving. We present a selective, narrative review of the literature showing that there is a trend toward a development of basal cell carcinomas in women at younger ages, and highlight potential causes of this trend. We review evidence that indoor tanning is associated with the development of NMSC and show that young women use indoor tanning more than any other age-sex group. We discuss societal factors that relate to the tanning behavior of young women. Finally, we argue that facial NMSCs may have more of a negative impact on quality of life in women than in men. © 2018 Published by Elsevier Inc. on behalf of Women's Dermatologic Society. This is an open access article

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Introduction

Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) comprise the vast majority of nonmelanoma skin cancer (NMSC) cases both in the United States and worldwide. For this review, NMSC will refer to these two entities exclusively. Worldwide, the incidence of NMSC has increased steadily over the past 50 years for both men and women, and this trend continues today (Abbas and Kalia, 2016; Christenson et al., 2005; Hollestein et al., 2012; Lomas et al., 2012; Muzic et al., 2017; Perera et al., 2015; Rogers et al., 2015; Xiang et al., 2014). Although many factors have been implicated in this increase (Leiter et al., 2014), there is general agreement that the primary cause of NMSC is exposure of the skin to ultraviolet radiation (UVR). Solar radiation and indoor tanning are two important sources of UVR, and this review will focus on these two sources exclusively.

This review seeks to draw attention to an emerging trend toward the development of BCC in women at younger ages than in previous generations, highlight the disproportionate use of indoor tanning by young women compared with other age-sex groups, and provide some degree of historical and psychosocial context for the relationship between young women and indoor tanning behavior.

* Corresponding author. *E-mail address:* henry.heaton@yale.edu. (H. Heaton). Historically, there has been a higher incidence of NMSC in men than women (Wu et al., 2013; Xiang et al., 2014), which some have attributed to a greater sun exposure in men (Abbas and Kalia, 2016; Gallagher et al., 1995). However, indoor tanning, which uses artificially produced UVR, is more commonly used by women than men. Indoor tanning has been shown to increase the risk of both BCC and SCC (Ferrucci et al., 2012; Karagas et al., 2002; Wehner et al., 2012, 2014; Zhang et al., 2012), and ultraviolet-emitting tanning devices are now classified as carcinogens by the International Agency for Research on Cancer (El Ghissassi et al., 2009).

Since the popularization of indoor tanning in the 1970s in the United States (Levine et al., 2005) and the 1980s and 1990s in Europe (Bataille et al., 2005; Flohil et al., 2013), women have consistently exhibited a higher propensity to use indoor tanning than men (Schneider and Kramer, 2010). This is true for all age groups (Wehner et al., 2014) but is especially pronounced in teenage and young adult women compared with their male counterparts (Centers for Disease Control and Prevention, 2012; Kann et al., 2016).

Over the past 50 years, there has also been a shift in the pattern of NMSC development in women relative to men. Men continue to develop more NMSCs per year than women, and the overall incidence of NMSC continues to increase for both sexes over time. However, there is evidence to support that women in Europe and the United States are developing BCCs at younger ages and in higher numbers than their male counterparts (Demers et al., 2005; Evans et al., 2014; Flohil et al., 2013; Muzic et al., 2017; Skellett et al., 2012).

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The trend toward increased incidence of BCCs in young women has not been observed in Australia (Perera et al., 2015), where indoor tanning is less prevalent (Wehner et al., 2014) and more restricted (Schneider and Kramer, 2010) than in the United States and Europe.

Basal cell cardinomas are developing at younger ages in women

Flohil et al. (2013) conducted a population-based study to define BCC incidence in the southeast Netherlands between 1973 and 2009. The authors found that, although there was a roughly equivalent increase, in the overall incidence of BCCs for both men and women over the 36 years of the study (from 34.4 to 157.3 per 100,000 person-years in women vs. 40.2 to 164.7 per 100,000 person-years in men), the ages at the time of diagnosis differed widely between the sexes.

The greatest increase in BCC incidence for any single age-sex group was found in women under age 40 years (1.82-22.2 per 100,000 person-years in women vs. 2.4 to 9.9 per 100,000 person-years in men). The next most remarkable change in incidence was seen in women in the 40-64 year old age group (increase from 35.4 to 242.8 per 100,000 person-years for women vs 53.9 to 203.1 per 100,000 person-years in men).

These findings were mirrored by a U.S. population-based study of SCC and BCC incidence in Olmsted County, Minnesota, between 1976 and 2010 (Muzic et al., 2017). In this study, Muzic et al. found that, although BCC incidence increased for both men and women over the study period for all age-sex groups other than the group of 18-to 29-year-old men (slight decrease in incidence), the magnitude of the increased incidence was higher for women than for men in each age group. Women in the 40- to 49-year-old age group had the fastest rate of increase in BCC incidence of any single age-sex group (2.46-fold), and women in the 30- to 39-year-old age group had the second fastest increase in incidence (1.91-fold). Additionally, the absolute BCC incidence in the most recent study period (2000-2010) was higher for women in each of the youngest three age groups (age <50 years) than for men in the same age groups.

In a single-center retrospective cohort study of 17,000 patients treated between 2006 and 2013 at a private dermatology practice in Texas, study authors found that, although the majority of SCCs and BCCs were found in men, there was a statistically significant reversal at the youngest age group: Within the 10- to 49-year-old age group, women had a higher incidence of BCC than men (Evans et al., 2014).

A Canadian study conducted using the Manitoba cancer registry showed that, in the age group <40 years, women developed more BCCs than men (male/female ratio: 0.76) over the 40 years of the study, and this difference in incidence increased over time (Demers et al., 2005). The study also compared the incidence of BCC development at the beginning of the study period in 1960 to the incidence in 2000 and found that for all patients age <60 years, the percent change in the incidence of BCC was higher in women than in men.

Finally, a small study analyzing the incidence of BCCs in a population age <30 years in the east of the United Kingdom found that the majority of BCCs between 1998 and 2006 were in women (53 in women vs. 41 in men; Skellett et al., 2012).

Squamous cell carcinoma in women

There is evidence that the incidence of SCC in women is also increasing both in crude numbers and within each age group, but there is no widely reported analogous shift toward young women like the one observed for BCC. Some studies have found that SCC is increasing more in young women than in young men (Muzic et al., 2017), but others have not (Evans et al., 2014; Hollestein et al., 2012).

Indoor tanning is used most commonly by young women and is associated with the development of NMSC. There is a critical period in early life when UVR is uniquely harmful

The use of indoor tanning devices has been associated with an increased risk for the subsequent development of NMSC in several large studies (Ferrucci et al., 2012, 2014; Karagas et al., 2002; Wehner et al., 2012, 2014; Zhang et al., 2012). The causal relationship between the use of indoor tanning and the development of NMSC has been acknowledged by international health organizations (El Ghissassi et al., 2009), and the practice has been restricted or banned by many national and regional governments (O'Sullivan and Tait, 2014; Pawlak et al., 2012). In 2009, the World Health Organization determined that there was sufficient evidence to classify UVR-emitting tanning devices as class I carcinogens (El Ghissassi et al., 2009). Since then, evidence in support of this conclusion has accumulated.

In 2012, Wehner et al. published a comprehensive meta-analysis in which they found that ever exposure to tanning beds was associated with an increased risk of both SCC (summary relative risk [RR]: 1.67; 95% confidence interval [CI], 1.29-2.17) and BCC (summary RR: 1.29; 95% CI, 1.08-1.53) compared with never exposure. In a large follow-up study published in 2014 on the international prevalence of indoor tanning, Wehner et al. used their 2012 results to show that across Australia, the United States, and Europe, more than 450,000 cases of NMSC are attributable to indoor tanning each year (Wehner et al., 2014).

This systematic literature review and meta-analysis also demonstrated a striking relationship wherein the prevalence of indoor tanning use varies widely as a function of both sex and age. Specifically, the authors found that for each age group studied (adults, university students, and adolescents), women had higher rates of both ever and past-year exposure than their age-matched male counterparts (Wehner et al., 2014). University students had the highest rate of active indoor tanning exposure (43% past year use, 55% ever use), followed by adolescents (18% past year use, 19% ever use) and adults (14% past year use, 35% ever use). These data echoed an earlier systematic literature review of American, European, and Australian papers published between 2000 and 2008 in which Schneider and Kramer (2010) succinctly summed up the overall demographic pattern of tanning prevalence by stating that "the typical [indoor tanner] is female, between 17 and 30 [years old]."

Recent epidemiological data from the United States exhibit a similar pattern. The Youth Risk Behavior Survey from 2015 showed that, among U.S. high school students, the overall rate of indoor tanning use was 7.3%. Of the white students surveyed, women had the highest rate of indoor tanning use (15.2% for women vs. 3.7% for men), and 12th grade women had the highest rate of any single age-sex group (16.2% for 12th grade women vs. 5.8% for 12th grade men; Kann et al., 2016).

The 2010 National Health Interview Survey revealed that the highest rate of indoor tanning use over the previous year for any single age group in the United States was white women between the ages of 18 and 29 years (18.9% in women vs. 3.9% in men). The National Health Interview Survey also showed that, for all age groups under age 49 years, the lowest female tanning rate (9.2% use of indoor tanning in the previous year, both in 30-39 and 40-49 year olds) was still more than double the highest rate in men (3.9% for men age 18-29 years; Centers for Disease Control and Prevention, 2012).

Furthermore, within the population of male and female tanners in the United States, women tan more frequently than men (57.7% of women tanned >9 times per year vs. 40% of men). Unsurprisingly, young female indoor tanners tanned more frequently than any other age-sex group of indoor tanners. In the age group of 18- to 29-year-olds, 61.1% of women tanned >9 times per year versus

35.8% of men. In the 30- to 39 year-old age group, 61.2% of women tanned >9 times per year versus 40% of men.

During their initial meta-analysis, Wehner et al. (2012) made another important observation. They found statistically significant evidence that first exposure to indoor tanning at a younger age corresponded with an increased risk of subsequent development of NMSC. For patients exposed to indoor tanning before 25 years old, an increased risk of BCC (RR: 1.40; 95% CI, 1.29-1.52) but not SCC (RR: 2.02; 95% CI, 0.70-5.86) was found. This conclusion lent support to earlier observations (Corona et al., 2001; Gallagher et al., 1995; Iannacone et al., 2012; Kricker et al., 1995) of a critical period in early life when UVR is especially important for the subsequent development of NMSC. Gallagher et al. (1995) first proposed this critical period. They conducted a population-based case control study on risk factors for BCC in men using tumor information from the Alberta Cancer Registry from 1983 to 1984. Their data showed that increased exposure to recreational sunlight during childhood and adolescence (0-19 years old) was associated with an increased risk of BCC development in adulthood (Gallagher et al., 1995).

A similar pattern was identified in a population-based case control study in Western Australia in 1988 by Kricker et al. (1995). In this study, the authors attempted to determine which pattern of sun exposure most increases the risk for BCC development (i.e., intermittent intense exposure or continuous occupational exposure) and found that intermittent exposure was more likely to lead to BCC development than occupational or chronic exposure. The authors also found that the risk of BCC development was higher in teenagers with intermittent sun exposure than in any other age group.

Using a Mediterranean population in central-southern Italy, Corona et al. (2001) found a statistically significant dose-response relationship between the annual number of weeks spent at the beach before the age of 20 years and the subsequent development of BCC in adulthood.

Finally, a more recent case-control study in Florida showed that blistering sunburns in childhood or teenage years were associated with an increased risk of both BCC and SCC (Iannacone et al., 2012).

Although the latter studies were not conducted using indoor tanning specifically, their findings nevertheless lend support to the idea that there is something uniquely important about exposure to significant UVR at a young age with regard to the subsequent development of NMSC. Exposure to indoor tanning beds is associated with the development of NMSC, and women who range in age from their late teens to 30 years have the highest exposure to indoor tanning beds. A young age at the time of first exposure to UVR may enhance the risk of subsequent NMSC regardless of sex, which means that young women concentrate their exposure to indoor tanning during the years when they are most likely to increase their risk of NMSC.

Motivations that drive indoor tanning behavior in women and opportunities for intervention

An understanding of the reasons behind the higher propensity for indoor tanning in women is critical if the behavior is to be successfully curtailed. This has been an area of intense study in recent years, and several high-quality reviews (Friedman et al., 2015; Holman and Watson, 2013; Levine et al., 2005; Madigan and Lim, 2016; Watson et al., 2013) outline the various factors that motivate tanning behavior. Even though an exhaustive review of the subject is beyond the scope of this discussion, the concept of physical appearance with regard to external influences will be reviewed briefly.

The societal factors that influence a person's concept of his or her own physical appearance include both norms with regard to what each individual believes is broadly perceived to be attractive, as well as individual attitudes and behaviors related to these perceptions. Although not universally held, there is a pervasive belief in a segment of the population that a cosmetic benefit or enhancement in interpersonal attractiveness accompanies a darker or tanner skin tone (Holman and Watson, 2013; Madigan and Lim, 2016; Robinson et al., 2008; Sahn et al., 2012). As Albert and Ostheimer (2002, 2003a, 2003b) discussed in their exhaustively researched threepart historical series, this idea has a long and complicated history.

The ideal skin tone shifted significantly over the course of the late 19th and early 20th centuries and evolved from pale to tanned at a faster rate for men than women during the 1910s and 1920s (Albert and Ostheimer, 2002). This overall shift in societal perception was reflected in the fashion and cosmetic marketing at the time. A study of Harper's Bazaar and Vogue magazines found that in the early 1920s, the preponderance of articles and advertisements favored bleaching agents and photoprotection, but the late 1920s saw a shift toward the promotion of tanning behavior (Albert and Ostheimer, 2003a; Martin et al., 2009).

Whether the ideas that were portrayed in popular media in the 1920s contributed to or were a byproduct of the changing societal idea of what skin should look like is subject to debate. Regardless, the result was a shift in attitude with regard to ideal skin tone that persisted in successive generations of 20th-century America.

Albert and Ostheimer discuss the fascinating evolution of medical and popular opinion with regard to UVR and the use of sun lamps over the following decades in the United States. There was initial endorsement of the health benefits of UVR (including vitamin D production) by the medical community, which was followed by a belated acknowledgement of carcinogenicity in the 1930s. There were continuous unsubstantiated claims of health benefits by the industry, which became increasingly regulated in the 1940s, 1950s, and 1960s. Throughout, a persistent belief remained among the public that a tanned appearance was desirable. Thus, the increase in indoor tanning behavior in the 1970s can be attributed, at least in part, to the persistence of the early 20th century shift in attitude toward perceiving tanned skin as attractive (Albert and Ostheimer, 2002, 2003a, 2003b; Levine et al., 2005).

Despite all the negative consequences of indoor tanning that have come to light in recent years, analyses of contemporary femaletargeted advertising show that, for women, things have not changed since the 1920s. Cho et al. (2010) conducted a content analysis of eight magazines that target American women of various age groups between 1997 and 2006. The authors found that the amount of coverage that was devoted to the negative consequences of indoor tanning was less than half that of the coverage of tanning benefits, of which the most frequently cited was looking healthy. The consequences of indoor tanning were covered one-fifth of the amount that consequences of outdoor tanning were discussed. Furthermore, their analysis revealed that magazines that target young women covered the negative consequences of tanning only half as frequently as magazines that target older women. A recent study of Canadian magazines targeting women between 2000 and 2012 found similar results: 41% of articles and 53% of images promoted a tanned look as attractive, but only 15% of articles and 1% of images discouraged indoor tanning (McWhirter and Hoffman-Goetz, 2015).

In 2008, Poorsattar and Hornung published a commentary on the negative impact that portrayals of indoor tanning in popular media and endorsement of the practice by Hollywood celebrities can have on children and adolescents. The authors drew from literature on childhood development and social psychology to highlight one of the most concerning facets of the problem: Adolescent women are uniquely susceptible to media-driven portrayals of what is and is not attractive. The existence of this increased susceptibility in adolescent women and its relevance to indoor tanning behavior have been validated. Holman and Watson (2013) conducted a large systematic literature review to assess the self-reported reasons behind adolescent tanning. Though causality was not assessed, this analysis found

that intentional tanning was related to having a positive attitude about a tanned appearance, using sunless tanners, dieting, and "trying to look like celebrities," observations which led the authors to conclude that concern with one's own physical appearance plays an important role in tanning.

The importance attributed to one's own physical appearance may also be used to reduce indoor tanning behavior. Hillhouse et al. (2008) published a randomized control trial in which appearancefocused interventions were effective in modifying indoor tanning behavior in young adult (age 17-21 years) female tanners specifically. Indeed, this appearance-focused study was cited in a recent systematic review for the U.S. Preventive Services Task Force as the only trial in which an intervention had any effect on the rates of indoor tanning (Henrikson et al., 2018), despite relying on a lowtech booklet. Internet-based interventions have also demonstrated efficacy in improving self-reported skin cancer prevention behaviors in young adults of both genders (Heckman et al., 2016), which is an area in which additional development is possible. With regard to interventions that individual clinicians can put in place short term (Boyers et al., 2014), displaying media (both in the clinical setting and on social media platforms) that emphasizes the consequences of UVR on personal appearance may be an effective approach.

Shifting incidence in nonmelanoma skin cancer by body site

In both men and women, the head and neck are the most common locations for the development of NMSC. However, specific sites on the head and neck have been shown to develop NMSC at different rates as a function of sex. In 2013, Dawn and Lawrence published a retrospective cohort study of all NMSCs treated with Mohs micrographic surgery on the lips at a single institution between 1995 and 2010. The authors found that tumors on the upper lip were more likely to be BCCs and were more likely to occur in women, but those on the lower lip were more likely to be SCCs and were predominantly in elderly men. These findings were consistent with prior results from Brazil and Australia (Leibovitch et al., 2005; Souza et al., 2011). Similarly, Lee et al. (2012) published a retrospective cohort study in which they found that the overwhelming majority of patients with SCCs on the ears were male. Again, this result was consistent with previous studies (Ragi et al., 2010).

Although the vast majority of NMSCs continue to occur on the head and neck for both men and women, multiple studies have identified a shift in the incidence of NMSC as a function of body site (Flohil et al., 2013; Muzic et al., 2017; Skellett et al., 2012; van Hattem et al., 2009). Flohil et al. (2013) found that, for the final 4 to 6 years of their study, the body site with the steepest increase in BCC incidence was the trunk. From 2003 to 2009, there was a 14.8% estimated annual percentage change (EAPC) for women and a 12.8% EAPC in men for BCCs on the trunk, but the head and neck had increases of 5.8% and 4.7%, respectively. These findings were mirrored by another study in which the proportion of BCCs on the trunk and SCCs on the extremities more than doubled for both men and women between the earliest and latest included time periods (1976-1984; 2000-2010; Muzic et al., 2017). Similarly, in Alberta, Canada, between 1988 and 2007, the steady yearly increase in the incidence of both BCC and SCC on the head and neck ceased between 1997 and 2001, but the incidence continued to rise for tumors on the trunk for both men and women throughout the study period (Jung et al., 2010).

Van Hattem et al. (2009) found that BCC incidence increased with an increase in socioeconomic status for men at all body sites, but the only female age and body-site group for which the same trend held true was truncal BCCs in patients age <65 years.

Treatment of nonmelanoma skin cancer in women

Whether the slow shift in NMSC development from the head and neck to the trunk (BCCs) and extremities (SCCs) reflects an increase in deliberate tanning behavior is subject to interpretation. From the perspective of a physician who is tasked with treating skin cancers wherever they arise, a shift in incidence away from the face may be viewed as a positive development. Surgery leaves scars, and posttreatment facial appearance is a uniquely important outcome for many patients (Brown et al., 2008; Caddick et al., 2012; Essers et al., 2007; Sobanko et al., 2015).

The appearance of facial skin clearly matters to both men and women. However, observations in the psychology literature suggest that the negative impact of a facial lesion or scar on the overall well-being of a female patient might be greater than that of the same lesion or scar in a male patient. First, there is literature to support the idea that self-esteem is more directly tied to the appearance of the skin for women than for men (Gentile et al., 2009; Jobanputra and Bachmann, 2000). Second, there is also evidence that physical appearance in general is more central to self-esteem for women than for men (Gentile et al., 2009). Women's perceptions of their own attractiveness are more likely to be negative than those of men (Gentile et al., 2009). Finally, there is a link between a negative selfassessment of facial appearance and negative affect in women that is either not present or much weaker in men (Mirams et al., 2014). Taken together, these findings suggest that, by impairing physical appearance, facial lesions or scars may be more damaging to the overall quality of life (measured by both self-esteem and affect [mood]) of women than of men.

Several validated tests may be used to assess quality of life related to facial skin cancers (Sobanko et al., 2015). Using these tests, concrete evidence of a greater impact on women is admittedly sparse to date. One report assessed the overall impact of facial skin cancers on quality of life for 53 patients, and although the results were not significant, women showed lower global (p = .198) and appearance-related (p = .116) pre- and postoperative disease-related quality of life than men (Caddick et al., 2012). Whether facial lesions or scars have a greater negative impact on women than on men is not clear based on existing data, but the possible existence of this difference warrants further study.

If women are more affected than men by facial lesions or scars, evolutionary biology may explain why this is the case. In a study published in 2001, Fink et al. point out that even though many authors in multiple disciplines have advanced the idea that the appearance of female skin plays an important role in signaling mate quality, empirical data in support of this claim were lacking (Fink et al., 2001). The authors then described their own study, in which they found that skin texture affects men's judgment of female attractiveness, and homogeneous or smooth skin was judged to be the most attractive skin texture. Subsequent research has reinforced these findings and provided evidence that color homogeneity and topographical features of female facial skin correlate with attractiveness, youthfulness, and perceived overall health (Fink et al., 2006; Matts et al., 2007; Samson et al., 2011).

Conclusions

We have shown evidence that indoor tanning increases the risk of subsequent development of NMSC and that tanning at a young age may especially lead to NMSC. Additionally, we have presented evidence that women use indoor tanning more than men and that young women have the highest exposure to indoor tanning of any age-sex group. Although not proven, the possibility of a causal relationship between these findings and the overall shift toward the development of BCCs in younger women must be considered. The high prevalence of indoor tanning use in young women is not surprising given that this group is both targeted by and uniquely susceptible to external influences that promote a tanned appearance. It is sadly ironic that, by tanning in response to these external pressures, young women increase their own risk of facial scarring and potentially decrease their overall quality of life.

Appendix A. Supplementary data

For patient information on skin cancer in women, please click on Supplemental Material to bring you to the Patient Page. Supplementary data to this article can be found online at https:// doi.org/10.1016/j.ijwd.2018.08.007.

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